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EVALUATION OF ECHOCARDIOGRAPHIC PARAMETERS FOR LEFT VENTRICLE SYSTOLIC AND DIASTOLIC DYSFUNCTION IN PATIENTS WITH LIVER CIRRHOSIS

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Abstract: *Prevalence of cirrhotic cardiomyopathy is an issue hard to estimate, both nationally and worldwide. This clinical research sets out a more precise evaluation of systolic and diastolic functions in cirrhotic patients using proved parameters - the TEI Index- to estimate systolic and diastolic dysfunction and the E/Vp ratio for diastolic dysfunction. These parameters were compared with classic parameters typically employed. Study population was represented by 70 patients diagnosed with liver cirrhosis.Results showed increased sensitivity of the TEI Index - in detecting systolic dysfunction in cirrhotic patients, with an increased accuracy compared to left ventricular ejection fraction. Regarding the parameters for diastolic dysfunction, it was proved that E/Vp ratio, had an increased specificity in detecting diastolic dysfunction due to cirrhotic cardiomyopathy. In conclusion, the hypothesis that patients with liver cirrhosis could benefit from an improvement of diagnostic sensitivity of cirrhotic cardiomyopathy using the two suggested parameters was confirmed in our study. And more important, a significant positive correlation between the severity of diastolic dysfunction and the severity of liver disease was found.*

Key words: *liver cirrhosis, cirrhotic cardiomyopathy, systolic and diastolic dysfunction, TEI Index, E/Vp*

1. Introduction

Cirrhotic cardiomyopathy is classically defined by the impaired systolic response to physical stress, the presence of diastolic dysfunction, and electrophysiological alterations [1]. Traditionally, the parameter employed for evaluating systolic dysfunction was the ejection fraction (EF), with normal values over than

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50%, a value below 50% indicating the presence of systolic dysfunction.

Also, the Cirrhotic Cardiomyopathy Consortium gathered in 2019 recommended that apart from EF, global longitudinal strain (GLS) is a valuable tool in determining systolic function in cirrhotic patients, especially in those with normal EF.

Other methods used for assessing systolic function include the the Myocardial Performance Index (MPI) or TEI Index. TEI Index assesses global myocardial function through systolic and diastolic performance of the right and left ventricle. Cardiac MRI is also used for systolic function evaluation, but further research is needed for validation.

The E/A ratio was used for diastolic dysfunction. for electrophysiological changes on the electrocardiogram (ECG), the corrected QT interval (QTc interval) alterations were employed.

Diastolic function is a complex and multifactorial process that combines the pressure gradient between the left atrium and left ventricle, passive and active relaxation of ventricles, and end-diastolic left ventricle compliance [2]. It's estimation by the classic E/A parameter has significant limitations in detection of diastolic dysfunction.

In the modern era, based on recent data concerning diastolic function, it is recommended to utilize four parameters. The peak mitral annular velocity during early filling (e^{l}), the ratio between the peak early diastolic velocity (E) and e^{l} , tricuspid regurgitation peak velocity and left atrial indexed volume [3].

However, there are important limitations of all systolic and diastolic parameters previously mentioned.

As for the left ventricular ejection fraction, significant limitations appear in left ventricular hypertrophy, in patients with bundle branch block, in patients with tachycardia and in estimating the longitudinal systolic dysfunction. Also, the ejection fraction is dependent on preload and afterload and has a high inter-observer variability [4].

GLS has the disadvantage of needing a dedicated software and trained physicians. Also it is susceptible to preload conditions, and normal values are influenced by age, and sex of the patient [5].

Regarding diastolic parameters limitation, it should be noted that both E/A and e^{l} are age and preload dependent and E/A specifically requires sinus rhythm and manifests a U shape relation to diastolic function so that both healthy and advanced diastolic dysfunction patients have the same values. E/e^{l} ratio loses its value when values <14 are obtained and cannot trace filling pressures over time [6]. The tricuspid regurgitation velocity is not useful in cases of portopulmonary hypertension or when other causes of tricuspid regurgitation are present, as it is highly dependent on preload. In case of undetected systolic and diastolic dysfunctions it cold be adverse clinical consequences and detecting them early can lead to a better prognosis for the patients.

This reaserch aims is to evaluate systolic and diastolic dysfunction in cirrhotic patients by estimating the TEI Index after physical activity, a parameter that is more accurate in detecting early a reduction of systolic performance compared to the classic EF parameter.

TEI index is not dependent on the quality of image, preload and afterload, and has a lower inter-observer dependency. At the same time, it was proved that it is a marker of early detection of systolic dysfunction compared to EF [7]. In previous studies, a high TEI

Index was proved to be a marker of negative prognosis in patients with coronary disease and heart failure [8].

For the detection of diastolic dysfunction with a higher accuracy compared to the classic parameter E/A, the E/Vp ration was used. This parameter combines two different evaluations, one for transmitral flow (E), evaluated by pulsed Doppler echocardiography, and the other one (Vp) representing the flow propagation velocity evaluated by mode-M echocardiography. This marker has been proven in numerous previous studies as being closely correlated with the tele-diastolic left ventricular filling pressure thus being a trusted parameter in accurately determining the presence of diastolic dysfunction [9, 10].

It is not dependent on filling conditions and is not conditioned in term of evaluation by the presence of sinus rhythm [10].

2. Objectives

- Comparison between TEI Index and EF at rest and after physical effort in predicting systolic dysfunction.
- To determine if TEI Index could diagnose early systolic dysfunction in patients with normal EF
- Comparison between E/A and E/Vp in detecting diastolic dysfunction after physical effort
- To determine if there is a correlation between TEI Index, E/Vp values and the severity of liver disease
- Assessing possible differences between TEI Index and E/Vp values regarding patients gender and age.

3. Materials and method

During November 2022 and march 2024 we conducted evaluations in 70 patients with different stages of liver disease (Figure 1).

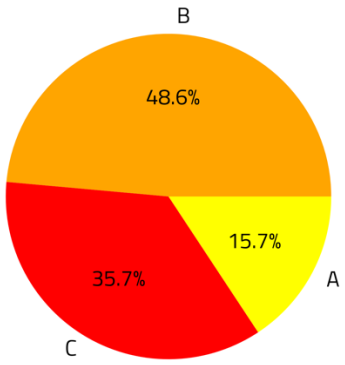

Fig.1. *Distribution of cirrhosis severity classes among patients. Class A indicates a cirrhosis with unaffected liver function, while for class B the liver function is moderately affected, and for class C liver function is severely affected*

Patients age distribution was between 45-85 illustrated in Figure 2.

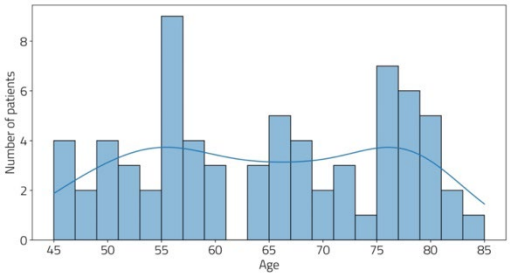

Fig. 2. *Age distribution among patients*

Approximately 63% were male and 37% were female (Figure 3).

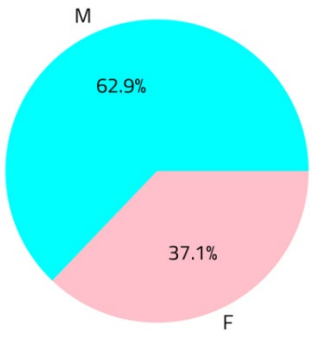

Fig. 3. *Gender distribution among patients: Female F, Male-M*

Patients with a major preexisting heart pathology, persistent or permanent atrial fibrillation, uncontrolled hypertension, end stage kidney disease, ischaemic or haemorrhagic stroke and those who could not carry out the physical activity were excluded from the study.

Patients were advised to stop beta blocker medication 24 hours prior to evaluation.

They were subjected to physical activity having to do 10 squats and then they were immediately evaluated by echocardiography. Child C patients who were unable to perform 10 squats were excluded from the study. Systolic function was assessed by measuring the ejection fraction using the Simpson method (with normal values being above 50%) and by evaluating the TEI Index through Doppler echocardiography, calculated as the sum of isovolumic contraction time and isovolumic relaxation time divided by the ejection time. (Figure 4). The values indicating systolic dysfunction were those above 0.50 [11].

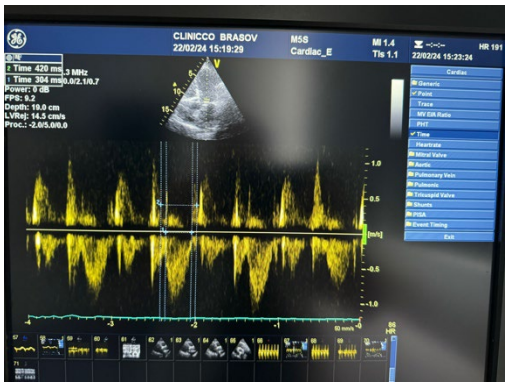

Fig. 4. *Measuring TEI Index*

Then, we evaluated the diastolic dysfunction by measuring E/A through pulsed Doppler echocardiography at mitral valve level and E/Vp by measuring Vp by means of colour M-mode echocardiography (Figure 5). Values above 1 are considered normal, while for the E/Vp ratio, values above 2 are regarded as a marker of diastolic dysfunction, and those exceeding 2.5 are considered an indicator of obstructed capillary pressures greater than 15 mmHg. [12].

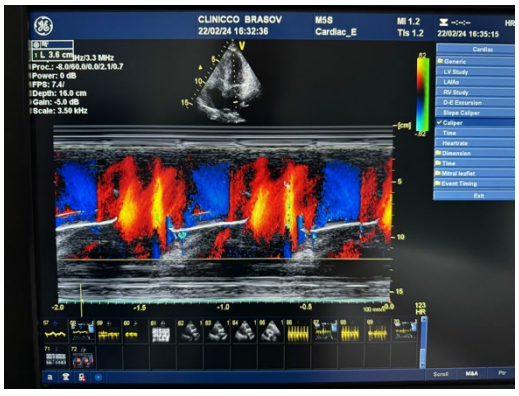

Fig. 5. *Measuring E/Vp*

The echocardiography machine used is General Electric Vivid E9 with a cardiac transducer with a frequency of 4.2 MHz. The physical activity was supervised by

healthcare professionals and the echocardiography was done immediately after.

The percentage of patients with systolic dysfunction was recorded based on the ejection fraction, as well as the percentage of patients with systolic dysfunction assessed using the TEI Index. A comparison between the two methods was done.

Simultaneously, the presence of diastolic dysfunction was assessed using the E/A ratio and the E/Vp ratio. Subsequently, these two methods were compared.

4. Results

The baseline characteristics were comparable between the groups, with no significant differences observed in coronary artery disease, obesity, hypertension or dyslipidemia (all p values over 0.05) (Table 1).

Comorbidities of the groups Table 1

Characteristic	**Child A(n=6)**	**Child B(n=35)**	**Child C(n=29)**	**p**
Hypertension, n (%)	2 (33)	12(34)	9 (31)	0.90
Type 2 diabetes, n (%)	2 (33)	13 (37)	11 (37)	0.06
Coronary artery disease, n (%)	1 (16)	5 (14)	4 (13)	0.80
Chronic kidney disease, n (%)	1 (16)	5 (14)	6 (20.6)	0.06
Dyslipidemia, n (%)	1 (16)	8 (25)	5 (17)	0.19
Smoking, n (%)	4 (66)	19 (56)	18 (62)	0.61

Ejection fraction (EF) measurements at rest showed that all patients had values over 50%, with an average of 55%, thus indicating the lack of systolic dysfunction at rest in cirrhotic patients according to this parameter. The lowest value determined at rest was of 50% and the highest of 60%.

Table 2

Descriptive statistical analysis of the entire data set

Number of patients		70
Age [years old]	**Average**	64.3 ± 11.6
	Interval	45 - 85
Ejection fraction [%]	**Average**	58.6 ± 4.4
	Interval	40 - 60
	Average	**0.57 ± 0.09**
	Interval	**0.37 - 0.79**
Number of patients with E/A <1		64
E/Vp ratio	**Average**	2.02 ± 0.25
	Interval	1.5 - 2.6

EF measurement after physical activity generated a different situation, with values between 40% and 60%, and an average of 58%.

The TEI Index had values under 0.5 at rest in all patients from the batch, also excluding resting systolic dysfunction. After the physical activity, the values obtained were between 0.37 and 0.79, with an average of 0.57.

In relation to parameters for diastolic dysfunction after physical activity 64 patients out of 70 showed a type of diastolic dysfunction with impaired relaxation and an E/A ratio lower than 1. The E/Vp ratio values had an average of 2.02 with an interval between 1,5-2,6 (Table 2).

The TEI Index showed average values almost identical in female and male, with a slightly higher variation in female but without statistical significance (p>0.05).

The number of patients with E/A <1 was similar in both female and male as reported to the total number of patients suggesting that the majority presents this cardiac characteristic. Similarly, the variability between male and female regarding E/Vp ratio is low. Hence, no statistical significance was met in regard to patient gender (p>0.05).

In relation to liver damage, the results obtained showed that the average age is similar in Child-Pugh classes A and B, and slightly lower in class C.

The ejection fraction has very close average values among classes, with a slight variation (p=0.512). The TEI index presents an increase in average values from class A to class C suggesting a cardiac affection that progresses with the severity of cirrhosis. (p=0.01)

E/Vp ratio had average values that increase progressively from class A to class C suggesting the worsening of diastolic dysfunction is correlated with the worsening of cirrhosis.(p=0.022)

Analysis on distribution of parameters according to sex

The Mann-Whitney U nonparametric test was used to compare the distribution of parameters (ejection fraction, TEI Index, E/A ratio and E/Vp ratio) between male and female. Regarding the ejection fraction, the p-value = 0.272 is higher that the threshold of p< 0.05, which means that there is not enough evidence to reject a null hypothesis. Thus, we cannot conclude that there is a statistically significant difference between the distribution of ejection fraction regarding gender. If we refer to the TEI Index, the p-value = 0.995 is also much higher than the threshold of p<0.05 indicating that there is no statistically significant difference between the distribution of the TEI Index regarding gender. Similarly, the E/A ratio is not significantly different regarding gender. (p= 0.286). The same observation with the E/Vp ratio - no significantly different (p higher than 0.05) in both, male and female.

Analysis on distribution of parameters according to cirrhosis class

The following results were observed. Regarding the ejection fraction, the value of p= 0.512 is higher than the threshold of p<0.05. with no significant difference in distribution of ejection fraction among cirrhosis classes. In relation to the TEI Index, the value of p = 0.072 is also higher than the threshold of p< 0.05 suggesting that it was no significant difference in the distribution of TEI Index among cirrhosis classes. Similarly, about the E/A ratio p = 0.213. On the other hand, the distribution of the E/Vp ratio was significantly different among cirrhosis classes with a p-value = 0.022 indicating a statistically significant difference among these groups.

Analysis of correlation among age and EF variables, TEI Index

Analysing the correlation between age and EF it was obtained a Pearson's correlation coefficient of -0.041 indicating a very weak and negative relation. The p-value of 0.734 suggests that this correlation is not statistically significant. The correlation coefficient between age and the TEI Index was 0.253 indicating a moderate and positive relation. This suggests that as the age increases, the values of the TEI Index tend to increase. The value of p=0.034 suggests that this correlation is statistically significant. Looking at the correlation between age and the E/A ratio, the Pearson correlation

coefficient is -0.072, suggesting a very weak and negative relation between the two variables. The value of p=0,555 indicates that this correlation is not statistically significant. As for the E/Vp ratio, the correlation coefficient is 0,118, which indicates a slightly positive relationship. However, the value of p= 0,330 shows that this correlation is not statistically significant either.

Analysis of the distribution of EF, TEI Index, E/A and E/Vp parameters

The distribution of the ejection fraction (EF) is strongly asymmetric to the right, with a significant concentration of patients in the upper part of the range. Most patients had an ejection fraction of 50% or more, which indicates normal cardiac function. Only a small number of patients have EF values below the 50% threshold diagnosing systolic dysfunction (Figure 6).

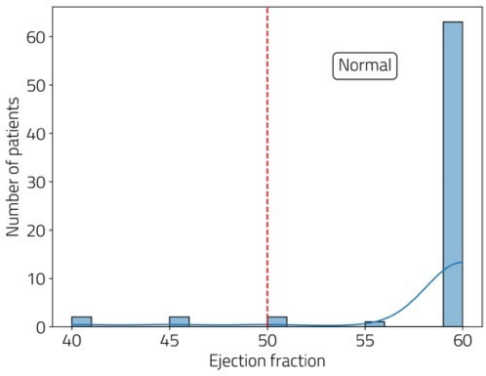

Fig. 6. *Distribution of the ejection fraction among patients. The red dotted line marks the threshold values that separate the range into normal and abnormal values*

The distribution of the TEI Index values is more uniform compared to the EF. There is a considerable proportion of patients with TEI Index values above the threshold of p<0.05, indicating a potential abnormal heart function in the systole. The distribution shows several high frequency areas suggesting a variability of the TEI Index among patients. The highest concentration is just above the threshold of p<0.05, which indicates that a significant part of patients is within the range considered abnormal according to the TEI Index (Figure 7).

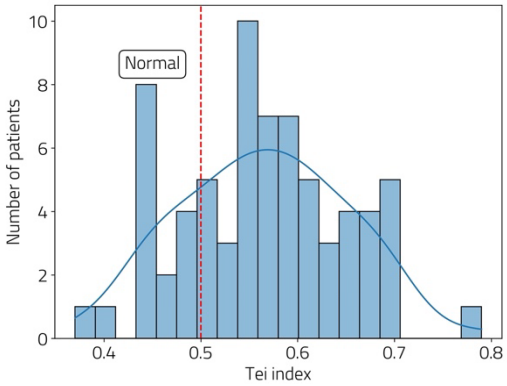

Fig. 7. *Distribution of the TEI Index among patients. The red dotted line marks the threshold values that separate the range into normal and abnormal values, with the normal segment highlighted in each histogram*

The distribution of the E/Vp ratio shows considerable variability among patients, with a slightly asymmetric trend to the right. The median value is around the threshold of 2.0, up to which the ratio is considered to be normal. However, there is a significant proportion of patients with E/Vp ratio values above this threshold indicating a possible increase of sensitivity in detecting diastolic dysfunction in cirrhotic patients (Figure 8).

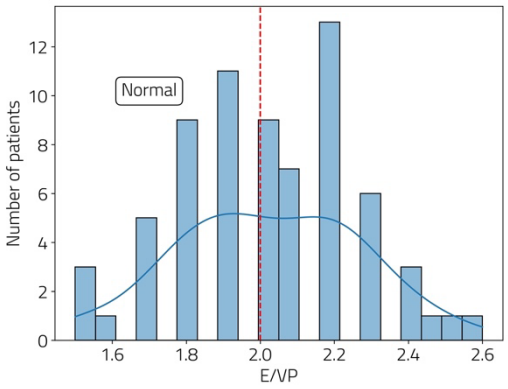

Fig. 8. *Distribution of the E/Vp ratio among patients. The red dotted line marks the threshold values that separate the range into normal and abnormal values, with the normal segment highlighted in each histogram*

The distribution of the E/A ratio values is strongly dominated by patients with a "YES" value (E/A < 1), indicating that most patients have diastolic dysfunction (Figure 9).

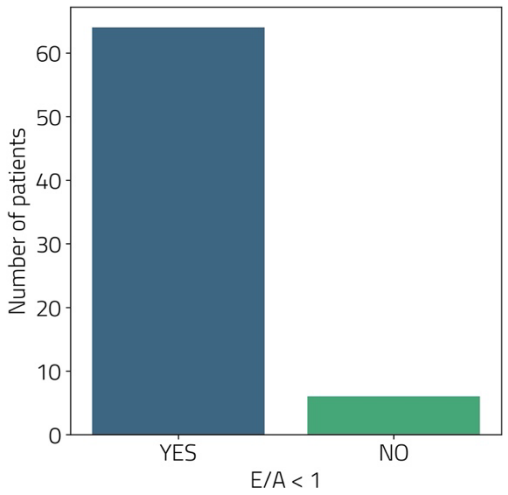

Fig. 9. *Distribution of the E/A ratio among patients*

The E/A ratio leads to the highest proportion of patients with abnormal values (91%).

The TEI index could also be a sensitive indicator of potential cardiomyopathy, as it classifies a large proportion of patients as potentially affected (77%). This ensures a low rate of false negative results reducing at the same time the rate of false positive.

On the other hand, the E/Vp ratio, with a proportion of 59% of abnormal values, indicates that this parameter can detect diastolic dysfunction in a significant number of patients. Although not as sensitive as the E/A ratio, it still provides valuable information about the hemodynamic state of patients.

The ejection fraction could be the parameter with the highest specificity, as it classifies fewer patients as affected (9%), ensuring a low rate of false positive results, with the risk of many patients being wrongly classified as "healthy".

Analysis of the correlation among EF, TEI, E/A and E/Vp parameters

The analysis results of the correlation between the ejection fraction and the TEI index indicate a very weak correlation (Pearson correlation coefficient of 0.04) and statistically insignificant (p value of 0,772). This suggests that there is no significant linear relation between the two variables in this dataset. Therefore, EF and TEI index seem to measure distinct aspects of cardiac function, and values of one variable do not provide predictive information about the other.

Analysing the correlation between the ejection fraction and the E/A ratio, we see a weak and negative correlation (coefficient of -0.09), with a p value of 0,435. This suggests that there is no significant linear relation between these two variables.

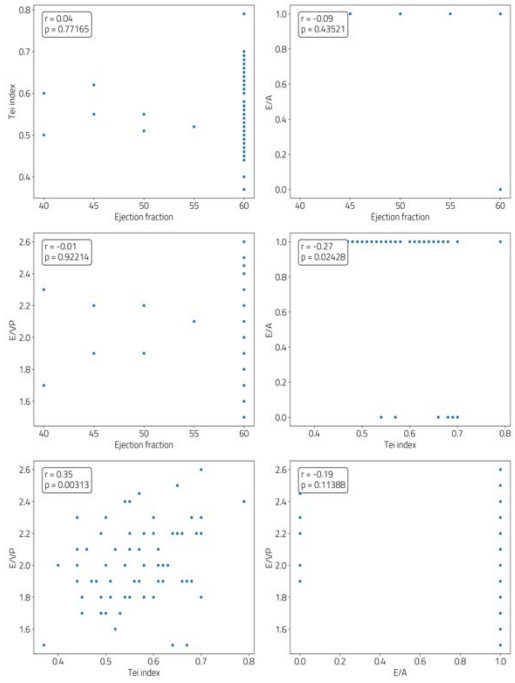

Fig. 10. *Dispersion diagrams between each two parameters, i.e. correlation coefficients and corresponding p values*

There is also no correlation between the ejection fraction and the E/Vp ratio (coefficient of -0.01 and p value of 0,922).

As for the correlation between the TEI index and the E/A ratio, we see a moderate negative correlation (coefficient of -0.27) and statistically significant (p-value of 0,024). This suggests that there is an inverse relation between these two variables, where the increase of one tends to be associated with the decrease of the other.

The correlation between the TEI Index and the E/Vp ratio shows a moderate positive correlation (coefficient of 0.35) that is statistically significant (p-value of 0,003). This result indicates a direct linear relation between TEI Index and E/Vp, suggesting that increased TEI Index values are associated with increased E/Vp ratio values.

Finally, the correlation between the E/A ratio and the E/Vp ratio is weak and negative (coefficient of -0.19) and statistically insignificant (p-value of 0,114). This suggests that there is no significant linear relation between these two variables in the analysed data set (Figure 10).

Detection of cardiomyopathy based on parameters

It was attempted to determine the presence of cardiomyopathy by applying threshold values for EF and TEI variables. First, it was determined that the data obtained are heterogeneous and not normally distributed. For example, for the distribution of results obtained based on EF, the variation coefficient is higher than 30 and the p value is $3.6 \cdot 10^{-14}$. Therefore, the Mann-Whitney U nonparametric test was applied to the classification results obtained based on threshold values (Figure 11).

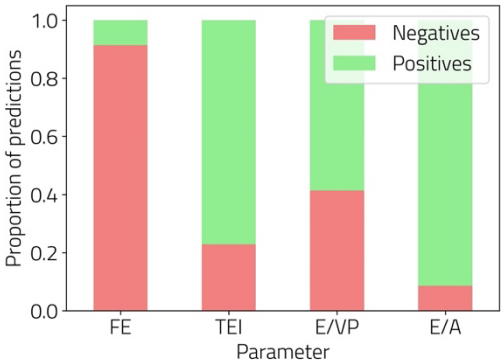

Fig. 11. *Distribution of positive (patient has cardiomyopathy) and negative (patient does not have cardiomyopathy) predictions for each parameter*

The analysis was applied for all relevant variables (EF, TEI Index, E/A and E/Vp) using specific threshold values for each parameter: EF < 50, TEI > 0.5, E/Vp > 2, and E/A < 1.

The extremely low p-value ($p<0.01$) indicates that the results obtained based on EF and TEI Index differ significantly. Similarly, the results obtained using EF differ significantly from those obtained with the E/A ratio ($p<0,001$) and from those determined based on the E/Vp ratio ($p <0.01$). The value of $p=0.021$ between the TEI Index and the E/A ratio and the value of $p=0,019$ between the TEI index and the E/Vp ratio suggests that there are statistically significant differences between the results obtained using these parameters. Similarly, the results obtained based on the E/A ratio differ significantly ($p =0,0000078$) from those determined by the E/Vp ratio.

5. Discussions

The results led to the conclusion that both parameters for systolic dysfunction (EF and TEI Index) had normal values at rest. It is a finding consistent with known data, partially explained by the marked systemic vasodilatation present in hepatic cirrhosis leading to a reduced afterload [13-15].

This represents an additional proof that diagnosing cirrhotic cardiomyopathy using strictly echocardiographic determinants at rest is extremely difficult. This situation contributes further to underdiagnosing systolic dysfunction in cirrhotic patients having adverse consequences on prognosis [16-18].

It is also worth mentioning that no statistically significant differences were observed between sexes, an expected result based on the fact that there is no reports in literature of statistically significant differences between the two genders regarding EF and TEI Index.

Although some studies from the literature describe a directly proportionate correlation between the grade of hepatic affection and the grade of systolic dysfunction measured by EF [19], in our study were no statistically significant differences regarding systolic disfunction among the different Child-Pugh classes, in contrast to the literature data.

On the other hand, when TEI Index was assessed, a positive correlation was observed between systolic dysfunction and the severity of end stage liver disease, with statistical significance. This finding is consistent with data from previous studies on systolic dysfunction measured by GLS [20].

One possible explanation of this fact is that as much as cirrhosis progresses, there is progressive alterations in the cardiomyocyte membrane, a decrease in the density of beta adrenergic receptors, alterations in the muscarinic receptors, as well as in potassium and calcium receptors, all concurring to progressive contractile dysfunction. Other possible mechanism could be a increased NO production in systemic vasculature leading to additional drop in systemic vascular resistance and decreased myocardial contractility despite increased chronotropic response [21].

The same conclusions resulted from the analysis of the less specific parameter E/A. Most patients had a sub unitary E/A ratio, which suggest that this parameter is a sensitive indicator of diastolic dysfunction, but at the same time it is known to have a low specificity for diastolic dysfunction

due to liver cirrhosis [22]. This can be useful for the initial screening to identify patients who need additional investigations. However, a high sensitivity can lead to a high rate of false positive results indicating the need for the diagnosis to be confirmed through other methods.

In contrast, about E/Vp parameter, it was proven a direct proportional correlation between the grade of hepatic affection and the severity of diastolic dysfunction evaluated by this highly specific parameter.

This result once again confirms, accordingly to known data, that this parameter is a fine tool in the assessment of the diastolic function, it's correlation with the severity of the hepatic disease having clear physio-pathological grounds through increased alterations in the cardiac receptors and biomarkers due to hepatic worsening function [23].

Regarding the accuracy of systolic dysfunction detection by means of the two methods, it was established that the TEI Index is more sensitive that EF in this respect with statistical significance.

Moreover, based on these results, we recommend inclusion of the TEI Index in the standard assessment of suspected cirrhotic cardiomyopathy and also in patients with normal EF.

The wide usage of this parameter could lead to an increased sensitivity for the cirrhotic cardiomyopathy diagnosis with subsequent improvement of the prognosis of these patients whether without liver transplant, or after liver transplant or after TIPS implantation.

Also, when the results of the two diastolic parameters were analyzed and compared, it was noted that E/Vp is a more reliable and statistically significant more accurate parameter in assessing diastolic function than E/A. This finding in concordant to what is mentioned in previous research in the cardiac field [24], but this finding was not validated in the setting of cirrhotic cardiomyopathy.

6. Conclusions

These results suggest that the combined use of these parameters (EF, TEI Index, E/A and E/Vp) can offer a more comprehensive overview on the presence and the severity of cardiomyopathy, each parameter contributing with singular information on cardiac function. The use of multiple criteria can help with a more precise identification of affected patients and with avoiding high rate of false positive or false negative results associated with the use of a single criterion.

In accordance with the results obtained, the use of TEI Index as a superior parameter to EF in term of detecting systolic dysfunction in patients with liver cirrhosis. Also TEI Index is a parameter that correlates positively with the severity of end stage liver disease.

Our research points out on one hand the precision of E/Vp parameter in diagnosing diastolic dysfunction and correlating it with the grade of hepatic affection, and on the other hand the lack of specificity of the E/A parameter.

Implementing these two parameters (TEI Index and E/Vp ratio) widely could lead to a better diagnosis of systolic and diastolic dysfunction in cirrhotic patients with a positive effects on their prognosis.

7. Study limitations

- relatively small cohort of patients; due to

the small size of the study group, further research is needed to conclusively determine the role of these methods in evaluating heart dysfunction in patients with cirrhosis.

- lack of a „gold standard" examination for systolic and diastolic dysfunction such as cardiac MRI, for comparation of the 4 parameters
- lack of comparison with more accurate parameters such as GLS for systolic dysfunction or e^{l}, E/e^{l} and left atrial indexed volume for diastolic dysfunction.

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