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TEZĂ DE DOCTORAT

**ASSOCIATION BETWEEN NON-ALCOHOLIC HEPATIC
STATOSIS AND SUBCLINICAL MYOCARDIAL
DYSFUNCTION**

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LIST OF PUBLISHED WORKS

1. **Andrei Vitel**, Ioan Sporea, Ruxandra Mare, Christian Banciu, Diana-Aurora Bordejevic, Tudor Parvanescu, Ioana Mihaela Citu, Mirela Cleopatra Tomescu: "Association Between Subclinical Left Ventricular Myocardial Systolic Dysfunction Detected by Strain and Strain-Rate Imaging and Liver Steatosis and Fibrosis Detected by Elastography and Controlled Attenuation Parameter in Patients with Metabolic Syndrome", Diabetes MetabSyndrObes 2020 Oct15; 13: 3749-3759. doi:10.2147/DMSO.S268916; IF:2,8
2. **Andrei Vițel**, Tudor Parvanescu, Vlad Ioan Morariu, Diana Aurora Bordejevic, Mirela Cleopatra Tomescu Non-alcoholic Fatty Liver Disease Associated With Metabolic Syndrome, a Major Risk Factor for Atherosclerotic Disease, RESEARCH AND CLINICAL MEDICINE JOURNAL The European Journal of Innovative, Integrative and Translational Medicine Volume V, Issue1, 2021;
3. Tudor Parvanescu, **Andrei Vitel**, Ioan Sporea, Ruxandra Mare, Bogdan Buz, Diana Aurora Bordejevic, Mirela Cleopatra Tomescu, Sergiu Florin Arnăutu, Vlad Ioan Morariu, Ioana Mihaela Citu: "Significant Association between Left Ventricular Diastolic Dysfunction, Left Atrial Performance and Liver Stiffness in Patients with Metabolic Syndrome and Non-Alcoholic Fatty Liver Disease", Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy, 9 April 2021 Volume 2021:14 Pages 1535—1545; IF:2,8

LIST OF ABBREVIATIONS

SM	–sindromul metabolic
BFGNA	–boala ficatului gras nonalcoolic
SHNA	–steatohepatită nonalcoolică
AS	–atriul stâng
VS	–ventriculul stâng
OMS	–Organizația Mondială a Sănătății
ETCVH	–elastografie tranzitorie controlată de vibrațiile hepatice
PCA	–parametrul de control al atenuării
EST-2D	–ecocardiografia de tip speckle tracking bidimensională
BCV	–boli cardiovasculare
DZT2	–diabetul zaharat de tip 2
TGL	–trigliceride
HDL	–lipoproteinelor cu densitate înaltă
VLDL	–lipoproteinelor cu densitate foarte scăzută
RI	–rezistența la insulină
HTA	–hipertensiune arterială
IECA	–inhibitori al enzimelor de conversie ai angiotensinei
DZ	–diabet zaharat
ILK	--inteleukina-6
CHC	–carcinom hepatocelular
AST	–aspartat-aminotransferaza
ALT	–alanina-aminotransferaza
ET	–elastografiatranzitorie
IMC	–indice de masă corporală
LDL	–lipoproteine cu densitate scazută

X

AVC	–accident vascular cerebral
TA	–tensiunea arterială
ESC	–societatea europeană de cardiologie
SR	–rata de deformare
MESA	–Studiul Multi-Etnic al Aterosclerozei
RSAS	–rata de deformare a atriului stâng
FEVS	–fracție de ejectie a ventriculului stâng
HbA1c	–hemoglobinaglicozilată
S	–deformare/strain
ATP	–adenozin trifosfat
IMA	–infarct miocardic acut
TDI–	–doppler tisular
FID	–Federația Internațională a Diabetului
TAS	–tensiunea arterială sistolică
TAD	–tensiunea arterială diastolică
GJ	–glicemie ajeun
TRIV	–timpul de relaxare isovolumetric
FE	–fracția de ejectie
SL	–strainul/deformarea longitudinală
SC	–strainul/deformarea circumferențială
FC	–frecvența cardiacă
DTDVS	–diametrul telediastolic al ventriculului stâng
DTSVS	–diametrul telesistolic al ventriculului stâng
FS	–fracția de scurtare
SLG	–strainul longitudinal global

RSLG	–rata de deformare longitudinală globală
SCG	–strainul circumferențial global
RSCG	–rata de deformare circumferențială globală
RSRG	–rata de deformare radială globală
SRG	–strainul radial global
MRF	–masurătoarea rigidității ficatului
RF	–rigiditatea ficatului
IC	–insuficiență cardiacă
VAS	–volumul atriului stâng
DVM	–deschiderea valvei mitrale
IVM	–închiderea valvei mitrale
VTASE	–volumul total atrial stâng ejectat
VEAAS	–volumul de ejeecție active al atriului stâng
FEAS	–fracție de ejeecție a atriul stâng
SAS	–strainul/deformarea atriului stâng
IcpFE	–insuficiență cardiacă cu fracție de ejeecție prezervată
BC	–boala coronariană

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INTRODUCTION

Over the years, several definitions of metabolic syndrome have been proposed by major scientific associations. These definitions differ somewhat in terms of criteria and threshold values, but in general, all agree on the essential components of the syndrome. The proposed definitions are intended to help identify people at high risk of developing long-term cardiovascular pathologies who may benefit from primary cardiovascular prevention.

The diagnosis of metabolic syndrome should be used in conjunction with standard prediction algorithms, such as the Framingham risk score and the Diabetic Prediction Model, which have a more accurate prediction of short-term risk. Metabolic syndrome (MetS) has a major involvement in public health and is a global clinical challenge. Due to urbanization, the prevalence of obesity is higher and is due to sedentary lifestyle habits associated with increased caloric intake.

THE GENERAL PART

1. CURRENT AFFAIRS IN DEFINING METABOLIC SYNDROME

Although the term "metabolic syndrome" was first used by Hanefeld and Leonhardt in the early 1980s [1, 2], the observation that certain metabolic disorders appeared to coexist has been observed since the beginning of the last century, when doctors Kylin and Marañón who have independently described the frequent association of diabetes and hypertension [3]. Since then, metabolic syndrome has been labeled differently as X syndrome or insulin resistance syndrome, and its definition has changed as Gerald Reaven introduced the concept of insulin resistance as a common etiological factor for the group of metabolic disorders and disorders he collectively referred to as Syndrome X. In addition to hypertension, Reaven's definition of including decreased glucose tolerance, hyperinsulinemia, high levels of very low density lipoprotein (VLDL) and low levels of high-density lipoprotein (HDL) [4].

Central obesity was later added as a clinical feature of metabolic syndrome by Norman Kaplan [5], and current definitions now include the following key features: hyperinsulinemia or insulin resistance, dyslipidemia, hypertension, and obesity with a particular focus on central obesity. Over the past 15 years, several organizations, including the World Health Organization (WHO), the International Diabetes Foundation (IDF), the American Heart Association (AHA), and the National Heart and Lung Institute (NHLBI) have proposed a set of criteria. to better define metabolic syndrome in adults [6].

1.1. INCIDENCE AND PREVALENCE OF METABOLIC SYNDROME

According to the 2015 Global Obesity Survey in 60 countries, 604 million adults and 108 million children were obese. Since 1980, the prevalence of obesity has doubled in 73 countries and increased in most other countries.

Over the last three decades, the prevalence has risen from 1.1% in 1980 to 3.85% in 2015. Between 1990 and 2015, the overall rate of BMI-related deaths increased by 28.3%.

1.1. PATHOPHYSIOLOGY OF METABOLIC SYNDROME

Metabolic syndrome involves a state of chronic inflammation as a consequence of the complex interaction between genetic and environmental factors. this syndrome [9].

1.2.1 ABDOMINAL OBESITY

Adipose tissue is a heterogeneous mixture of adipocytes, preadipocytes and can respond rapidly and dynamically to changes in excess nutrients through hypertrophy and adipocyte hyperplasia [10]. At the same time, the blood supply to the adipocytes is reduced, causing hypoxia at this level [34]. Hypoxia appears to be the etiopathogenic factor that causes necrosis in macrophages in adipose tissue which in turn will lead to an overproduction of biologically active metabolites known as adipocytokines which include: glycerol, proinflammatory mediators, tumor necrosis factor alpha ($TNF\alpha$) interleukin (IL-6), plasminogen inhibitor-activator-1 (PAI-1) and C-reactive protein (CRP) [9].

1.2.2 TUMOR NECROSIS FACTOR

It is a paracrine mediator in adipocytes and appears to act locally to reduce the insulin sensitivity of adipocytes [9]. $TNF-\alpha$ induces adipocyte apoptosis and promotes insulin resistance by inhibiting the insulin receptor.

1.2.3 C REACTIVE PROTEIN

Elevated CRP levels are associated with leukocytosis, insulin resistance, increased body mass index, and hyperglycemia. in metabolic syndrome.

1.2.4. INTERLEUKIN 6

Interleukin 6 (IL-6) is released by both adipose tissue and skeletal muscle tissue. Its elevated levels have been shown to be associated with elevated body mass index, elevated insulin levels, the development of type II diabetes, and low HDL cholesterol levels [16].

1.2.5 ADIPONECTIN

It regulates lipid and glucose metabolism, increases insulin sensitivity, regulates food intake and body weight, and protects against chronic inflammation [17]. Adiponectin levels are inversely proportional to those of triglycerides, LDL-cholesterol and blood pressure levels.

1.2.6 LEPTIN

Represents an adipokine involved in the regulation of satiety and caloric intake [20]. Plasma levels of leptin are increased during the development of obesity and decreased during weight loss. Most overweight or obese people have a high level of leptin that does not suppress appetite, thus causing the appearance of leptin resistance, being considered a fundamental pathology in the pathogenesis of obesity [21].

1.2.7 ENDOTHELIAL DYSFUNCTION

It is characterized by impaired endothelium-dependent vasodilation, a reduction in arterial complaint, and an accelerated process of atherosclerosis [23].

1.2.8 CHRONIC STRESS AND THE ACTION OF GLUCOCORTICOIDS

Hypersecretion of stress mediators such as cortisol in individuals with a genetic predisposition associated with environmental factors may lead to the accumulation of visceral adipocytes due to chronic hypercorticism, decreased growth hormone secretion, and hypogonadism. In fatty acid synthesis and promotes lipoprotein secretion, increases glucose synthesis by gluconeogenesis, promotes the differentiation of preadipocytes into adipocytes, which could lead to an increase in adipose tissue [25].

2. NON-ALCOHOLIC FATTY LIVER DISEASE

INTRODUCTION

Nonalcoholic fatty liver disease is the most common form of liver disease and a leading cause of morbidity and mortality in both developed and developing countries [28]. A large number of studies currently suggest that BFGNA it is not limited to the liver, but may be a major part of a multisystem disease. As early as 1995, it was first suggested that BFGNA was a systemic condition with a specific cardiometabolic involvement [28], a notion that is now universally accepted.

To date, nonalcoholic fatty liver disease is an exclusionary diagnosis, and liver biopsy is the gold standard for diagnosis.

In this paper we will try to describe the association between nonalcoholic fatty liver disease and cardiometabolic disorders [30].

2.1 DEFINITION AND DIAGNOSIS

This condition describes the presence of hepatic steatosis in the absence of a secondary cause of accumulation of liver fat, such as alcohol ingestion, defined as a daily consumption of alcohol > 20 g / day for women or > 30 g / day

for men [31]. NAFLD is a diagnosis of exclusion and, conventionally, there are two possible approaches to their diagnosis, by invasive and non-invasive evaluation. Depending on the method chosen, there is a great variability of prevalence rates reported in different studies.

2.2 DIFFERENTIAL DIAGNOSIS

As mentioned above, NAFLD is a diagnosis of exclusion. Excessive alcohol and other causes of hepatic steatosis, such as hepatitis C virus (HCV), celiac disease, Wilson's disease, haemochromatosis, hypobetalipoproteinemia, and other rare causes of hepatic steatosis, should be ruled out (Table 1).

Tabelul 1 Diagnostic diferențial al BFGNA[36].

Condiții asociate cu Steatoza hepatică	Mecanism de acțiune	Referința
Alcool (> 20 g / zi (femei) sau > 30 g / zi (bărbați))	Schimbarea stării Redox: inhibarea oxidării acidului gras, inducerea de lipogeneză, alterarea secreției VLDL în ficat	[22]
HCV	Alterarea secreției VLDL în ficat rezistentă la insulin. Disfuncție mitocondrială și stres oxidative	[23]
Medicamente (metotrexat, corticosteroizi)	Inhibarea oxidării acidului gras, inducerea lipogenezei, disfuncție mitocondrială, secreție hepatică lipidică afectată, rezistentă la insulin	[24]
Tulburări ale metabolismului lipidelor: a/hipobetalipoproteinaemia,	Secreție hepatică lipidică afectată, hidroliza deteriorată a esterilor colesterolului și a trigliceridelor.	[25],[26]

boala Wolman		
Tulburări de depozitare a metalelor: Wilson Boală	Disfuncție mitocondrială indusă de cupru	[27]
Hepatită autoimună	Efecte mediate de medicamente	[28]
Boala celiacă	Creșterea în greutate la dieta fără gluten Mobilizare lipidică hepatică afectată Malabsorbție intestinală	[29]
Tulburări endocrine: hipotiroidism, hipopituitarism, sindromul ovarului polichistic	Utilizarea redusă a lipidelor hepatice Rezistența la insulina Secreție de insulină afectată	[30-33]
Înfometarea, alimentația parenterală	Secreție hepatică lipidică afectată Beta-oxidare mitocondrială redusă	[34]
Lipodistrofia	Rezistență la insulină și acumulare ectopică de grăsime	[35]

2.3 EPIDEMIOLOGICAL CHARACTERISTICS OF NON-ALCOHOLIC FATTY LIVER DISEASE

NAFLD is the main etiology of liver disease in developed countries, with its prevalence increasing in developing countries [36,37]. According to a study by Younossi et al, the overall prevalence of NASH in the adult population is 25% [37].

2.4 THE NATURAL EVOLUTION OF NON-ALCOHOLIC FAT LIVER

NAFLD includes a broad spectrum of liver damage caused by fatty deposits in the liver that over time will lead to liver fibrosis and hepatocellular carcinoma

(HCC).

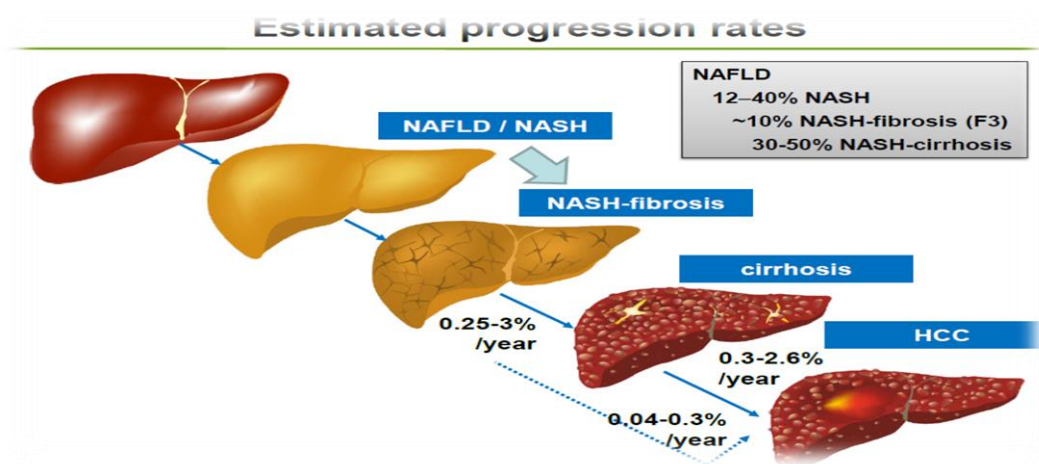


Figura 1 Evoluția naturală a steatozei hepatice[49]

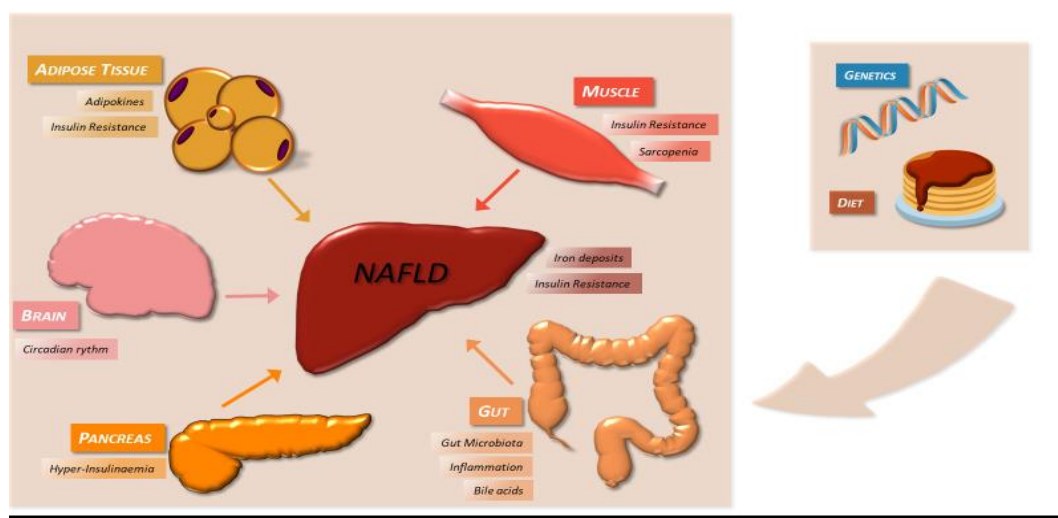


Fig 2 Patogeneza multifactorială a BFGNA[50]

2.5 NAFLD CHARACTERISTICS

The distinguishing feature of NAFLD is the accumulation of triglycerides in the liver as a result of an imbalance between the inflow and outflow of fatty acids in the liver.

2.5.1 GENETIC FACTORS

Genomic association and gene expression of several genes may contribute to the development and progression of BFGNA. These sequences play a central role in various ways: lipogenesis, iron oxidation, lipoprotein transport, glucose homeostasis, inflammation.

2.5.2 INSULIN RESISTANCE AND METABOLIC FACTORS

Insulin resistance has traditionally been identified as the key pathophysiological factor in the development of NAFLD, so many authors consider it the hepatic manifestation of metabolic syndrome.

2.5.3 DIET.

As mentioned above, diet is responsible for 15% of hepatic triglycerides in BFGNA [65]. The prevalence of steatosis has increased markedly worldwide with the spread of diets in industrialized countries.

2.5.4 OBESITY

Obesity is closely linked to hepatic steatosis. Adipose tissue is a highly active endocrine organ that produces hormones and cytokines known as adipokines or adipocytokines. They mediate endocrine, inflammatory, and immunological interactions, protecting or promoting insulin resistance and hepatic steatosis [68].

2 5.5 IRON DEPOSITS

Iron deposits appear to play a role in disease progression leading to inflammation and fibrosis, while their role in the development of steatosis is still debated. Indeed, the IIRON2 study provided new evidence for the relationship between hepatic iron deposits and insulin sensitivity, showing that high iron concentrations are associated with higher serum adiponectin and increased insulin sensitivity..

3 CONVENTIONAL 2D ECOCARDIOGRAPHICAL EVALUATION IN METABOLIC SYNDROME

3.1 EVALUATION OF SYSTOLIC FUNCTION

INTEGRAL TIME-VELOCITY

One of the parameters for evaluating systolic function is the speed-time integral (IVT). This parameter is obtained in the 5-chamber apical section by placing the pulsed Doppler sample immediately proximal to the aortic valves. The IVT value is obtained by drawing the contour of the resulting area, with a normal value between 18-22 cm³, a value that is not influenced by the body surface [74].

IVT benefits:

- easy to measure
- independent on body surface
- easy to reproduce

Disadvantages:

- It is not a parameter of contractility
- Does not appreciate the regional function
- It must be integrated in the context of the other measurements

DP / DT - LEFT VENTRICULAR PRESSURE INCREASE RATE

LV systolic performance can be assessed by the rate of increase in pressure inside the LV.

Benefits:

- easy to measure
- correlates with the values obtained for cardiac catheterization
- provides complementary information to other systolic function parameters

Disadvantages:

- requires the existence of a mitral regurgitation jet to be measured
- may be influenced by changes in kinetics
- threshold values are not clearly defined

MYOCARDIAL SPEED

Longitudinal systolic function can be assessed by measuring the trip of the LV base to the apex in the systole. This movement is produced by the contraction of the longitudinal fibers located subendocardially. The maximum S-wave velocity and the time interval from the onset of the QRS complex to the S-wave peak are thus recorded on the resulting tire.

Benefits:

- easy to measure
- allows the evaluation of the segmental function
- can be reproduced
- detects subclinical LV dysfunction

Disadvantages:

does not appreciate the overall systolic function - requires several measurements and the calculation of an average value

3.2 EVALUATION OF DIASTOLIC FUNCTION

TRANSMITRAL FLOW EVALUATION

The evaluation of the transmutral distolic flow is obtained from the apical section of 4 chambers by placing the pulsed Doppler sample between the tips of the mitral cusps. The following parameters are thus obtained:

- maximum wave velocity of the E wave-
- maximum wave velocity A

- E / A ratio
- deceleration time of the E wave
- isovolumic relaxation time

Factors that may influence the transmission profile:

- preload
- post-pregnancy
- heart rate, frequency and flow



Figura 6 Evoluția fluxului transmitral (Ecocardiografia Doppler – B.A.Popescu, C.Ginghina; Ed.Medicala 2011)

LUNG VENOUS FLOW

The evaluation of the pulmonary venous flow is made from the apical section of 4 chambers with the pulsed Doppler sample at the site of the discharge of the right superior pulmonary vein in the AS.

This results in a profile consisting of 4 waves:

S1 wave - atrial relaxation

- S2 wave - movement towards the apex of the mitral ring during systole
- D wave - ventricular relaxation
- Ar - atrial reflux

Mandatory measurements:

- maximum speed of the S wave
- maximum speed of the D wave
- S / D report
- maximum speed and duration of atrial reflux
- D deceleration time D

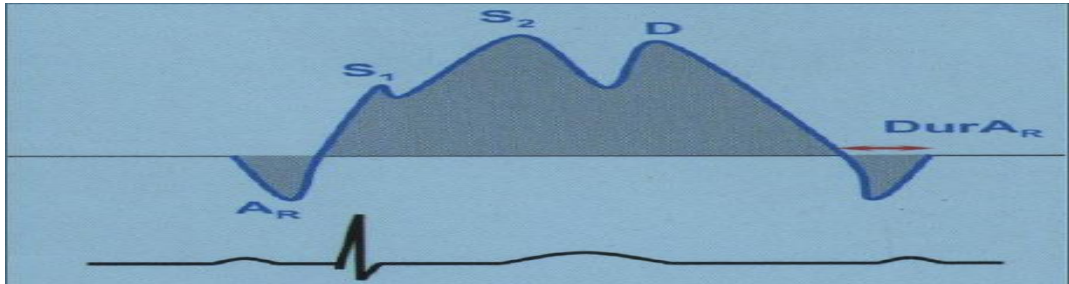


Figura7 Evaluarea fluxului venos pulmonar (Ecocardiografia Doppler-B.A.Popescu,C.Ginghina; Ed. Medicala 2011)

MITRAL FLOW PROPAGATION SPEED

Also from the 4-chamber apical section, under color Doppler guidance, the mitral flow is identified over which the M mode cursor overlaps. V_p represents the slope of the segment that identifies the color transition for the early diastolic filling wave. ($V_N > 50 \text{ cm / sec}$). The profile thus obtained shows 2 waves:

- E wave: the first wave propagated from the mitral ring to the apex, can have 2 components:
 - stage 1: the initial movement of the blood column inside the LV due to the transmission of the pressure wave
 - stage 2: propagation of the maximum velocity due to the propagation of the annular vortex
- wave A: the second wave, produced by atrial contraction [74].

4 EVALUATION OF SYSTOLIC FUNCTION THROUGH SPECKLE TRACKING TECHNIQUE

Spekle tracking echocardiography (STE) is a new non-invasive method of assessing global and regional left ventricular (LV) function. To eliminate the dependence on the insonance angle, the study of myocardial deformity can be performed by the speckle tracking technique. ultrasound with myocardial tissue [75].

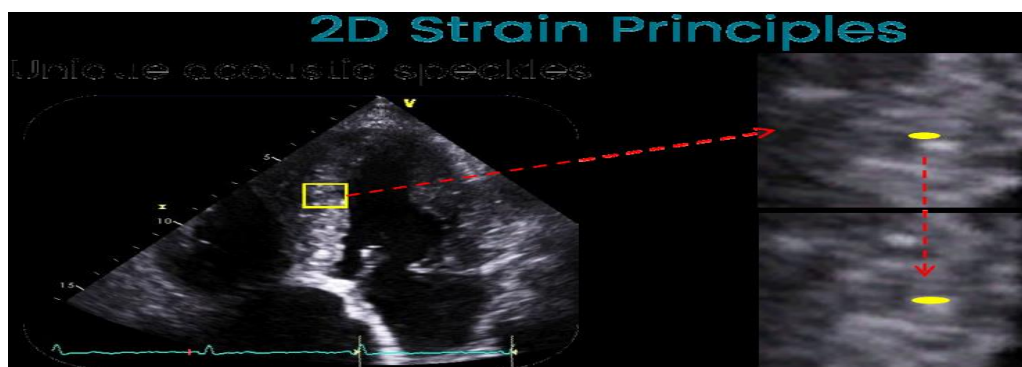


Figura10 Markeri de urmarire (spiculi)

Direction of Motion			
Direction	Longitudinal	Radial	Circumferential
Systole (Diastole)	Shortening = -ve (Lengthening = +ve)	Thickening = +ve (Thinning = -ve)	Shortening = -ve (Lengthening = +ve)

Figura 11 Direcția de mișcare a cordului

Tabel Nr2: Valori Nominale

Longitudinal Strain	Circumferential Strain	Radial Strain
Apical septal 21 ± 4	Anterior 24 ± 6	Anterior 39 ± 16
Mid septal 19 ± 4	Lateral 22 ± 7	Lateral 37 ± 18
Basal septal 17 ± 4	Posterior 21 ± 7	Posterior 37 ± 17
Apical lateral 21 ± 7	Inferior 22 ± 6	Inferior 37 ± 17
Mid lateral 19 ± 6	Septal 24 ± 6	Septal 37 ± 19
Basal lateral 19 ± 6	Anteroseptal 26 ± 11	Anteroseptal 39 ± 15

Nomenclature

By convention, positive values are intended to lengthen, thicken or rotate clockwise, while negative values are intended to shorten, thin or rotate counterclockwise..

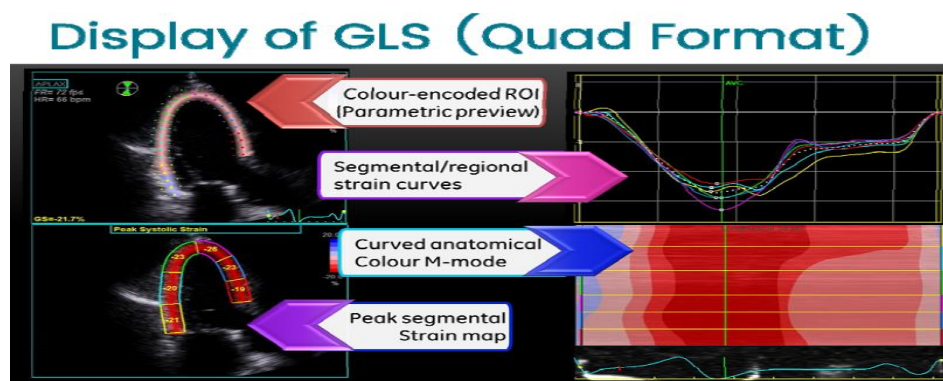


Figura 12 Elemente de nomenclatură în ecografia speckle tracking

Definition of segments

Anatomical segments are the anatomical units of the myocardium to which the results of various deformation analyzes will be reported. left / right region of interest (ROI): ROI from left / right base to apex

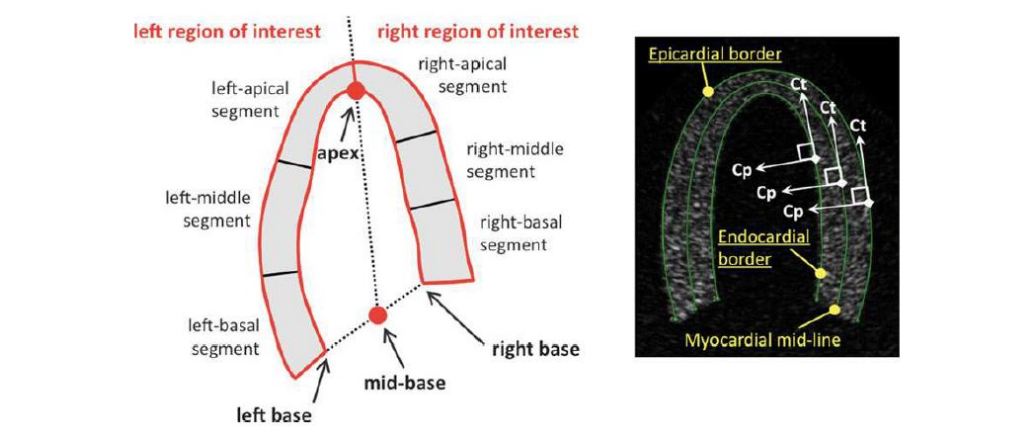


Figura 12 În partea dreaptă: parametrii de urmărire sunt raportați la linia endo-epicardică sau miocardică mijlocie sau la întregul perete ventricular. În partea stângă, componenta longitudinală sau circumferențială a multor parametri este direcționată tangențial de linia respectivă (Ct), în timp ce componenta radială este direcționată perpendicular pe aceasta (Cp)[78]

Most Common Clinical Application

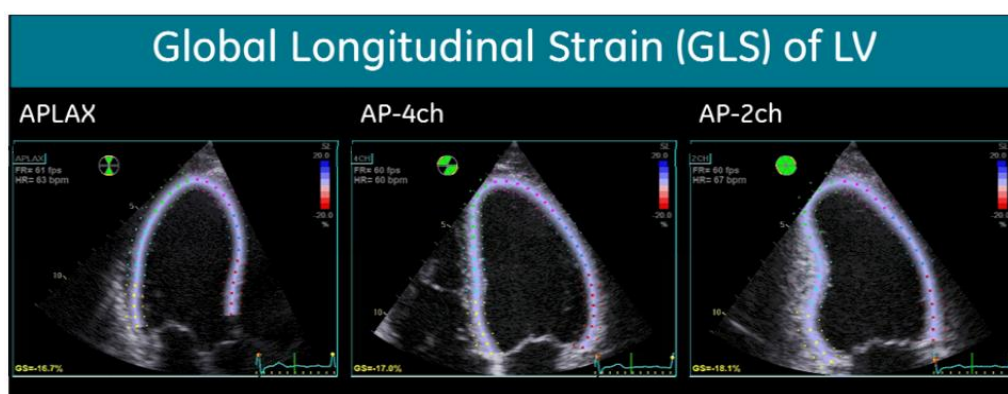


Figura 13 Incidentele cele mai folosite în ecografia speckle tracking [78]

Display of GLS (Bull's Eye Plot)

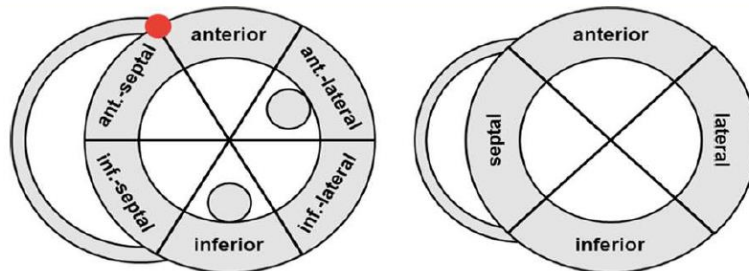
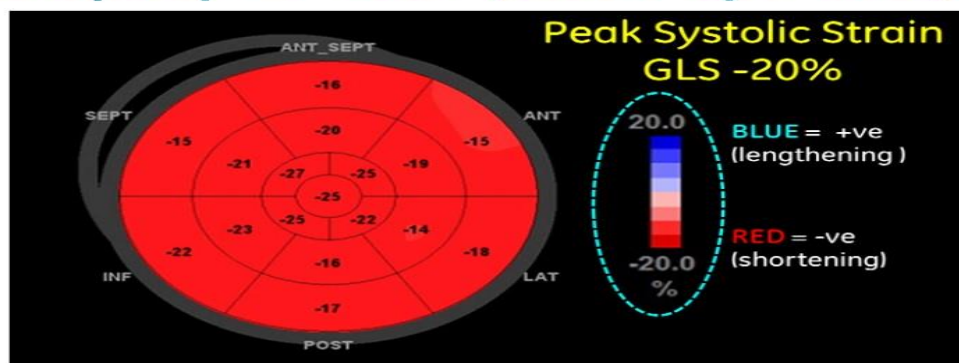


Figura 14 Segmentele ventriculului stâng în incedența parasternal ax scurt

THE SPECIAL PART

5. RESEARCH OBJECTIVES

The main objectives of the thesis were:

1. Conventional echocardiographic evaluation of the left ventricle in patients with metabolic syndrome.
2. Establishing a correlation between ventricular dysfunction (assessed by the longitudinal strain using speckle tracking cardiac ultrasound) and hepatic steatosis and fibrosis (detected by elastography and controlled attenuation parameter).
3. Identify the optimal parameters for the evaluation of cardiac dysfunction in patients with metabolic syndrome and non-alcoholic fatty liver disease.

6 CARDIOVASCULAR RISK IN PATIENTS WITH METABOLIC SYNDROME AND NON-ALCOHOLIC FATTY LIVER DISEASE

6.1 Pathophysiological Mechanisms of Interaction between Cardiometabolic Disorders and Non-Alcoholic Fatty Liver Disease

It is well established that steatosis is associated with an increased prevalence of traditional cardiovascular risk factors, especially type 2 diabetes and obesity, with nonalcoholic fatty liver being a predictor of cardiovascular events regardless of the association with traditional risk factors.

6.2 RISK OF THROMBOEMBOLIC EVENTS

Patients with NAFLD may have a persistent, systemic prothrombotic condition, which may be a risk of thrombotic complications compared to hemorrhagic

complications [88]. A recent study showed that secondary cirrhosis of BFGNA is associated with an increased risk of thromboembolism [89].

6.3 SIGNIFICANT ATHEROSCLEROSIS MARKERS

Patients with BFGNA, adults, and children who meet the diagnostic criteria for metabolic syndrome (abdominal obesity, hypertension, dyslipidemia, and impaired carbohydrate metabolism) also have numerous risk factors for atherosclerotic cardiovascular disease [90].

6.3.1 CAROTID ATHEROMATIC INJURIES AND RISK OF CEREBROVASCULAR EVENTS

Ischemic stroke in patients with BFGNA is one of the leading causes of long-term mortality and disability. The degree of liver fibrosis, assessed by liver elastography, has been associated with the risk of ischemic stroke, so the higher the degree of fibrosis, the higher the risk of stroke [95].

6.3.2 CORONARY ATHEROSCLEROTIC INJURIES

It has been observed that patients with nonalcoholic fatty liver disease have an increased risk of coronary events compared to the general population and consequently an increased risk of cardiovascular mortality [93, 99]. As mentioned above, BFGNA appears to influence cardiovascular risk, regardless of the presence of traditional cardiovascular risk factors such as high blood pressure and dyslipidemia.

6.4 BLOOD PRESSURE IN NON-ALCOHOLIC FATTY LIVER DISEASE

High blood pressure is considered a major cardiovascular risk factor and is the leading cause of stroke and ischemic heart disease. In a Korean study, patients with NAFLD evaluated by ultrasound were independently associated with an increased incidence rate of hypertension.

6.5 NON-ALCOHOLIC FATTY LIVER DISEASE AND STRUCTURAL AND FUNCTIONAL HEART DISEASE

BFGNA has been associated with myocardial and structural valvular abnormalities. %) this association remaining significant even after the adjustment of other cardiovascular risk factors [109].

6.5.1 ABNORMALITIES IN CARDIAC METABOLISM

Perseghin et al. [114] showed that non-diabetic, normal-weight, normotensive young men recently diagnosed with BFGNA had excessive accumulation of lipids in the epicardial area and impaired metabolism in the left ventricle (measured by phosphocreatine / adenosine ratio) compared to patients without steatosis of the same age, sex and body mass, these changes being present despite a normal morphology and function of the left ventricle.

6.6 HEART ARRHYTHMIA

6.6.1 SUPRAVENTRICULAR ARRHYTHMIA

To date, atrial fibrillation is the most common arrhythmia seen in clinical practice. BFGNAs have a higher risk of developing atrial fibrillation (AF) compared to patients without BFGNA [117].

6.6.2 VENTRICULAR ARRHYTHMIA

There are various mechanisms that have been proposed regarding the specific contribution of hepatic steatosis as a cardiovascular risk factor (insulin resistance, systemic inflammation and prothrombotic status) involved in the pathogenesis of ventricular arrhythmias. For example, prolongation of the QT interval is a strong predictor of ventricular tachyarrhythmias and predicts an

increase in cardiac mortality as well as other causes of death in both patients with type 2 diabetes and those without diabetes [120].

6.7 FATTY LIVER DISEASE AND VALVULAR SCLEROSIS

Until recently, aortic valve sclerosis, defined as focal or diffuse thickening and calcification of the aortic ring without restriction of valve movement, was considered an echocardiographic finding of no clinical significance because it did not obstruct the left ventricular ejection tract. However, aortic valvular sclerosis is known to have some epidemiological and histopathological similarities to coronary atherosclerosis [95].

6.8. CONCLUSION

In conclusion, the data published so far show that patients with non-alcoholic fatty liver disease have multiple cardiovascular risk factors and that in this category of patients, cardiovascular mortality is more common than liver disease.

7.ASSOCIATION BETWEEN LEFT SUBCLINIC VENTRICULAR SYSTOLIC DYSFUNCTION EVALUATED BY SPECKLETRACKING ECOGRAPHY AND HEPATOSIS AND HEPATIC FIBROSIS DETECTED BY ELASTOGRAPHY AND ALAMETACUM CONTROL

7.1 MATERIAL AND METHODS

The prospective study was performed between January 2019 and January 2020 within the Department of Cardiology of the Timișoara Emergency Hospital and the Department of Gastroenterology and Hepatology of the Timișoara County Emergency Hospital. We enrolled adult subjects with

metabolic syndrome (MS) and compared their demographic, clinical, biological, and echocardiographic characteristics with those of a control group, which included adult subjects of the same age and sex without metabolic syndrome. All patients with metabolic syndrome were evaluated by conventional mono (M) and two-dimensional (2D) echocardiography and Speckle Tracking 2D-STE, as well as by Vibration Controlled Transient Elastography (VCTE) and the controlled attenuation parameter (CAP).

7.2 INCLUSION CRITERIA

Patients aged ≥ 18 years diagnosed with metabolic syndrome according to the criteria of the International Diabetes Federation (IDF) of 2006.

7.4 EXCLUSION CRITERIA

- History of heart disease or newly diagnosed heart disease:
 - Systolic heart failure, defined as (left ventricular ejection fraction $\leq 50\%$)
 - Resting or exertional angina pectoris (cardiovascular exercise test)
 - hypertrophic cardiomyopathy
 - moderate or severe valvular heart disease;
 - Implanted cardiac devices (pacemakers, cardiac defibrillator)
- chronic liver disease known due to viral infections
- alcohol abuse (> 20 g / day in women and > 30 g / day in men) or use of drugs that induce steatosis (such as steroids or tamoxifen)
- renal disease in the final stage
- pregnancy or lactation
- autoimmune diseases (lupus, scleroderma)
- neoplasm.

Clinical features, clinical outcomes were analyzed during the 1-year follow-

up period. Reference data were extracted from hospital records and included age, sex, New York Heart Association (NYHA) functional hospitalization class, laboratory data, 12-lead resting electrocardiogram, echocardiographic data, and medical history. Medical history includes data on smoking, diet, obesity, coronary heart disease (CAD), old myocardial infarction (MI), high blood pressure, valvular disease, peripheral arterial disease, diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD), history of stroke and demyelination, autoimmune diseases, medication prescribed at home. All patients underwent a complete clinical examination with the measurement of BP, abdominal circumference, ankle-arm index.

7.5 CONVENTIONAL ECHOCARDIOGRAPHY EVALUATION AND PATIENT SPECKLE TRACKING TECHNIQUE

Echocardiographic evaluation of patients was performed within the first 24 hours of hospitalization using a VIVID S5 General Electric echocardiograph, a high-performance clinical echocardiograph. M and 2D images, pulsed and continuous Doppler, as well as tissue Doppler were obtained for all patients. The left ventricular ejection fraction was calculated using the Simpson method according to the American echocardiography guide. After evaluating the anterograde mitral flow and tissue doppler parameters, the I / O ratio was determined [17].

The echocardiographic parameters obtained for conducting the clinical research were as follows:

In M mode:

- determination of the diameter of the left atrium in the incidence of PAL (parasternal long axis), in telediastole

- determination of the size of the ventricular septum (SIV), posterior wall of the left ventricle (PPVS), telediastolic diameter of the left ventricle (DTDVS), telesystolic diameter of the left ventricle (DTSVS).

In 2D mode:

Doppler examination was performed in the 4-chamber apical incidence, with the volume sample placed at the top of the mitral valves. We determined the following parameters: E wave (maximum protodiastolic velocity of the transmissive flow), A wave (maximum telediastolic velocity), I / O ratio and isovolumetric relaxation time (TRIV). Simpson method. The 2D spekle tracking (EST) image was evaluated for peak myocardial deformity using a frequency of 70-80 frames / s. The device was adjusted to achieve optimal sector depth and width. After selecting the image that allowed the best endocard definition, the edge of the endocard was automatically drawn and corrected manually (Figure 10). The software automatically divided the ventricle into 6 equal segments.

The strain in these 6 segments was analyzed in 4.3 and 2-chamber apical incidences. The peak of the longitudinal strain (SL) and the strain rate (SR) were calculated as the average of the measured values in the 18 segments analyzed. The radial peak (SR) and the circumferential peak (SC) were calculated from the mean systolic values recorded in 18 LV segments in the incidence of the short parasternal axis - at the apex, middle segment and basal LV segment. The circumferential and radial peak deformation rates were also calculated. All foreign-type measurements were performed over 3 consecutive cardiac cycles and their arithmetic mean was recorded. All echocardiographic assessments were performed by the same investigator. Limit values for LV diastolic dysfunction were $E / A < 0.8$ and $IVRT > 100$ msec; for LV systolic

dysfunction: FE <50%, peak SL <-18%, peak SC <-19%, peak SR <40% [169].

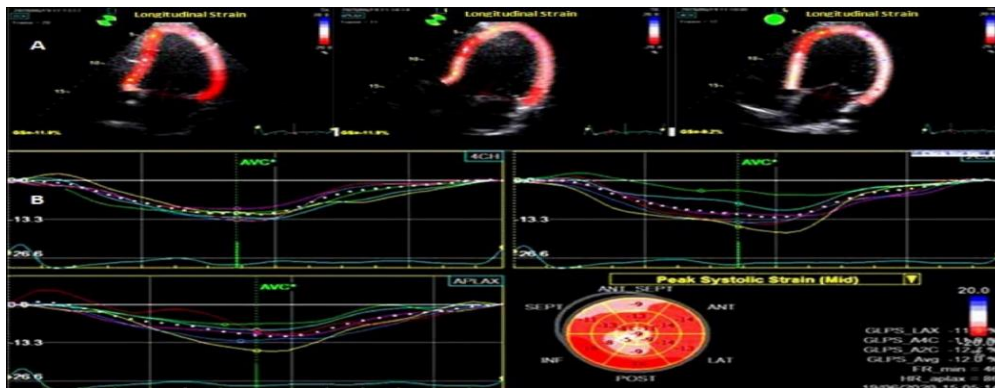


Figura 15. Ecocardiografie bidimensională speckle-tracking la nivelul ventriculului stâng. (A) Analiza longitudinală a deformării în apical 2,3, și 4 camere de vedere (GLPS); (B). Rezultate.

7.6 CONTROLLED VIBRATION TRANSITIONAL ELASTOGRAPHY (VCTE) AND CONTROLLED MITIGATION PARAMETER (CHAPTER).

VCTE was performed on the right hepatic lobe, by intercostal approach, fasting or postprandial at 4 hours, using a FibroScan® device (EchoSens, Paris, France). The patients were examined lying on their backs, with their right arm held above their heads. According to European standards, M (3.5 MHz transducer frequency) or XL (2.5 MHz transducer frequency) probes were used. In each patient, the examiner performed 10 measurements of liver stiffness (MSM) and then calculated their mean value. Correct measurements were considered to have an average value of the ratio between the interquartile range / average ratio <30%. Limits of hepatic stiffness were expressed in kilopascals (kPa). To stage the stages of fibrosis, we used the following limits of liver stiffness: for F \geq 2: 8.2 kPa; for F \geq 3: 9.7 kPa; and for F4: 13.6 kPa. To frame the steatosis stage, we used the following CAP limits: S1

(mild) - 274 dB / m, S2 (moderate) - 290 dB / m, S3 (severe) - 302 dB / m.

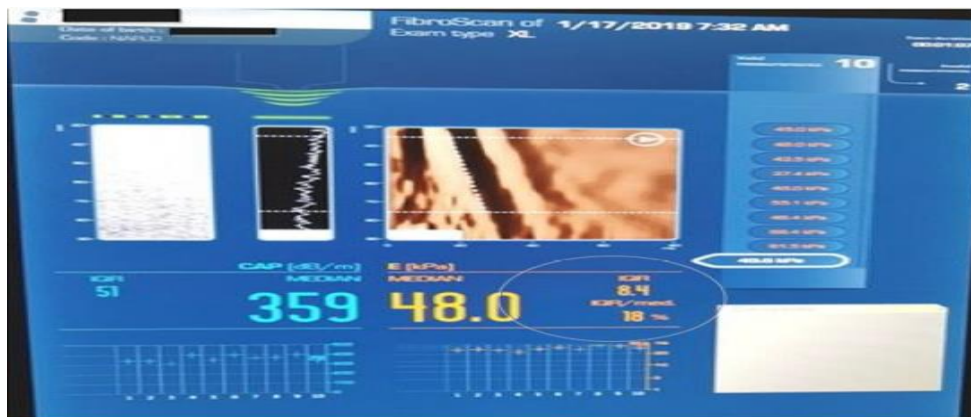


Figura16 Masuratori prin elastografia tranzitorie controlată de vibrații și paramentru de atenuare controlată

7.7 LABORATORY ANALYSIS

Serum biomarkers determined for inclusion in the study were sodium-reticrial peptide (BNP) and N-terminal fraction of sodium-retrial sodium-peptide (NT-proBNP), and left ventricular dysfunction markers were served. of high sensitivity (hs-CRP) were considered as markers of systemic inflammation.

Other laboratory data collected included:

- hemoleukogram
- blood sugar
- serum creatinine
- serum electrolytes
- lipidogram.

- Serum albumin
- Serum wound
- Protein electrophoresis
- TSH
- FT4
- Glucose tolerance test
- ALAT, ASAT

BNP was measured using fluorescence immunoassays (Triage®; Biosite Incorporated, San Diego, CA, USA). The normal range of BNP values was between 5 and 5000 picograms / m.

Glucose tolerance test

The glucose tolerance test was performed and interpreted according to WHO criteria (2010) as follows:

The test was performed in the morning after at least 8 hours of caloric rest (post-night).

Venous blood was collected for fasting blood glucose dosing.

The patient then ingested 75 g of glucose powder dissolved in 300 ml of water (25% concentration) within 5 minutes.

After two hours, blood was taken in the same way.

the interpretation of the results was made according to the blood glucose value at 2 hours:

- blood glucose <140 mg / dl - normal
- blood glucose 140-199 mg / dl - decreased glucose tolerance
- blood glucose \geq 200 mg / dl - diabetes mellitus.

7.8 STATISTICAL ANALYSIS

Statistical analysis was performed using MedCalc statistical software version 12.7.7 (MedCalc Software, Ostend, Belgium). Continuous data were presented as mean \pm 1 standard deviation (SD). Qualitative variables were expressed as numbers and percentages. between groups were compared by the associated t test. Linear regression and logistic regression were used to analyze univariate and multivariate factors that may influence left ventricular functional echocardiographic variables. The association between two or more variables was assessed using the Pearson correlation coefficient r). 95% confidence intervals were calculated for each predictive test. A P value <0.05 was considered significant for all statistical tests.

7.9 DATA COLLECTION

All the data obtained from the anamnesis and the clinical examination of the patients, respectively the cardiovascular risk factors, the results of the complementary investigations that were performed (ECG, chest radiography on admission, ultrasound measurements), the results of the laboratory tests performed were recorded in the individual files. patients.

Patients were considered to be hypertensive in the presence of elevated blood pressure values during hospitalization (\geq 140/90 mmHg), a previous diagnosis of hypertension or normal blood pressure values under antihypertensive treatment (14).

Valvulopathies have been identified from patient history, physical examination, and echocardiographic data (15).

Peripheral arterial disease was diagnosed based on the patient's history, physical examination, ankle-arm index, and doplex ultrasonography (16).

Chronic kidney disease was diagnosed in the presence of an estimated glomerular filtration rate $<60\text{ml} / \text{min} / 1.73 \text{ sqm}$ calculated according to the MDRD formula (17,18).

Metabolic syndrome has been defined in accordance with the criteria of the International Diabetes Federation, such as:

central obesity (waist circumference $> 94 \text{ cm}$ for men; $> 80 \text{ cm}$ for women) or $\text{BMI} > 30 \text{ kg} / \text{sqm}$ and the second of the following:

- triglycerides $150 \text{ mg} / \text{dl}$ or specific treatment for this dyslipidemia
- reduced HDL cholesterol value $<40 \text{ mg} / \text{dl}$ in men, $<50 \text{ mg} / \text{dl}$ in women or specific treatment for this dyslipidemia
- elevated blood pressure: systolic blood pressure $> 130 \text{ mmHg}$ and / or diastolic blood pressure $> 85 \text{ mmHg}$, or treatment for previously diagnosed hypertension
- altered tolerance to oral glucose loading $> 100\text{mg} / \text{dl}$, or previously diagnosed type II diabetes.

Diabetes was diagnosed in accordance with the recommendations of the World Health Organization / International Diabetes Federation and included in the presence of one of the following:

- glycated hemoglobin (Hb A1c) $> = 6.5\%$
- determined fasting blood glucose $> 126 \text{ mg} / \text{dl}$
- plasma glucose level $> = 200 \text{ mg} / \text{dl}$ 2 hours after oral loading with 75 g of glucose (20).

Obesity has been defined as a body mass index $> = 30 \text{ kg} / \text{sqm}$ (20).

7.10 RESULTS

A total of 208 patients with metabolic syndrome were examined. Thirty (16%) were excluded from the study due to inadequate echocardiographic imaging quality, while 28 patients (15%) were excluded due to inconsistent values resulting from VCTE and CAP measurements. One hundred and fifty patients with metabolic syndrome were enrolled in the study. 150 patients were also registered as a control group without metabolic syndrome but with similar sex and age characteristics. Demographic, clinical and biochemical characteristics are presented in Table 4 .

Tabelul3: Caracteristicile clinice si bioclinice ale pacientilor cu SM si grupul de control

	With MS (n=150)	Controls (n=150)	P value
Systemic hypertension (n, %)	120 (80%)	68 (45%)	<0.0001
Diabetes mellitus	134 (89%)	36 (24%)	<0.0001
Smoking (current, %)	15 (10%)	18 (12%)	0.58
Systolic BP (mmHg)	141.6±18	131.27±12	<0.0001
Diastolic BP (mmHg)	84.6±11	73.23 ± 6.97	<0.0001
Heart rate (beats/min)	75.6 ± 11.4	73.11 ± 10.8	0.05
BMI (kg/m ²)	32.7± 5.2	29.7±3.8	<0.0001
Weight (kg)	91±7	77±9	<0.0001
Waist circumference (cm)	112±13	97.00 ± 4	<0.0001
Total cholesterol	174±39	197±44	<0.0001
HDL (mg/dL)	45.2± 12.7	48.3±13	0.03
LDL (mg/dL)	109.4±33	110.5±32	0.76
Triglyceride (mg/dL)	159.1± 89.5	134.4±80.4	0.01
FPG (mg/dL)	130± 42	109±12	<0.0001
HbA1c	7.1±0.9	5.2±0.8	<0.0001
ASAT	24±9	23±5	0.23
ALAT	37±7	36±5	0.15

Note: Datele sunt exprimate ca medie ± SD sau număr (procent). Valorile semnificative statistic sunt prezentate cu caractere aldine (P <0,05).

Abrevieri: SM, sindrom metabolic; IMC, indicele de masă corporală; TA, tensiune arterială; HDL, lipoproteine de înaltă densitate; LDL, lipoproteine cu densitate mică; HbA1c, hemoglobină glicozilată; ASAT, aspartat amino transferază; ALAT, alanină amino transferază.

The mean age of the patients was 62.4 ± 10 years (range: 31-85), 54% (82) were male. The age distribution of patients with metabolic syndrome is shown in Figure 3. No significant differences were observed between subjects with metabolic syndrome and control patients regarding the presence of active smoking, heart rate, low-density lipoprotein (LDL), and serum transaminase levels. . Patients with metabolic syndrome in the study group frequently presented with diabetes mellitus and systemic hypertension, are overweight, with indices of increased body mass and circumference, elevated levels of postprandial plasma glucose, glycosylated hemoglobin (HbA1c), elevated triglycerides, and Significantly lower values of high-density lipoprotein (HDL). Data on echocardiographic measurements are presented in Table 2. We did not find statistically significant differences between patients with metabolic syndrome and control patients on conventional measurements of left ventricular systolic structure and function. One hundred and thirty-five (90%) patients with metabolic syndrome had a reduced I / O ratio and prolonged isovolumetric relaxation time (IVRT), these parameters indicating diastolic dysfunction of the left ventricle of delayed relaxation type.

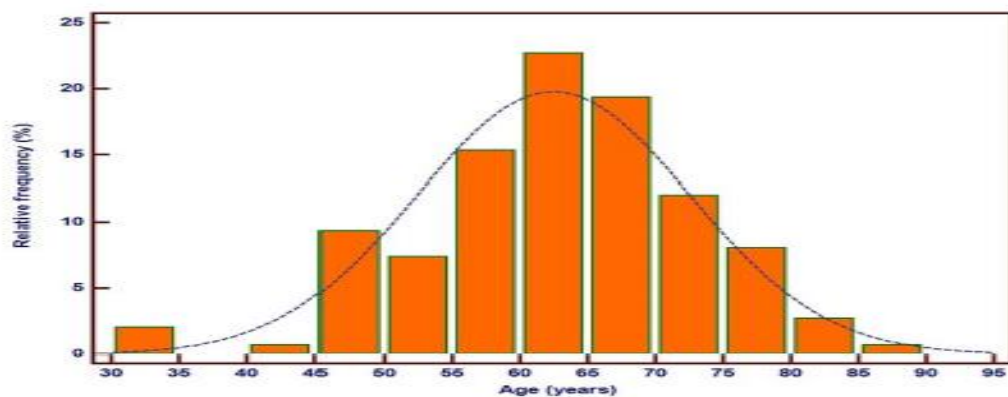


Figura 17 Distribuția vârstei la pacienții cu sindrom metaboli

Tabel 4 Caracteristicile ecografice ale pacienților din studiu

	MS (n=150)	Controls (n=150)	P value
Conventional echocardiography			
End DD (mm)	49.00 ± 3.20	48.69 ± 2.94	0.38
End SD (mm)	30.34 ± 2.50	29.85 ± 2.68	0.10
EF (%)	51.7±0.6	51.8±0.2	0.05
FS (%)	37.93 ± 2.91	38.00 ± 3.50	0.85
E (m/s)	0.69 ± 0.15	0.88 ± 0.12	<0.0001
A (m/s)	0.89 ± 0.17	0.61 ± 0.10	<0.0001
E/A ratio	0.81 ± 0.21	1.47 ± 0.23	<0.0001
IVRT (msec)	110.1±18	105.3±21	0.02
2D Speckle tracking echocardiography			
GLS (%)	19.9 ± 2.3	21.3 ± 1.9	<0.0001
GLSR (1/sec)	1.58 ± 0.18	1.62 ± 0.1	0.01
GCS (%)	22.7 ± 2.1	23.0± 2.2	0.22
GCSR (1/sec)	1.59 ± 0.4	1.62 ± 0.4	0.51
GRS (%)	47.5 ± 5.5	47.7 ± 5.0	0.74
GRSR (1/sec)	2.3 ± 0.5	2.4 ± 0.4	0.05

SM, sindrom metabolic; EDD: Diametru telediastolic; ESD: Diametru telesistolic; EF, fracție de ejeție; FS, Fractia de scurtare; E, umplerea protodiastolica rapida; A, umplere diastolică lentă ; IVRT, timp de relaxare izovolumetrică; 2D, bidimensional; GLS, deformare longitudinală globală; GLSR, viteza de deformare longitudinală globală; GCS, deformarea circumferențială globală; GCSR, rata de deformare circumferențială globală; GRS, deformarea radială globală; GRSR, viteza de deformare radială globală.

Deformation images and deformity rate (SI and SRI) detected early systolic dysfunction of the left ventricle in 47 patients (31%) with metabolic syndrome, reflected by longitudinal deformity and reduced longitudinal deformity (LS and LSR). Compared to control patients, patients with metabolic syndrome have a statistically significant subclinical impairment of LS ($P < 0.0001$) and LSR ($P < 0.0001$). There were no statistically significant differences among patients with metabolic syndrome and control patients regarding circumferential deformity, circumferential deformity velocity (CS, CSR), radial deformity, and radial deformity velocity (RS and RSR).

In the respective study group the 150 subjects with metabolic syndrome, the distribution of steatosis severity assessed by CAP was as follows: 14% (21)

patients did not have steatosis - S0, 7% (11) had S1, 7% (11) had S2 and 71% (107) S3 patients. S0 distribution was significantly lower, while S3 distribution was significantly higher compared to control patients ($P < 0.0001$), Table 3

Tabel 5 Evaluarea hepatica a fibrozei si steatozei

	MS (n=150)	Controls (n=150)	P value
CAP, dB/m	335.2 \pm 51.2	255.56 \pm 60.8	<0.0001
Steatosis stage			
S0	21 (14%)	95 (63%)	<0.0001
S1	11 (7%)	15 (10%)	0.35
S2	11 (7%)	3 (2%)	0.03
S3	107 (71%)	37 (25%)	<0.0001
LSM, kPa	7.24 \pm 3.25	6.52 \pm 2.85	0.04
Fibrosis stage			
F0-I	87 (58%)	118 (79%)	0.0001
F2	28 (19%)	11 (7%)	0.002
F3	20 (13%)	14 (9%)	0.26
F4	15 (10%)	8 (5%)	0.10

Abrevieri: CAP, parametru de atenuare controlat; LSM, măsurători ale rigidității ficatului; S, steatoză; F, fibroză.

Regarding the severity of liver fibrosis, according to the measurements of elastography (VCTE), 58% (87) of the subjects with metabolic syndrome had mild fibrosis - F0 and F1, 19% (28) patients had F2, 13% (20) patients F3, and 10% (15 subjects) F4. In the case of control patients, most subjects (79%) did not have fibrosis or have mild fibrosis ($P < 0.001$) and (7%) had fibrosis grade F2 ($P = 0.002$).

In the univariate regression analysis, the variables associated with low longitudinal deformity in patients with metabolic syndrome were diabetes, waist circumference, age and severity of liver stiffness, while factors associated with reduced longitudinal deformity rate LSR were diabetes, waist circumference and stiffness. In the multivariable analysis, the independent factors associated

with reduced deformity were diabetes ($P < 0.005$) and the degree of hepatic fibrosis LSM ($P < 0.0001$). The reduced longitudinal deformity rate (LSR) was also an independent factor associated in the multivariable analysis with diabetes ($P < 0.02$) and LSM ($P < 0.001$) as shown in Table 5.

Tabel 6 Factorii asociați cu disfuncția sistolică în cazul pacienților cu sindrom metabolic

GLS						
Variables	Univariate Analysis			Multivariate Analysis		
	β	SE	P	β	SE	P
Waist circumference	-0.997	0.440	0.02	–	–	–
Diabetes mellitus	-1.451	0.375	0.0002	-1.026	0.353	0.004
Age (years)	-0.047	0.019	0.01	-0.030	0.017	0.08
LSM (kPa)	-0.593	0.100	<0.0001	-0.293	0.052	<0.0001
GLSR						
Variables	Univariate analysis			Multivariate analysis		
	β	SE	P	β	SE	P
Waist circumference	-0.003	0.001	0.008	-0.001	0.001	0.08
Diabetes mellitus	-0.098	0.030	0.001	-0.074	0.029	0.01
LSM (kPa)	-0.018	0.004	<0.0001	-0.0158	0.004	0.0006

Abrevieri: SM, sindrom metabolic; GLS, deformare longitudinală globală; GLSR, viteza de deformare longitudinală globală; LSM, măsurarea rigidității ficatului, coeficientul beta (β) din analiza de regresie; SE, eroare standard.

Correlations between independent variables associated with subclinical impairment of left ventricular systolic function in patients with metabolic syndrome are shown in Figure 4. Left ventricular ejection fraction was similar in the two groups ($P = 0.05$) by standard ultrasound evaluation. , but the evaluation of spekle tracking identified a significant difference in longitudinal deformity (LS) values between patients with metabolic syndrome and the control group. By 2D-STE it was possible to evaluate an early systolic dysfunction of the left ventricle in 47 patients with metabolic syndrome (46%) and in 12 patients in the control group (8%), $P < 0.0001$. The risk of LV systolic

dysfunction was 3 times higher in hypertensive patients (OR = 8.7; 95% CI: 5.1 to 14.8, $P < 0.0001$) and 5.5 times higher high in diabetic patients with metabolic syndrome (OR = 18.3; 95% CI: 9.8 to 34.2, $P < 0.0001$). The risk of left ventricular diastolic dysfunction was 3.6 times higher in patients with metabolic syndrome with severe steatosis (OR = 3.6; 95% CI: 1.9 to 6.8, $P < 0.0001$) and 8 times higher in patients with severe fibrosis (OR = 14, 8; 95% CI: 8.7 to 25.1, $P < 0.0001$). The risk of left ventricular systolic dysfunction was doubled in patients with metabolic syndrome with severe steatosis (OR = 3.6; 95% CI: 1.9 to 6.8, $P < 0.0001$) and 1.7 times higher in patients with severe fibrosis metabolic syndrome (OR = 4.1; 95% CI: 2.1 to 7.7, $P < 0.0001$).

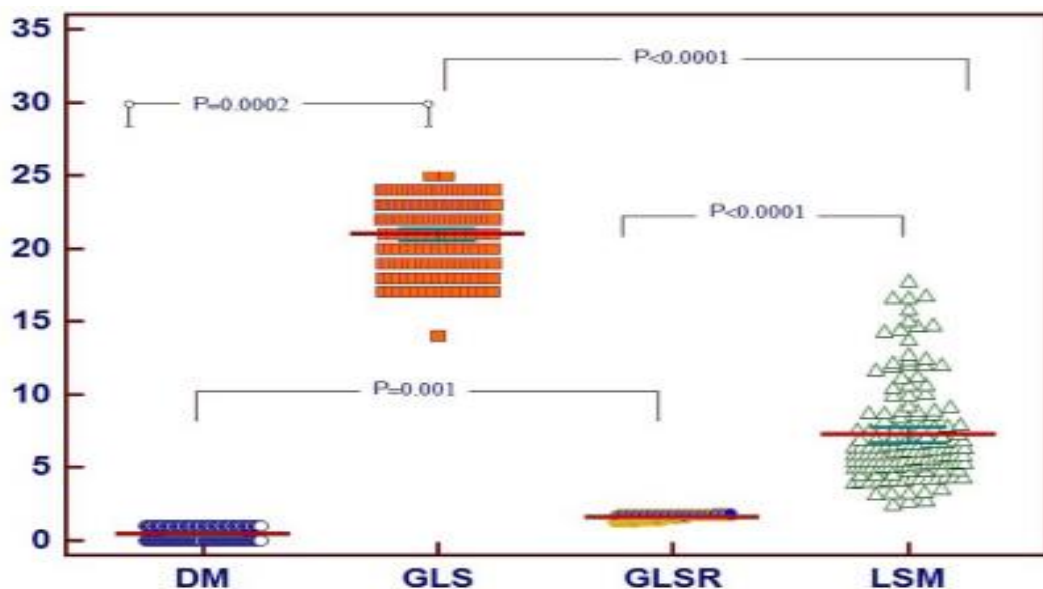


Figura18 Corelații între variabilele independente asociate cu afectarea subclinică sistolică a VS la pacienții cu SM.

Abrevieri: SM, sindrom metabolic; DM(diabetul zaharat), LSM(măsurarea rigidității ficatului); GLS,(deformare longitudinală globală);GLSR (viteza maximă de deformare longitudinală globală).

7.11 DISCUSSIONS

This condition is associated with an increased risk of diabetes, stroke, myocardial infarction, and heart failure (HF). HF is a clinical syndrome induced by any structural or functional damage to the heart that reduces the ability of the ventricles to fill or pump blood. Heart failure syndrome has been compared to an iceberg. The visible segment includes patients with symptomatic heart failure, most of whom are diagnosed in primary care facilities. The "below the waterline" invisible segment includes asymptomatic patients with subtle left ventricular dysfunction.

More sensitive assessments of contractile function, such as left ventricular shortening fraction, tissue doppler, and myocardial deformity (circumferential and longitudinal), have been shown to be affected in the presence of obesity and / or metabolic syndrome [133,134].

Early identification of subclinical left ventricular dysfunction in patients with metabolic syndrome, as well as the role of each of the components of this syndrome in structural and functional myocardial impairment, could help establish and predict the risk of cardiovascular disease in patients with metabolic syndrome.

Early determination of left ventricular systolic dysfunction can be determined using 2D tracking echocardiography.

In our study, metabolic syndrome was associated with reduced cardiac function and hepatic steatosis and fibrosis. This is important because all participants in the study had no symptoms and had no history of heart failure with a low ejection fraction <50%, atherosclerotic cardiovascular disease, or

liver

disease.

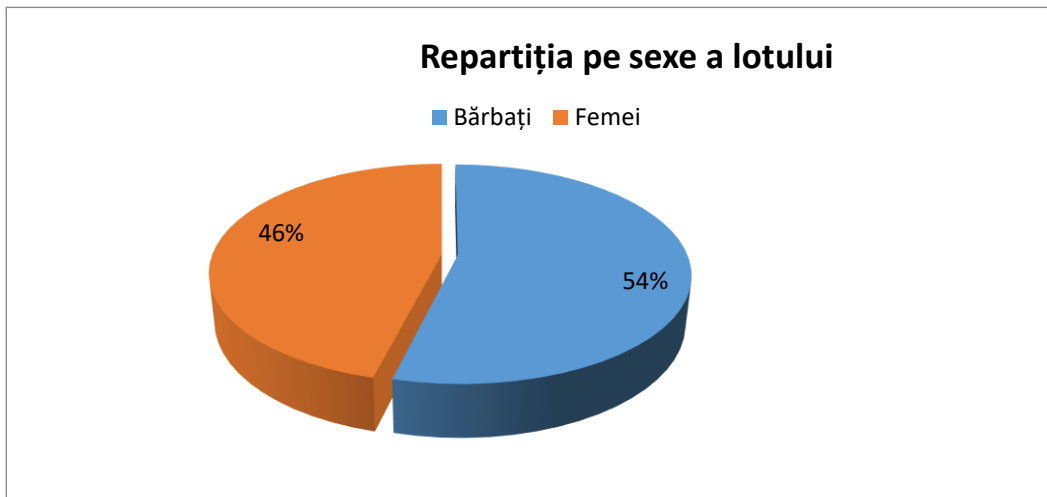


Figura 19 Repartiția lotului studiat pe sexe

To our knowledge, this is the first work to evaluate the association between subclinical LV dysfunction, assessed by 2D speckle echocardiography, and hepatic fibrosis and steatosis, assessed by CAP and elastography, in adult subjects with metabolic syndrome. In the present study, 150 patients with metabolic syndrome were enrolled in the study, being compared with 150 apparently healthy subjects of the same age and sex. The age of the patients ranged from 31 to 85 years. Fifty-four percent were men. Eighty-nine percent of patients with metabolic syndrome had diabetes mellitus, based on HbA1c levels, and 80% were hypertensive. Body mass index (BMI) in patients with metabolic syndrome ranged from 24 to 42 kg / m², while waist circumference ranged from 85 to 140 cm.

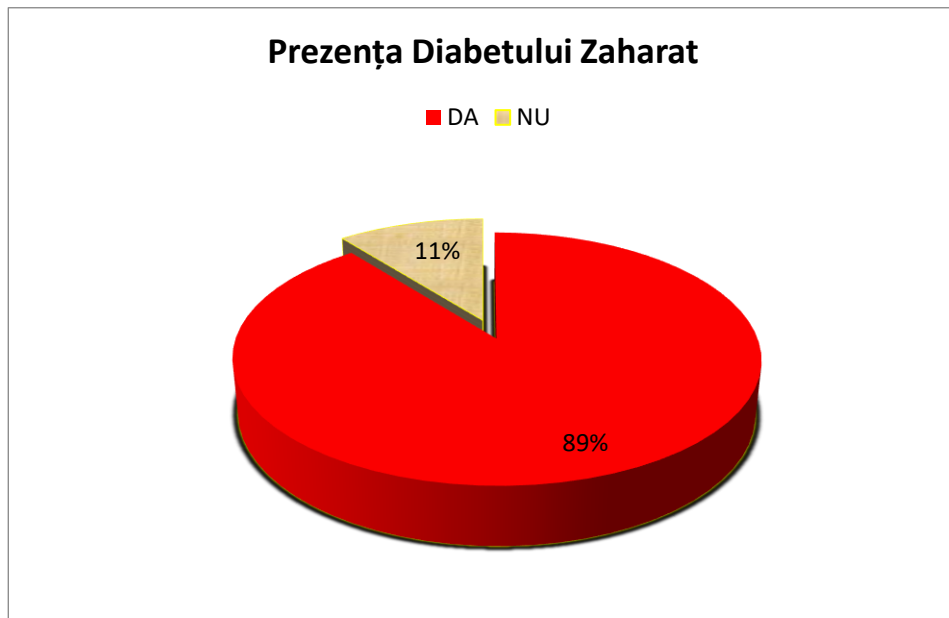


Figura 20 Prezența diabetului zaharat în lotul studiu

Conventional 2D Doppler echocardiography identified LV diastolic dysfunction in 135 patients with MS (90%) and 30 (20%) controls, $P < 0.0001$. The risk of left ventricular diastolic dysfunction was 1.6 times higher in patients with metabolic syndrome and hypertension (OR = 2.25, 95% CI: 1.1 to 4.3, $P = 0.01$). In the Strong Heart Study, metabolic syndrome was also found to be related to systolic and diastolic dysfunction of the left ventricle.

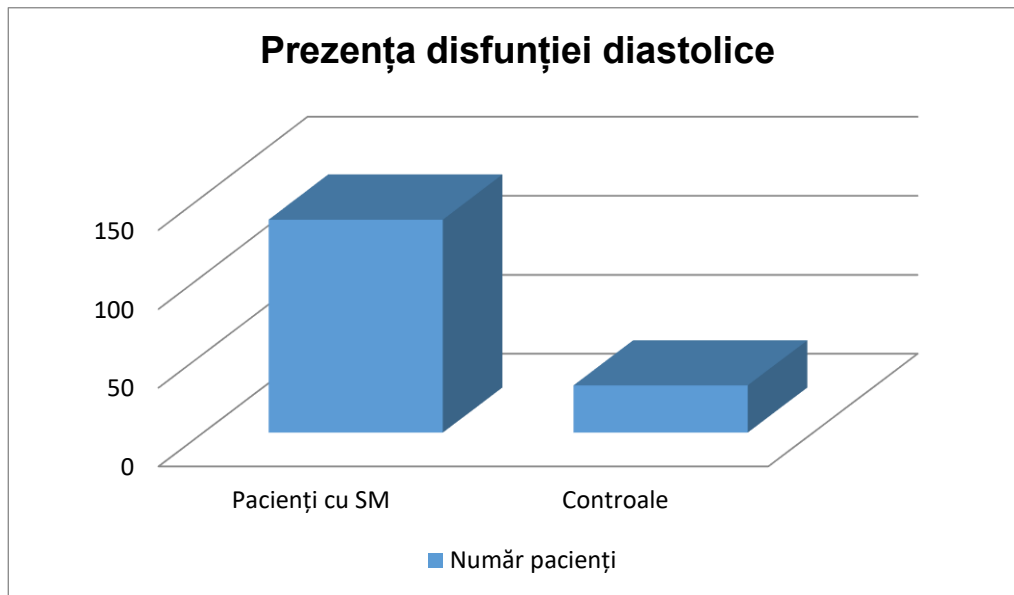


Figura 21 Prezența disfuncției diastolice

Although left ventricular ejection fraction was similar in the two groups ($P = 0.05$), 2D-STE identified left subclinical systolic dysfunction in 47 patients with MS (46%) and 12 controls (8). % $P < 0.0001$.

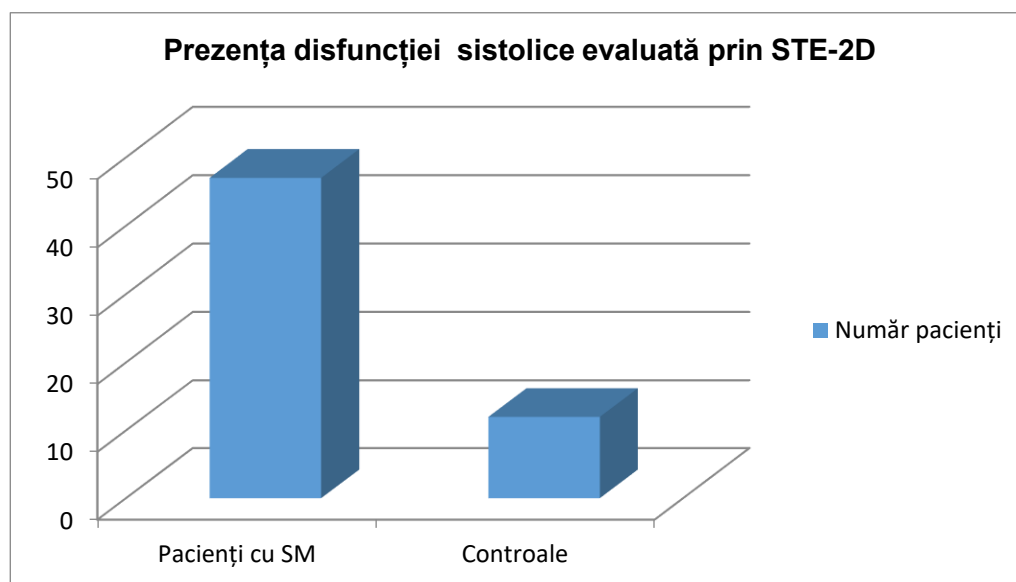


Figura 22 Prezența disfuncției sistolice a VS în lotul studiat

The risk of left ventricular systolic dysfunction was 3 times higher in hypertensive patients ($P < 0.0001$) and 5.5 times higher in diabetic patients with metabolic syndrome ($P < 0.0001$). In the multivariate analysis, diabetes mellitus and liver stiffness were independently associated with left ventricular diastolic and systolic dysfunction ($P < 0.0001$). The risk of left ventricular diastolic dysfunction was 3.6 times higher in patients with metabolic syndrome and severe steatosis ($P < 0.0001$) and 8 times higher in patients with severe fibrosis ($P < 0.0001$). The risk of left ventricular systolic dysfunction was doubled in patients with metabolic syndrome with severe steatosis ($P < 0.0001$) and 1.7 times higher in MS with severe fibrosis ($P < 0.0001$).

Although some studies have suggested that subjects with BFGNA are at risk for structural damage to LV and diastolic dysfunction, the association with steatosis and liver fibrosis has not been proven due to insufficient use of

ultrasonography or computed tomography. In our study, participants were carefully investigated using conventional echocardiography and 2D STE for cardiac assessment and elastography and hepatic CAP to identify and measure the severity of steatosis and liver fibrosis. The present study also demonstrated for the first time that subclinical systolic dysfunction of the left ventricle, detected by measuring myocardial deformity and deformity using STE 2D myocardial damage being significantly related to fibrosis and hepatic steatosis.

LIMITATIONS OF THE STUDY

With existing equipment, the speckle tracking measurement had a rather poor signal-to-noise ratio and is sensitive to load. Speckle measurements are also performed alongside a single ultrasound scan line. Assessment of hepatic steatosis and fibrosis has been made non-invasive in all patients without performing a liver biopsy, which is the gold standard for the identification of hepatic steatosis and fibrosis.

CONCLUSION

- Our study indicates that patients with metabolic syndrome have a high prevalence of left ventricular diastolic and systolic dysfunction.
- While diastolic heart dysfunction can be detected by conventional echocardiographic measurements, evaluation of subclinical systolic dysfunction requires speckle tracking echocardiography.
- This finding recommends STE 2D as a routine echocardiographic examination in patients with metabolic syndrome, as early detection and

treatment of heart disorders are vital issues for better outcomes in these subjects.

- Cardiac dysfunction in patients with metabolic syndrome was significant and independently associated with the severity of steatosis and hepatic fibrosis detected by transient VCTE and CAP.
- Early assessment of cardiac and hepatic pathology in patients with metabolic syndrome is important to initiate lifestyle changes and drug therapy, designed to correct all cardiovascular risk factors, including abdominal obesity.

8 ASSOCIATION BETWEEN LEFT VENTRICULAR DIASTOLIC DYSFUNCTION, LEFT ATRIUM PERFORMANCE, AND DEGREE OF HEPATIC AFFECTION IN PATIENTS WITH METABOLIC SYNDROME AND NON-ALCOHOLIC FATTY LIVER DISEASE

8.1 MATERIAL AND METHODS

This case-control observational study was conducted from January 2019 to January 2020 in the Department of Cardiology and the Department of Gastroenterology and Hepatology of the University of Medicine and Pharmacy Victor Babes, Timisoara.

Adult patients diagnosed with metabolic syndrome but with normal LVEF were included in the study, and they were scheduled for a medical consultation at the Department of Cardiology, agreeing to undergo an evaluation of liver elastography.

The control group consisted of adults with normal LVEF without metabolic syndrome, being of the same sex and age as enrolled patients with metabolic syndrome, who agreed to participate in this study. The clinical and paraclinical characteristics of the two groups were compared.

All patients were evaluated by ETCVH, PCA, as well as conventional two-dimensional (2D) echocardiography and ispeckle-tracking.

The inclusion criteria for the study group were patients older than 18 years with metabolic syndrome. Exclusion criteria were: chronic hepatopathy caused by viral infections, excessive alcohol consumption (≤ 20 g / day woman, > 30 g / day) or drug use, systolic heart failure (LV ejection fraction $< 50\%$); heart failure with preserved LVEF, identified by NT-proBNP ≥ 220 pg / m, known ischemic heart disease; history of atrial fibrillation / atrial flutter on the initial electrocardiogram; moderate or severe valvular heart disease; cardiomyopathies; intracardiac devices; peripheral arterial disease; history of stroke; severe systemic disease or malignancy; chronic renal failure; pregnancy or lactation. [185]

The diagnosis of metabolic syndrome was made on the basis of 2006 FID criteria: central obesity (circumference ≥ 94 cm in men and 80cm in women), associated with either of the following two criteria: increased fasting blood glucose (GJ) ≥ 100 mg / dL or treatment of type 2 diabetes two previously diagnosed; elevated triglyceride level ~ 150 mg / dL or specific treatment for this lipid abnormality; high density lipoprotein cholesterol < 40 / 50mg / dl (men / women); Systolic BP (BP) ≥ 130 or Diastolic BP (BP) ≥ 85 mmHg or antihypertensive treatment. [165]

8.2 CLINICAL EVALUATION

Patients were carefully examined and all data were extracted from the hospital registry and used as a data source. Smoker status has been declared as a smoker or non-smoker. Patients underwent a 12-lead resting electrocardiogram (ECG) and laboratory tests at the start of the study, prior to liver and cardiac ultrasound examinations.

Diabetes has been identified in the presence of fasting blood glucose ≥ 126 g / mL or outpatient insulin therapy and / or oral hypoglycaemic agent [165].

8.3.VERSION CONTROLLED TRANSIT ELASTOGRAPHY (ETCH) AND CONTROLLED MITIGATION PARAMETER (PCA) MEASUREMENTS

ETCVH was performed after a fasting period of more than 4 hours, using a FibroScan® device (EchoSens, Paris, France), by the same investigator. According to European recommendations, the M / 3.5MHz or XL / 2.5MHz transducer was used. 16. The examiner performed approximately ten liver stiffness (MRF) measurements on each patient, and their mean value was then calculated. The correct measurements were considered to be those with an average value with an average statistical interval / ratio of less than 30%. [171] MRF was counted in kilopascals (kPa). The following ETCVH limits were used to classify the severity of fibrosis: F₀: 8.2kPa; F₁: 9.7kPa; and F₄: 13.6kPa. and to differentiate the stages of steatosis, we used the following PCA cut-off values: S1 (mild) -274dB / m, S2 (moderate) -290dB / m, S3 (severe) -302dB /



Figura23.Elastografie tranzitorie controlată de vibrații(ETCVH) și parametrul controlat al atenuării(PCA)de pe dispozitivulFibroscan®.

8.4.CARDIAC ULTRASOUND

Conventional echocardiography was performed by the same investigator using a VIVID5S, G.E. 3.5MHz phase transducer matrix ultrasound. The dimensions of the heart cavities were measured according to the guidelines of the American Society of Echocardiography. LV values and AS volume were calculated from 4 and 2 chamber apical incidences, and the ejection fraction was calculated using the biplane method, Simpson. LV diastolic function was determined using 4- and 2-chamber apical Doppler by placing the volume sample at the tip of the mitral valves. The following parameters were determined: wave E (maximum proto-diastolic velocity of the transmitting flow), wave A (maximum telediastolic velocity), E / A ratio and isovolumetric relaxation time (TRIV). The cut-off values for LV

diastolic dysfunction were $tE / A \pm 0.8$ and $IVRT \pm 100\text{msec}$; for LV systolic dysfunction: $FEVS \geq 50\%$.

The maximum diameter of the AS was measured in long-axis parasternal incidence. The maximum volume of the left atrium (VASmax) was measured in the 4 and 2 chamber apical incidences at the end of the T-wave on the ECG before the opening of the mitral valves (DVM).

The minimum volume of AS (VASmin) was measured in the early phase of ventricular diastole, at the end of the QRS complex, immediately after mitral valve closure. Pre-contraction atrial volume (VAS-preA) was measured in the late phase of ventricular diastole, at the beginning of the P wave on the EKG. The values of the 2 incidences were averaged. The difference between VASmax and VASmin was total ejection atrial volume (VTASE). The difference between VASmax and VASpreA was the passive ejection volume of AS, while the difference between VAS-preA and VASmin was the active ejection volume of AS (VEAAS).

The left atrium ejection fraction (FEAS,%) was determined by the formula $100 \times [VAS_{\text{max}} - VAS_{\text{min}}] / VAS_{\text{max}}$ and shows the reservoir function of the left atrium. The active ejection fraction of AS (aFEAS,%) was calculated according to the formula: $[VAS_{\text{preA}} - VAS_{\text{min}} / VAS_{\text{preA}}]$ and represents the pump function of AS. FEpassive of AS (pFEAS,%) was calculated according to formula $100 \times [VAS_{\text{max}} - VAS_{\text{preA}} / VAS_{\text{max}}]$ and represents the drainage function of AS.

8.5.ECHOGRAPHY 2D SPECKLE TRACKING (EAST) ATRIAL LEFT

2D-speckletracking ultrasound of the left atrium was assessed using available software VividEchoPAC (GEMedicalSystem) using a frequency set between 60 and 90 frames / s. Three consecutive cardiac cycles during

respiratory apnea were recorded in apical incidences 4 and 2 cameras focused on The endocardium and epicardium of the left atrium were drawn automatically and corrected by the examiner. SAS-tank) and the peak of AS deformation during the pump phase, at the beginning of the P wave, as can be seen in figure22.

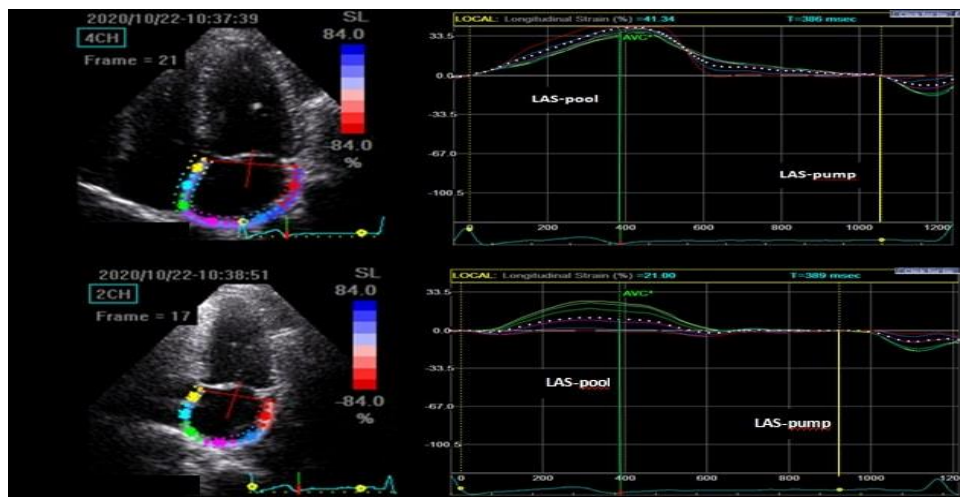


Figura 24 Ecografia 2d-speckletracking(STI) atriala stangă

The AS deformation in the duct phase was calculated as the difference between the AS deformations in the expansion phase and the pump phase. AS stiffening was calculated as the value of the I / O ratio in the atrial dilation phase. The maximum peak deformity of the AS during ventricular systole (RSAS-v) and the maximum values of AS deformity at the beginning of ventricular diastole (RSAS-e) and at the end of ventricular diastole or during preatrial contraction (RSAS-a) were also evaluated.

Data were obtained from the 2 apical incidences and averaged. Patients with a weak ultrasound window were not included in the study.

8.6.ETHICS

Written informed consent was obtained from all study participants. The study was conducted in accordance with the requirements of the Helsinki Declaration of Human Rights and was approved by the Ethics Committee of the "Victor Babeș" University of Medicine and Pharmacy in Timișoara.

8.7. STATISTICAL ANALYSIS

Statistical analysis was performed using version 19.6 of the statistical software MedCalc (Belgium). Continuous data were given as an average of 1 standard deviation (SD). Qualitative variables were given as numbers and percentages.

The difference between the two groups was compared using the associated t test. The association between the variables was assessed using the Pearson correlation coefficient. Factors significantly associated with AS dysfunction were subjected to univariate and multivariate logistic regression analysis.

The identified independent predictors were compared using the receiver performance characteristic (ROC) curves. $P \leq 0.05$ values were considered statistically significant for all tests.

8.8.PRODUCTIBILITY

The study was performed with a single ultrasound by a single physician. For intra-observer reproducibility, the intra-class correlation coefficient (ICC) was calculated. The ICC was 0.88 (95% 0.81-0.92) for echocardiography and 0.85 (95% CI 0.77-0.90) for liver ultrasound.

8.9.RESULTS

Of the 208 patients with metabolic syndrome initially evaluated, 30 (16%) were excluded due to the inadequate ultrasound window, and 28 (15%) were excluded due to inconclusive values at PCA and ETCVH.

As a result of these exclusions, there were 150 subjects with metabolic syndrome who were enrolled in the study group and together with 150 control subjects corresponding to age and sex who were included in the control group. The basic characteristics of the two groups are presented in Table 11. The age range of patients ranged from 31 to 85 years (mean 62.4-10 years).

The distribution of patients by age is shown in Figure 23, 164 subjects (54%) were men. No significant differences were observed between the two groups in terms of heart rate, smoking status, serum transaminases and low-density lipoprotein (LDL) -cholesterol levels.

Patients with metabolic syndrome were most often among hypertensive, diabetic, and obese patients. They showed higher levels of triglycerides, glycosylated hemoglobin (HbA1c), lower levels of total cholesterol and high-density lipoprotein (HDL).

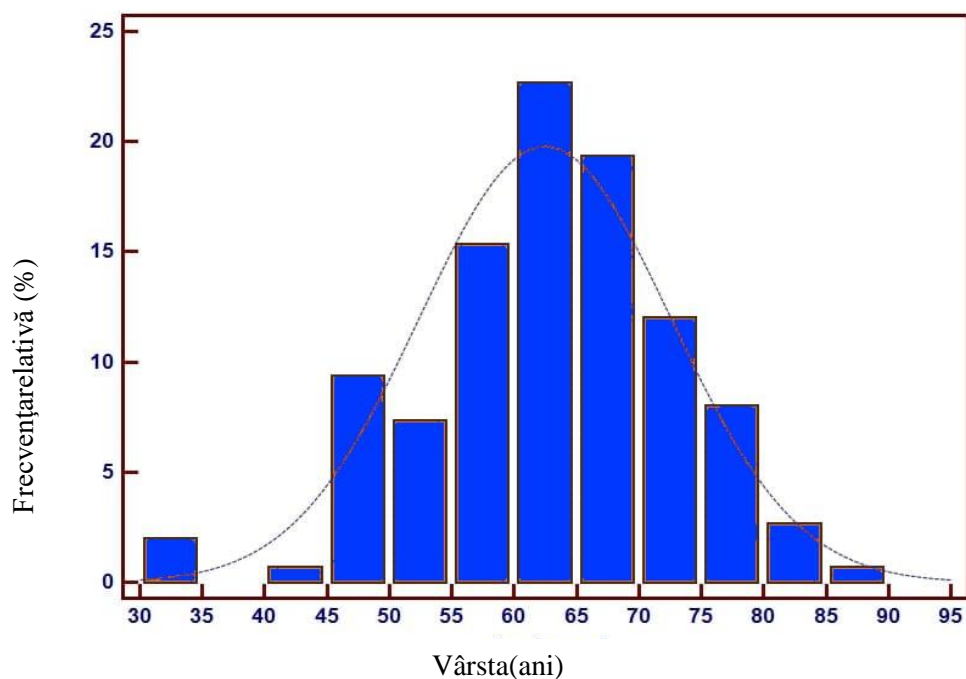


Figura25 Distribuția pacienților pe grupe de varstă

Patients with metabolic syndrome presented the following division of steatosis severity assessed by PCA: 21 (14%) - S0.11 (7%) - S1.11 (7%) - S2 and 107 (71%) - S3. Both hepatic steatosis, as well as fibrosis were more frequent and more severe in the group of patients with metabolic syndrome ($P < 0.0001$, respectively $P = 0.04$), as shown in Table 12.

Tabelul 7 Caracteristici clinice și biologice ale pacienților cu SM și a celor din grupul de control

	Cu SM (n=150)	Grup control (n=150)	P valoare
Vârstă (ani)	62.4±10	62.4±10	1
Sex masculin (%)	78(52%)	78(52%)	1
HTA (n, %)	120(80%)	68(45%)	<0.0001
Diabet zaharat (n, %)	134(89%)	36(24%)	<0.0001
Fumător (current, %)	15(10%)	18(12%)	0.58
TA sistolică (mmHg)	141.6±18	131.27±12	<0.0001
TA diastolică (mmHg)	84.6±11	73.23±6.97	<0.0001
Frecvență cardiacă (b/min)	75.6±11.4	73.11±10.8	0.05
IMC (kg/m ²)	32.7±5.2	26.7±2.1	<0.0001
Greutate (kg)	91±7	77±9	<0.0001
Circumferința abdominală (cm)	112±13	97.00±4	<0.0001
Colesterol total	174±39	197±44	<0.0001
HDL (mg/dL)	45.2±12.7	48.3±13	0.03
LDL (mg/dL)	109.4±33	110.5±32	0.76
Trigliceride (mg/dL)	159.1±89.5	134.4±80.4	0.01
GJ (mg/dL)	130±42	109±12	<0.0001
HbA1c	7.1±0.9	5.2±0.8	<0.0001
ASAT	24±9	23±5	0.23
ALAT	37±7	36±5	0.15
NT-proBNP	97±19	96±15	0.61

Note: Datele sunt exprimate ca medie ±SD sau număr (procent). Valorile semnificative statistic sunt prezentate cu caractere aldine (P<0,05).

Abrevieri: SM: sindrom metabolic, IMC: indice de masă corporală, TA: tensiune arterială, HDL, lipoproteine de înaltă densitate; LDL: lipoproteine cu densitate mică; GJ: glicemia a jeun; HbA1c: hemoglobină glicozilată; ASAT: aspartat amino transferază; ALAT: alanin amino transferază.

Tabelul8 Evaluarea steatozei și fibrozei hepatice

	CuSM (n=150)	Grupcontrol (n=150)	Pvaloare
PCA,dB/m	335.2±51.2	255.56±60.8	<0.0001
Gradsteatoza			
S0	21(14%)	95(63%)	<0.0001
S1	11(7%)	15(10%)	0.35
S2	11(7%)	3(2%)	0.03
S3	107(71%)	37(25%)	<0.0001
MRF,kPa	7.24±3.25	6.52±2.85	0.04
Gradfibroză			
F0-1	87(58%)	118(79%)	0.0001
F2	28(19%)	11(7%)	0.002
F3	20(13%)	14(9%)	0.26
F4	15(10%)	8(5%)	0.10

Note:Datele sunt exprimate ca medie ± SD sau număr(procent). Valorile semnificative statistic sunt prezentate cu caracter ealdine(P<0,05).

Abrevieri:SM:sindrom metabolic, CAP: parametru controlat al atenuarii,MRF:masuratoriile rigidității hepatice, S:steatoză,F:fibroză.

Echocardiographic results are shown in Tables 9.10. There were no significant differences between the two groups in terms of conventional parameters of LV structure and systolic function, but significantly more of the patients with metabolic syndrome had LV diastolic dysfunction. No differences were observed in AS diameters, volumes and ejection fractions between patients with metabolic syndrome and those in the control group. However, EST2D identified a subtle AS dysfunction in patients with metabolic syndrome, represented by low values of longitudinal deformity in the ventricular

contraction phase, and the incipient phase of ventricular diastole and during the atrial contraction phase. higher in subjects with MS ($P < 0.0001$).

Tabelul 9 Date ecografice la pacienții cu SM și ale celor din grupul de control

	SM(n=150)	Control(n=150)	Pvaloare
Ecografiiconvențională			
DTDVS(mm)	49.00±3.20	48.69±2.94	0.38
DTSVS(mm)	30.34±2.50	29.85±2.68	0.10
DiametruAS(mm)	3.34±0.36	3.27±0.38	0.10
FEVS(%)	51.7±0.6	51.8±0.2	0.05
FSVS(%)	37.93±2.91	38.00±3.50	0.85
E(m/s)	0.69±0.15	0.88±0.12	<0.0001
A(m/s)	0.89±0.17	0.61±0.10	<0.0001
E/Araport	0.81±0.21	1.47±0.23	<0.0001
TRIV(msec)	110.1±18	105.3±21	0.02
VSdisfuncțiediastolică(n,%)	78(52%)	59(39%)	0.02
VolumAS(mL)			
Maxim	27.3±5.2	26.6±5.7	0.26
Contractiepre-atriala	17.7±5.1	18.0±4.5	0.58
Minim	11.50±4.2	12.16±3.5	0.14
FEAS(%)			
Totala	58.2±4.0	57.8±3.4	0.35
Pasiva	37.9±4.7	38.8±3.9	0.07
Activa	35.6±15.0	33.4±12.3	0.16

Note: Datele sunt exprimate ca medie±SD sau număr (procent). Valorile semnificative statistic sunt prezentate cu bold ($P < 0.05$).

Abrevieri: SM:sindrom metabolic,DTDVS:diametrul telediastolic al ventriculului stâng,DTSVS:diametrul telesistolic al ventriculului stâng, AS:atriul stâng, FEVS:fracția de ejeție a ventriculului stâng,FSVS:fracția de scurtare a ventriculului stâng, E: unda E ,A:unda A,TRIV: timpul de relaxare izovolumetrică,VS:ventricul stâng,AS:atriul stâng,FE:fracție de ejeție

Tabel10 Date ecografice ale atriului stâng la pacienții cu SM și din grupul de control

Ecografie2DdetipSpeckle-tracking			
	SM(n=150)	Control(n=150)	Pvaloare
SAS-rezervor(%)	44.0±4.6	47.4±3.5	<0.0001
SAS-pompa(%)	17.4±2.3	19.7±1.8	<0.0001
SRAS-v(1/sec)	1.3±0.5	3.2±1.2	<0.0001
SRAS-e(1/sec)	-1.0±0.3	-1.5±0.5	<0.0001
SRAS-a(1/sec)	-1.5±0.7	-1.4±0.6	0.18
RigiditateaAS	0.34±0.12	0.20±0.04	<0.0001

Note: Datele sunt exprimate ca medie ± SD sau număr (procent). Valorile semnificative statistic sunt prezentate cu caractere aldine ($P < 0,05$).

Abrevieri: SAS: deformare longitudinală atrială stângă; SRAS-v: rata de deformare longitudinală atrială stângă în timpul contracției ventriculare; SRAS-e :rata de deformare longitudinală atrială stângă în timpul umplerii pasive ventriculare în diastola timpurie; SRAS-: rata de deformare longitudinală atrială stângă în timpul contracției pre-atriale, AS: atriul stâng.

In the univariate regression analysis, the variables associated with LV diastolic dysfunction in MS patients were: hepatic steatosis grade ≥ 2 , hepatic fibrosis grade ≥ 2 , peak longitudinal deformation of the AS in the reservoir phase, rate of deformation of the AS during contraction ventricular and AS stiffness. In the multivariate logistic regression, two variables were selected as independent predictors of LV diastolic dysfunction, namely, liver stiffness ($P = 0.0003$) and left atrium stiffness ($P < 0.0001$), as shown in Table 11. The variable adjusted in the multivariate analysis was the presence of metabolic syndrome.

Tabelul 11 Corelațiile dintre disfuncția diastolică a VS și parametrii ecografici ai ecografiei 2D-speckle-tracking la nivelul atriului stâng

Variabile	Analiza univariata			Analiza multivariata		
	β	ES	P	β	ES	P
Steatoza hepatică \geq S2	0.84	0.25	<0.001	-0.56	0.37	0.12
Steatoza hepatică \geq F2	2.04	0.29	<0.0001	1.38	0.38	0.0003
SAS-rezervor	-0.05	0.02	0.04	0.01	0.03	0.68
SAS-pompa	-0.04	0.04	0.43			
SRAS-v	-0.21	0.09	0.01	0.20	0.11	0.07
SRAS-e	-0.36	0.25	0.15			
Rigiditatea AS	9.23	1.30	<0.0001	8.29	1.81	<0.0001

Note: Datele sunt exprimate ca medie \pm SD sau număr (procent). Valorile semnificative statistic sunt prezentate cu caractere aldine ($P < 0,05$).

Abrevieri: SAS: deformare longitudinală atrială stângă; SRAS-v: rata de deformare longitudinală atrială stângă în timpul contracției ventriculare; SRAS-e: rata de deformare longitudinală atrială stângă în timpul umplerii pasive ventriculare în diastola timpurie; SRAS: rata de deformare longitudinală atrială stângă în timpul contracției pre-atriale; AS: atriul stâng.

Associations between independent variables related to LV diastolic dysfunction in patients with metabolic syndrome are shown in Figure 24. Stiffness of AS predicted subclinical LV diastolic dysfunction in patients with metabolic syndrome with a sensitivity of 45% and a specificity of 96% when

used. a limit value> 0.38.

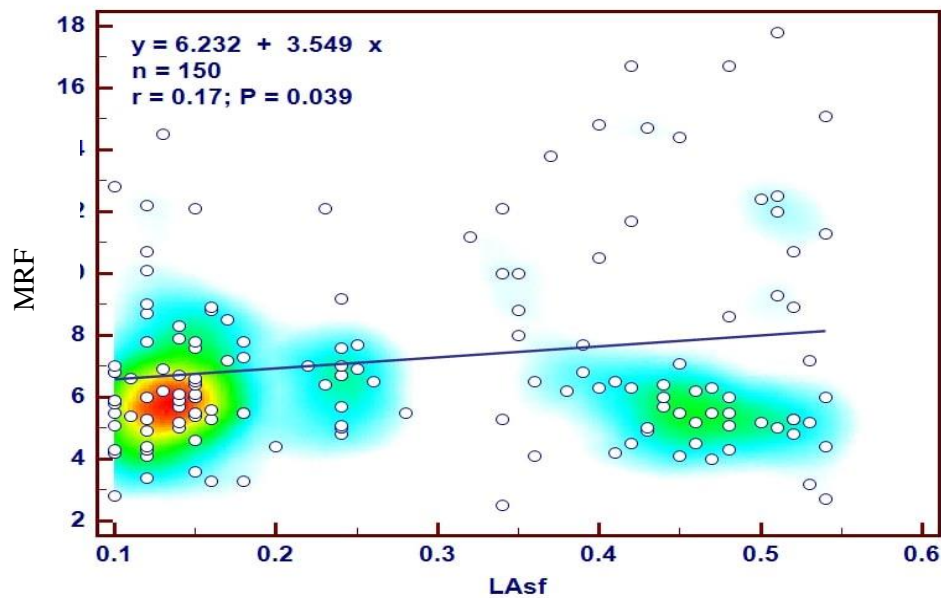


Figura26Corelații între variabilele independente asociate cu disfuncția diastolică subclinică a VS la pacienții cu sindrom metabolic.

When comparing the curves of the receptor function characteristics (ROC) of the two independent predictors of LV diastolic dysfunction, it was observed that the area under the curve (AUC) was slightly larger for left atrium stiffness than for liver stiffness measurement ≥ 2 , but the differences were not significant (Figure 25).

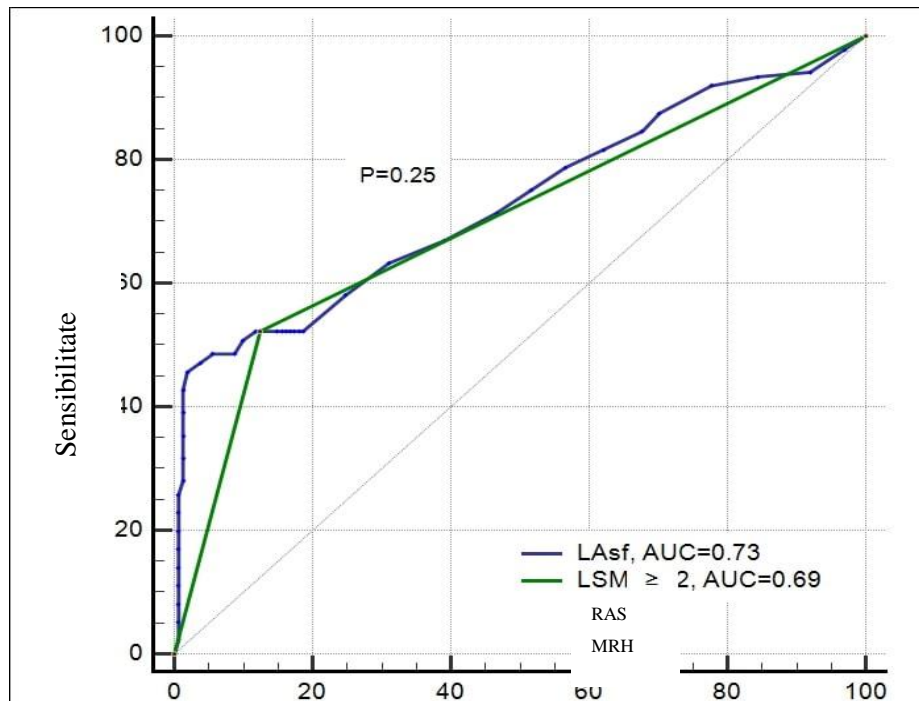


Figura 27 Comparația curbelor caracteristicilor de funcționare ale receptorului (ROC) ale variabilelor independente asociate cu disfuncția diastolică subclinică a VS la pacienții cu sindrom metabolic.

The stiffness of $AS \geq 0.38$ was observed in 36 (24%) of patients with MS and in 12 (8%) of patients in the control group ($P < 0.0001$). The relative risk of patients with MS to have a stiffness of $AS \geq 0.38$ was 3.0 compared to the control group (AUC = 0.666, 95% CI 1.62-5.53, $P < 0.001$). Stiffness $AS > 0.38$ was associated with hepatic fibrosis, $F \geq 2$ ($r = 0.59$, 95% CI 0.51 to 0.66, $P < 0.0001$) and hepatic steatosis $S \geq 2$ ($r = 0.42$, 95% CI 0.32 to 0.51, $P < 0.0001$).

8.10.DISCUSSIONS

Most studies have shown evidence of structural and functional changes in the left ventricle induced by metabolic syndrome. Most components of metabolic syndrome cause a degree of LV myocardial fibrosis.

In our study, the prevalence of LV diastolic dysfunction was 52% in patients with metabolic syndrome and 39% in the control group. The higher prevalence of LV diastolic dysfunction was due to the fact that 89% of patients with metabolic syndrome had diabetes and 80% had high blood pressure.

Left ventricular diastolic dysfunction in patients with metabolic syndrome has been confirmed by conventional echocardiography and Doppler.

Speckle-trackings echocardiography has proven to be a more reliable way to recognize incipient ventricular dysfunction, using a quantitative assessment of myocardial deformity. EST2D has recently been used to assess atrial performance, also allowing an accurate assessment of atrial deformity. [181]

AS dysfunction could play an important role in the pathophysiology of heart failure with preserved LV ejection fraction (ICpFE).

In our study, there were no statistically significant differences in the diameters, volumes, and ejection fractions of AS between patients with metabolic syndrome and controls. lower in patients with metabolic syndrome ($P \leq 0.0001$).

As already established, the deformation of the AS during the reservoir phase is significantly associated with the degree of myocardial fibrosis of the AS evaluated by cardiac magnetic resonance imaging or histopathologically

and is significantly related to the LV filling pressure quantified by cardiac catheterization.

Analyzing the ROC curve of predictive capacity for left atrium stiffness, for left ventricular diastolic dysfunction in subjects with metabolic syndrome, it was observed that the limit value of 0.38 had an increased specificity (96%) and a sensitivity of 45%, completing the data echocardiographic tests necessary to correct false positive statements [191].

The present study confirmed the association between hepatic fibrosis (stiffness ≥ 2) and left ventricular diastolic dysfunction in patients with metabolic syndrome. Patients with metabolic syndrome in our study group were three times more likely to have increased atrial stiffness. compared to the control group ($P \leq 0.001$). Increased atrial stiffness is another parameter that highlights the diastolic dysfunction of the left ventricle. A stiffness $AS \geq 0.38$ was positively associated with a stage of hepatic fibrosis $F \geq 2$ and a stage of hepatic steatosis $S \geq 2$ ($P \leq 0.0001$).

8.12.CONCLUSIONS

In patients with metabolic syndrome, LV diastolic dysfunction, assessed by conventional echocardiography, has been significantly and independently associated with a degree of hepatic fibrosis ≥ 2 . was independently associated with the severity of steatosis and liver fibrosis.

Our study suggests that conventional echocardiographic and speckle tracking evaluation along with liver elastography should become routine evaluations in patients with metabolic syndrome. The TSE parameters showed significantly better sensitivity and correlation with liver stiffness than conventional ones.

8.13. LIMITATIONS

The severity of liver damage has been quantified noninvasively, although liver biopsy is the gold standard assessment method. The results of PCA, ETCVH and EST measurements also depend on image quality. , but cut-off values should be validated in cohorts of patients greater in number of patients and number of studies.

9. FINAL CONCLUSIONS

The aim of the doctoral thesis was to detect early left ventricular dysfunction by clinical and paraclinical cardiac evaluation of patients with metabolic syndrome. The thesis followed the following aspects:

1. Evaluation of systolic and diastolic function by conventional echocardiography2D in patients with metabolic syndrome.
2. Ultrasound evaluation by speckle-tracking method of patients after conventional ultrasound evaluation to detect early systolic and diastolic dysfunction of the left ventricle.
3. Carrying out carotid Doppler in patients with metabolic syndrome and calculating the mean intimate index
4. Evaluation of the optimal parameters for assessing heart failure at onset, found in patients with metabolic syndrome and BFNA.
5. The existence of a correlation between ventricular dysfunction (interpreted by speckle-tracking ultrasound) and the severity of liver damage (fibrosis or hepatic steatosis), assessed by elastography.

6. Left atrial dysfunction, as a contributing factor for the occurrence of early left ventricular systolic dysfunction.
7. The prognostic value of non-alcoholic fatty liver disease and cardiovascular risk factor in patients with metabolic syndrome.

10.2 ORIGINALITY ASPECTS OF THE DOCTORAL THESIS

The doctoral dissertation addressed a topical issue, namely the group of cardiovascular risk factors known as metabolic syndrome in patients with or without liver damage.

The most obvious obstacle is the complex, interdependent multi-factorial nature of the syndrome itself, which makes it difficult to separate relevant factors or specific combinations of factors.

Pathophysiological changes associated with metabolic syndrome include changes in myocardial metabolism, microvascular dysfunction, imbalance between oxygen demand / supply, cardiac contractile dysfunction (systolic and diastolic), and concentric ventricular hypertrophy.

There is a clear need for ongoing exploration of these issues in order to better understand and treat obesity and cardiovascular disease associated with metabolic syndrome.

Early identification of patients with metabolic syndrome may allow the clinician to more accurately assess cardiovascular risk. .

As elements of originality it can be said that our evaluations showed that subclinical systolic dysfunction of LV (detected by EST2D) was significantly related to fibrosis and hepatic steatosis. In our research, all patients were properly investigated, standard cardiac ultrasound was used and

EST2D for the detection of left ventricular dysfunction and ETCVH and hepatic PCA for the identification and stratification of liver fibrosis and steatosis.

Our study shows that patients with metabolic syndrome and nonalcoholic fatty liver disease have an increased risk of developing heart dysfunction (diastolic or systolic dysfunction of the left ventricle). Speckle tracking echocardiography may be recommended as a routine echocardiographic examination in patients with metabolic syndrome, to detect cardiac dysfunction as early as possible and to apply appropriate treatment to ameliorate the cardiac lesions.

Impairment of heart structure (left ventricular dysfunction) in patients with metabolic syndrome has been associated with the severity of steatosis and hepatic fibrosis (detected by transient ETCVH and PCA).

Another parameter for the early detection of LV dysfunction is the stiffness of the left atrium. Stiffness of the left atrium, assessed by speckle-tracking ultrasound, has been independently associated with both hepatic steatosis and hepatic fibrosis.

Early detection of hepatic and cardiac changes in subjects with metabolic syndrome is of great importance, as lifestyle changes and drug therapy could prevent the onset of heart failure or liver cirrhosis. These measures could reduce morbidity and mortality, as well as health insurance costs.

Probably, in the future, all these clinical, paraclinical and therapeutic aspects will make important contributions to medical practice and will be helpful in implementing guidelines for the management of patients with metabolic syndrome.

10.3.PERSPECTIVES OPENED BY THE DOCTORAL THESIS

Metabolic syndrome and non-alcoholic fatty liver disease share common pathologies such as diabetes, hypertriglyceridemia and obesity. Because metabolic risk factors are so common in patients with non-alcoholic fatty liver disease, there is evidence that BFGNA may actually be a hepatic manifestation of metabolic syndrome.

Current evidence describes the association between fatty liver disease and an increased cardiovascular risk of subclinical atherosclerosis, in addition to structural and functional cardiac abnormalities.

Conventional echocardiography continues to be useful in cardiac imaging, however, STE has become increasingly useful for more specific assessment of cardiac function. Common measurements such as ejection fraction and I / O ratio are standard measurements, but are limited. With the help of STE, clinicians can obtain more specific data related to cardiac movements, both atria and ventricles. helped to identify subclinical abnormalities of myocardial function in patients with metabolic syndrome.

Therefore, EST2D should be a standard investigation in patients with metabolic syndrome. Newer, EST-derived parameters showed better sensitivity than those used in conventional ultrasound. It is possible that in the future EST2D will be replaced by EST3D, with the advent of more advanced equipment.

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