# A New Tissue Doppler Index to Predict Cardiac Death in Patients with Heart Failure

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## Abstract

**Background: It has been shown that a new tissue Doppler index, E/(E'×S'), including the ratio between early diastolic transmitral and mitral annular velocity (E/E'), and the systolic mitral annular velocity (S'), has a good accuracy to predict left ventricular filling pressure.**

**Objectives: We investigated the value of E/(E'×S') to predict cardiac death in patients with heart failure.**

**Methods: Echocardiography was performed in 339 consecutive hospitalized patients with heart failure, in sinus rhythm, after appropriate medical treatment, at discharge and after one month. Worsening of E/(E'×S') was defined as any increase of baseline value. The end point was cardiac death.**

**Results: During the follow-up period (35.2 ± 8.8 months), cardiac death occurred in 51 patients (15%). The optimal cut-off value for the initial E/(E'×S') to predict cardiac death was 2.83 (76% sensitivity, 85% specificity). At discharge, 252 patients (74.3%) presented E/(E'×S') ≤ 2.83 (group I) and 87 (25.7%) presented E/(E'×S') > 2.83 (group II), respectively. Cardiac death was significantly higher in group II than in group I (38 deaths, 43.7% vs. 13 deaths, 5.15%, p < 0.001). By multivariate Cox regression analysis, including variables that affected outcome in univariate analysis, E/(E'×S') at discharge was the best independent predictor of cardiac death (hazard ratio = 3.09, 95% confidence interval = 1.81-5.31, p = 0.001). Patients with E/(E'×S') > 2.83 at discharge and its worsening after one month presented the worst prognosis (all p < 0.05).**

**Conclusions: In patients with heart failure, the E/(E'×S') ratio is a powerful predictor of cardiac death, particularly if it is associated with its worsening. (Arq Bras Cardiol. 2014; 102(1):19-29)**

**Keywords: Heart Failure / mortality; Echocardiography, Doppler; Death, Sudden, Cardiac / prevention & control.**

## Introduction

The mortality rate after the onset of heart failure (HF) remains high despite recent advances in the management of this condition. The high mortality associated to left ventricular (LV) dysfunction results in the necessity to obtain prognosis information as soon as possible. A variety of indexes derived using echocardiography have been used to predict cardiac outcome of patients with HF, including left cavity dimensions, LV ejection fraction (LVEF), and transmitral flow patterns[1-4]. Some studies demonstrated that tissue Doppler imaging (TDI) parameters were capable of adding prognostic information to predict cardiac death in major cardiac diseases, such as HF[3,5-7], acute coronary syndrome[8,9], acute myocardial infarction[10], and hypertension[11].

Echocardiography is a mainstay of the diagnostic work-up of dyspneic patients[2], with Doppler echocardiography providing useful information regarding LV filling pressure[9]. However, elevated LV filling pressure may be clinically silent. The early diastolic transmitral velocity/early mitral annular diastolic velocity ratio (E/E') has been proposed as the best single Doppler predictor for evaluating LV filling pressure[12,13] and as a good predictor of cardiac death[1,5,6,9,10]. Recently, a new TDI index, E/(E'×S'), that associates a marker of diastolic function (E/E') and a parameter that explores LV systolic performance (systolic mitral annular velocity, S'), had been shown to be useful to assess the LV filling pressure in a heterogeneous population of cardiac patients, regardless of LVEF[14].

We believe that a precise assessment of prognosis in patients with cardiac diseases must take into account parameters that explore global LV function. Therefore, we investigated the value of E/(E'×S') ratio to predict cardiac death in patients with HF.

## Methods

### Patients

We analyzed prospectively 500 consecutive patients, hospitalized at our clinic between October 2006 and September 2007 with HF, in sinus rhythm. We included adult patients (age ≥ 18 years) with exacerbation of symptoms of

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HF with at least 1 New York Heart Association (NYHA) class deterioration, with typical signs of HF and echocardiographic evidence of systolic and/or diastolic LV dysfunction[15]. Patients with inadequate echocardiographic images, congenital heart disease, cardiac pacemaker/defibrillator, significant primary valvular heart disease, acute coronary syndrome at inclusion, coronary revascularization during follow-up, severe pulmonary disease, malignant neoplasia or renal failure, were excluded. The remaining 339 patients formed our study group. The study was approved by the local research ethics committee.

### Echocardiography

Before discharge and in a reasonably stable clinical condition (within 24 hour), our patients underwent an echocardiographic examination with an ultrasonographic system (Vivid 7 General Electric, Milwaukee, WI) equipped with multifrequency transducer. LVEF was calculated from apical two- and four-chamber views using a modified Simpson's rule[16]. Left atrial (LA) volume was calculated using the biplane area-length method at the apical four-chamber and apical two-chamber views at ventricular end-systole (maximum LA size). LA volume was indexed for body surface area[16]. The severity of mitral regurgitation was assessed from the apical views using proximal convergence method; the regurgitant orifice area (ROA) and the regurgitant volume (RV) were determined[17]. Transmitral flow patterns were recorded from apical four-chamber windows with 4-5 mm pulsed-sample Doppler volume placed between mitral valve tips in diastole during five consecutive cardiac cycles. Care was taken to obtain the smallest possible angle between the direction of transmitral flow and the ultrasound beam. Maximal velocities of E and late transmitral flow (A) waves were measured during end-expiratory apnea; the velocities were recorded for five consecutive cardiac cycles, and the results were averaged. Pulsed Doppler signals were recorded at a horizontal sweep of 100 mm/s. The global myocardial index (GMI) was determined using Doppler time intervals measured from mitral inflow and LV outflow Doppler tracings as the sum of isovolumic contraction and relaxation time divided by the ejection time[18]. Measurement of systolic pulmonary artery pressure was performed using the maximal regurgitant velocity at the tricuspide valve by continous Doppler.

The TDI program was set in pulsed-wave Doppler mode. Motion of mitral annulus was recorded in the apical four-chamber view at a frame rate of 80 to 140 frames per second[19]. A 4-5 mm sample volume was positioned sequentially at the lateral and septal corners of the mitral annulus. The peak early diastolic mitral annular velocity (E') was determined. The peak mitral annular systolic velocity (S') was defined as the maximum velocity during systole, excluding the isovolumic contraction. All velocities were recorded for five consecutive cardiac cycles during end-expiratory apnea, and the results were averaged. All TDI signals were recorded at horizontal time sweep set at 100 mm/s accordingly to current guidelines[19]. E/E' and E/(E'×S') were calculated; the average of the velocities from the septal and lateral site of the mitral annulus was used for the analysis. TDI measurements were repeated one month after hospital discharge (30 ± 3 days). Worsening of E/(E'×S') was defined as a value greater than the previous value determined at discharge. An experienced echocardiographer performed all measurements.

The inter- and intra-observer variabilities for E/E', S' and E/(E'×S') were examined. Measurements were performed in a group of 30 randomly selected subjects by one observer at two separate times and by two investigators who were unaware of the other's measurements and of the study time point.

### Clinical Variables Recorded

The following clinical variables were recorded at hospital discharge and included in the prognostic model: age, sex, body mass index, mean arterial pressures, heart rate, etiology of HF, NYHA functional class, N-terminal pro-brain natriuretic peptide (NTproBNP) levels (determined within 30 minutes before or after echocardiography). Prescription of the main therapeutic classes in HF was also recorded.

### Clinical Outcome

Patients were followed for ≥ 24 months. Cardiac death was regarded as the study end- point. The cause of death was determined from hospital documentation, information from attending physicians and death certificate. Cardiac death was defined as a death directly related either to cardiac disease, mainly congestive HF, or sudden death. Non-cardiac death was defined as a death that was not primarily due to cardiac causes.

### Statistical Analysis

Data are expressed as mean ± standard deviation for continuous variables and as proportions for categorical variables. Continuous variables were compared between groups using unpaired *t* test (variables with normal distribution) or Mann-Whitney U test (non-normally distributed variables). Proportions were compared using chi-square test and Fischer's exact test. Univariate Cox proportional hazards analysis was performed to investigate the significance of a number of variables in predicting cardiac death. Variables associated with outcome were put into a multivariate Cox regression model to identify independent predictors of cardiovascular death. The output of this analysis was expressed as hazard ratio with 95% confidence interval. Cumulative mortality curves were obtained using the Kaplan-Meier method. Patients who died of non-cardiovascular causes were censored (as non-events) at date of death. A p value $< 0.05$ was considered significant. Receiver-operator characteristic (ROC) curves were plotted to define cut-off values of independent predictors. Intra-observer variability and inter-observer variability for E/E', S' and E/(E'×S') were measured by the intraclass correlation coefficient and by the coefficient of variation (CV) with the root-mean-square method. The power calculation was conducted using the PS software version 3.0 from Vanderbilt University (Nashville, TN). For the power calculation, the threshold for significance was $\alpha = 0.05$ and the accrual time was 12 months. All other analyses were carried out with the

SPSS, version 18.0 (SPSS Inc., Chicago, Illinois) statistical software. This work was supported by CNCSIS-UEFISCU, project number PN II/RU, code PD 526/2010 and TD 530/2007.

## Results

The current study included 339 consecutive patients (62 ± 13 years; 106 women), hospitalized for HF, in sinus rhythm. The aetiology of HF was coronary artery disease (218 patients), non-ischemic cardiomyopathy (85 patients) and systemic hypertension (36 patients). The mean LVEF was 41 ± 14% and mitral annular velocities from TDI were recordable at both sites in all 339 patients. Baseline characteristics of the overall group are presented in Table 1.

During the follow-up period (average: 35.2 ± 8.8 months) cardiac death occurred in 51 patients (15%). The clinical and echocardiographic characteristics of the group of survivors and non-survivors are presented in Table 2. As compared with patients who did not develop cardiac death, patients who developed cardiac death had significantly higher NTproBNP levels and pulmonary artery systolic pressures, larger LA and LV, lower LVEF, E' and S' velocities and higher values for E, E/A, E/E' and E/(E'×S'). In addition, there was no difference with regard to the distribution of age, gender, etiology of HF, heart rate, mean arterial pressure, body mass index, NYHA class, medication (regarding beta blocker, angiotensin converting enzyme inhibitor/angiotensin receptor antagonist, nitrates and diuretics), E-deceleration time, ORA, RV and GMI. Mean E/(E'×S') at discharge was 3.67 ± 1.69 in patients who developed cardiac death, while it was 1.05 ± 1.09 in the rest ($p < 0.001$).

Figure 1 shows the ROC curve for E/(E'×S') at discharge to predict cardiac death. The optimal cut-off value for E/(E'×S') ratio was 2.83 with 76% sensitivity and 85% specificity. Patients were divided into 2 groups according to E/(E'×S') at discharge: group I consisted of patients with E/(E'×S') ≤ 2.83 (252 patients, 74.3%) and group II with E/(E'×S') > 2.83 (87 patients, 25.7%). Kaplan–Meier analysis showed that the survival rate during follow-up was significantly higher in group I than in group II (log rank, $p < 0.001$) (Figure 2a). The median survival time from the baseline echocardiography

**Table 1 - Baseline characteristics of the overall group of 339 patients with heart failure**

| Characteristics | Data |
|---|---|
| **Clinical characteristics** | |
| Age, years | 62 ± 13 |
| Female/male gender, n (%) | 106 (31.3) / 233 (68.7) |
| Body mass index, kg/m$^2$ | 26.1 ± 4.1 |
| Heart rate, beats/min | 75.5 ± 21 |
| Mean arterial pressure, mmHg | 97.2 ± 14.1 |
| Coronary artery disease, n (%) | 218 (64.3) |
| Non-ischemic cardiomyopathy, n (%) | 85 (25.1) |
| Systemic hypertension, n (%) | 36 (10.6) |
| NYHA class I/II/III/IV, n (%) | 20 (5.9)/167 (49.3)/133 (39.2)/19 (5.6) |
| NTproBNP, pg/ml | 3049 ± 3993 |
| **Medical therapy** | |
| Beta blocker, n (%) | 297 (87.6) |
| ACEI/angiotensin receptor antagonist, n (%) | 323 (95.3) |
| Diuretics, n (%) | 294 (86.7) |
| Digoxin, n (%) | 84 (24.8) |
| Nitrates, n (%) | 223 (65.8) |
| **Echocardiographic parameters** | |
| LV ejection fraction, % | 41 ± 14 |
| Left atrial volume, ml | 92 ± 44 |
| Indexed left atrial volume, ml/m$^2$ | 48 ± 25 |
| Systolic pulmonary artery pressure, mmHg | 40 ± 15 |
| Mitral regurgitant orifice area, mm$^2$ | 27.1 ± 10.1 |
| Mitral regurgitant volume, ml | 37.6 ± 14 |

*ACEI: angiotensin converting enzyme inhibitor; LV: left ventricle; NTproBNP: N-terminal pro-brain natriuretic peptide; NYHA: New York Heart Association.*

**Table 2 - Clinical and echocardiographic characteristics of the groups of patients at hospital discharge**

| Characteristics | Survivors (n = 288) | Cardiac death (n = 51) | p value |
|---|---|---|---|
| **Clinical characteristics** | | | |
| Age, years | 61.8 ± 12.9 | 64.1 ± 11.1 | 0.22 |
| Female/male gender | 88 / 200 | 18 / 33 | 0.51 |
| Body mass index, kg/m$^2$ | 25.7±3.8 | 28.4 ± 5.9 | 0.43 |
| Heart rate, beats/min | 75 ± 17 | 78 ± 22 | 0.47 |
| Mean arterial pressure, mmHg | 97.7 ± 13.8 | 94.8 ± 15.7 | 0.56 |
| Coronary artery disease, n (%) | 186 (64.6) | 32 (62.7) | 0.80 |
| Non-ischemic cardiomyopathy, n (%) | 74 (25.7) | 11 (21.6) | 0.53 |
| Systemic hypertension, n (%) | 28 (9.7) | 8 (15.7) | 0.20 |
| NYHA class I/II/III/IV, n | 17/140/118/13 | 3/27/15/6 | 0.13 |
| NTproBNP, pg/ml | 2454 ± 3039 | 6411 ± 6418 | < 0.001 |
| **Medical therapy** | | | |
| Beta blocker, n (%) | 254 (88.1) | 43 (84.3) | 0.73 |
| ACEI/angiotensin receptor antagonist, n (%) | 276 (95.8) | 47 (92.1) | 0.25 |
| Diuretics, n (%) | 247 (85.7) | 47 (92.1) | 0.21 |
| Digoxin, n (%) | 64 (22.2) | 20 (39.2) | 0.01 |
| Nitrates, n (%) | 187 (64.9) | 36 (70.5) | 0.43 |
| **Echocardiographic variables** | | | |
| LV end-diastolic volume index, ml/m$^2$ | 92 ± 32 | 113 ± 41 | 0.005 |
| LV end-systolic volume index, ml/m$^2$ | 53 ± 26 | 75 ± 29 | 0.008 |
| LV ejection fraction, % | 42 ± 14 | 33 ± 15 | 0.001 |
| Left atrial volume, ml | 87 ± 40 | 118 ± 49 | < 0.001 |
| Indexed left atrial volume, ml/m$^2$ | 45 ± 22 | 65 ± 29 | < 0.001 |
| Systolic pulmonary artery pressure, mmHg | 39 ± 14 | 47 ± 18 | 0.001 |
| Global myocardial index | 0.61 ± 0.42 | 0.72 ± 0.45 | 0.07 |
| Mitral regurgitant orifice area, mm$^2$ | 26.6 ± 10.3 | 29.9 ± 9.8 | 0.41 |
| Mitral regurgitant volume, ml | 37 ± 15 | 41 ± 22 | 0.22 |
| E, cm/s | 79 ± 25 | 101 ± 33 | < 0.001 |
| E/A ratio | 1.14 ± 0.76 | 1.64 ± 1.08 | 0.003 |
| E-deceleration time, ms | 171 ± 75 | 158 ± 71 | 0.27 |
| E', cm/s | 7.4 ± 2.7 | 5.5 ± 1.6 | < 0.001 |
| S', cm/s | 6.9 ± 2.6 | 5.1 ± 1.9 | < 0.001 |
| E/E' ratio | 10.9 ± 4.02 | 18.7 ± 5.91 | < 0.001 |
| E/(E'×S') ratio | 1.57 ± 1.09 | 3.67 ± 1.69 | < 0.001 |

*A: late transmitral flow velocity; ACEI: angiotensin converting enzyme inhibitor; E: early diastolic transmitral flow velocity; E': early mitral annular diastolic velocity; LV: left ventricle; NYHA: New York Heart Association; S': systolic velocity of mitral annulus; NTproBNP: N-terminal pro-brain natriuretic peptide.*

was 42.1 months in the group of patients with E/(E'×S') ≤ 2.83 and 26.2 months in those with E/(E'×S') > 2.83. Statistical analysis showed a power of 81% to detect the difference between median survival times for the two groups. To investigate the possible impact of LVEF, patients with LVEF ≥ 50% (108 patients, 31.9%) and with LVEF < 50% (231 patients, 68.1%) were analyzed separately. In both groups, the survival rate was significantly higher in patients from group I than in those from group II, as shown by Kaplan-Meier plots (Figures 2b and 2c).

Table 3 shows the variables that predicted cardiac death on univariate Cox regression analysis (p < 0.05): NTproBNP levels, LVEF, systolic pulmonary artery pressure, indexed LA volume, E/A ratio, E', S', E/E', E/(E'×S'), and LVEF ≤ 40%

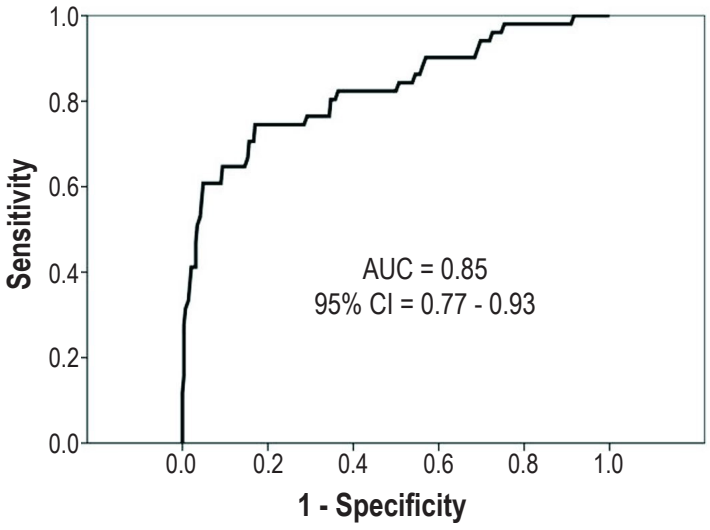


**Figure 1 -** *The receiver-operator characteristic (ROC) curve for E/(E'×S') ratio at hospital discharge to predict cardiac death. AUC: area under ROC curve; E: maximal early diastolic transmitral velocity; E': maximal early mitral annular diastolic velocity using the average of the medial and lateral site of mitral annulus; S': maximal systolic mitral annular velocity using the average of the medial and lateral site of mitral annulus; 95% CI: 95% confidence interval.*

combined with E/E' >15. Conversely, age, sex, heart rate, blood pressure, etiology of HF (coronary artery disease, etc.), NYHA functional class, LV end-diastolic volume index, LV end-systolic volume index, GMI, E-deceleration time, A, RV and ROA, were not significantly associated with cardiac death on univariate analysis. Only variables that affected outcome were included in the multivariate forward Cox regression analysis. This analysis identified E/(E'×S') at discharge as the best independent predictor of cardiac death in patients with HF (HR = 3.09, 95% confidence interval = 1.81-5.31, p = 0.001). Table 3 shows the final multivariate Cox model. Non-cardiac death was similar in group I compared to group II [4 (1.58%) vs. 2 (2.29%), p = 0.66].

The additional benefit of E/(E'×S') to predict cardiovascular death is shown in Figure 3. However, the addition of E/(E'×S') markedly improved the prognostic utility of the model containing LVEF, indexed LA volume, E/E' and S'. We included in this model only the traditional echocardiographic parameters and not all of the variables that predicted cardiac death on univariate analysis.

One month after hospital discharge we identified worsening of E/(E'×S') ratio in 97 patients (28.6%). Of these patients, 37 (10.9%) presented the initial value of E/(E'×S') greater than 2.83. However, as shown in Figure 4, E/(E'×S') worsening was associated with lower survival rate, regardless of the E/(E'×S') value at inclusion in the study (43.2% versus 66%, p = 0.021 in patients with the initial E/(E'×S') > 2.83, and 90.3% vs. 96.3%, p = 0.046 in those with E/(E'×S') ≤ 2.83 at hospital discharge, respectively). The subgroup of patients with an initial E/(E'×S') ratio > 2.83 and its worsening after one month presented the worst prognosis in the overall population, and in those with preserved or reduced LVEF (Figures 4 and 5). This analysis was underpowered (< 80%) because of small sample size, small difference in median survival, and subgroup comparisons.

The intra-observer intraclass coefficients for E/E', S' and E/(E'×S') were 0.95 (CV 2.6%), 0.93 (CV 3.1%), and 0.93 (CV 3%), respectively. The inter-observer intraclass coefficients for E/E', S' and E/(E'×S') were 0.93 (CV 2.8%), 0.91 (CV 3%), and 0.90 (CV 3.2%), respectively.

## Discussion

To the best of our knowledge, this is the first study investigating the value of a new TDI derived index, E/(E'×S') to predict cardiac death in patients with HF, in sinus rhythm. E/(E'×S') ratio at hospital discharge was the strongest predictor of cardiovascular death when compared to several other echocardiographic parameters, coronary artery disease, NYHA functional class and plasmatic NTproBNP levels.

The clinical importance of predicting cardiac death in patients with LV dysfunction has been increasing. Several previous studies with echocardiographic imaging have suggested that LVEF[20], LV volumes indices[20] and LA size[4,21] are strong predictors of outcome in the setting of congestive HF. In our study, LVEF, predictor of outcome on univariate analysis, was eliminated on multivariate analysis. Although indexed LA volume seemed to be a valuable echocardiographic parameter for prediction of cardiovascular death, E/(E'×S') was a better predictor in our patients.

TDI is now widely available on echocardiographic equipment of various manufacturers and is increasingly used in clinical practice but the relative importance of different

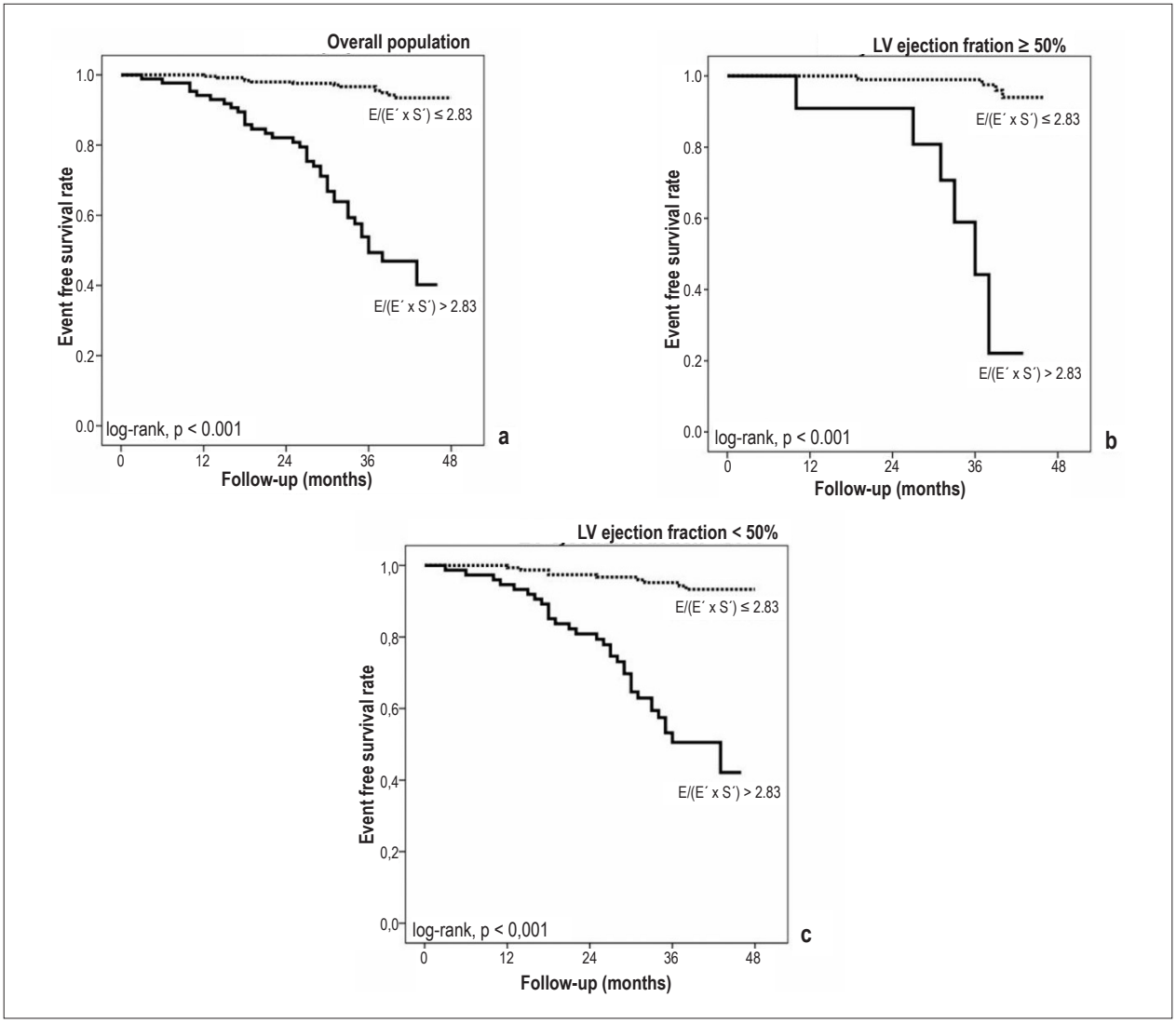


**Figure 2 -** *Kaplan-Meier survival curves in the overall population (339 patients) with heart failure (a), in those with preserved left ventricular (LV) ejection fraction (b), and in those with reduced LV ejection fraction (c), according to E/(E'×S') ratio at discharge below and above 2.83. E: maximal early diastolic transmitral velocity; E': maximal early mitral annular diastolic velocity using the average of the medial and lateral site of mitral annulus; S': maximal systolic mitral annular velocity using the average of the medial and lateral site of mitral annulus.*

variables remains to be firmly established. This new technique does not require tracing of endocardial contours, unlike LV volumes and LVEF[20]. The E/E' ratio has been proposed as the best single Doppler predictor for evaluating LV filling pressure[12,13]. In a previous study we demonstrated that a new TDI index including peak systolic velocity of mitral annulus (S') and E/E' ratio, E/(E'×S'), was useful to assess the LV filling pressure, regardless of LVEF[14]. Recent studies have addressed the prognostic implication of TDI parameters in major cardiac diseases, such as HF[3,5-7], acute coronary syndrome[8,9], acute myocardial infarction[10], and hypertension[11].

Wang et al[22] showed in a heterogeneous population of cardiac patients that both S' and E' velocities were predictors of cardiac mortality on univariate analysis, but that E' velocity was marginally superior on multivariate analysis. Other studies reported that E/E' ratio[1,5,6,9,10] and S' wave[20] were strong independent predictors of cardiac death in populations with systolic HF. Møller et al[23] studied a group of patients after first myocardial infarction and reported that E/E' was an independent predictor of all-cause death. More recently, Hirata et al[1] showed that a combined index including LVEF ≤ 40% and E/E' > 15 allowed the identification of patients at higher risk of cardiac outcome in patients with HF. This combined parameter was a good predictor of outcome on univariate analysis in our study, but it was eliminated on multivariate analysis. The present study has shown, for the first time, that E/(E'×S') is a strong independent echocardiographic predictor of cardiovascular death in patients with HF. It retains its prognostic value after adjustment for clinical data and other echocardiographic, conventional Doppler, and TDI indices. The superiority of

**Table 3 - Clinical, laboratory, and echocardiographic variables at hospital discharge associated with cardiac death in Cox univariate and multivariate analysis**

| Variables | Univariate HR (95% CI) | p-value | Multivariate HR (95% CI) | p-value |
|---|---|---|---|---|
| NTproBNP levels | 1.03 (1.01-1.05) | 0.002 | NA | NA |
| LVEF | 0.95 (0.93-0.97) | 0.003 | NA | NA |
| PASP | 1.03 (1.01-1.05) | 0.001 | 1.02 (0.97-1.03) | 0.029 |
| Indexed left atrial volume | 1.03 (1.02-1.04) | 0.001 | 1.03 (1.01-1.04) | 0.018 |
| E/A ratio | 1.72 (1.35-2.19) | 0.001 | NA | NA |
| E' velocity | 0.67 (0.57-0.81) | 0.001 | NA | NA |
| S' velocity | 0.62 (0.51-0.75) | 0.009 | NA | NA |
| E/E' ratio | 1.24 (1.17-1.3) | 0.007 | NA | NA |
| E/(E'×S') ratio | 2.41 (2.02-2.85) | 0.001 | 3.09 (1.81-5.31) | 0.001 |
| LVEF ≤ 40% and E/E'>15 | 6.88 (3.94-12.02) | 0.001 | NA | NA |

*A: late diastolic transmitral velocity; CI: confidence interval; E: early diastolic transmitral velocity; E': mitral annular diastolic velocity; HR: hazard ratio; LVEF: left ventricular ejection fraction; S': systolic velocity of mitral annulus; NA: not applicable; NTproBNP: N-terminal pro-brain natriuretic peptide; PASP: pulmonary artery systolic pressure.*

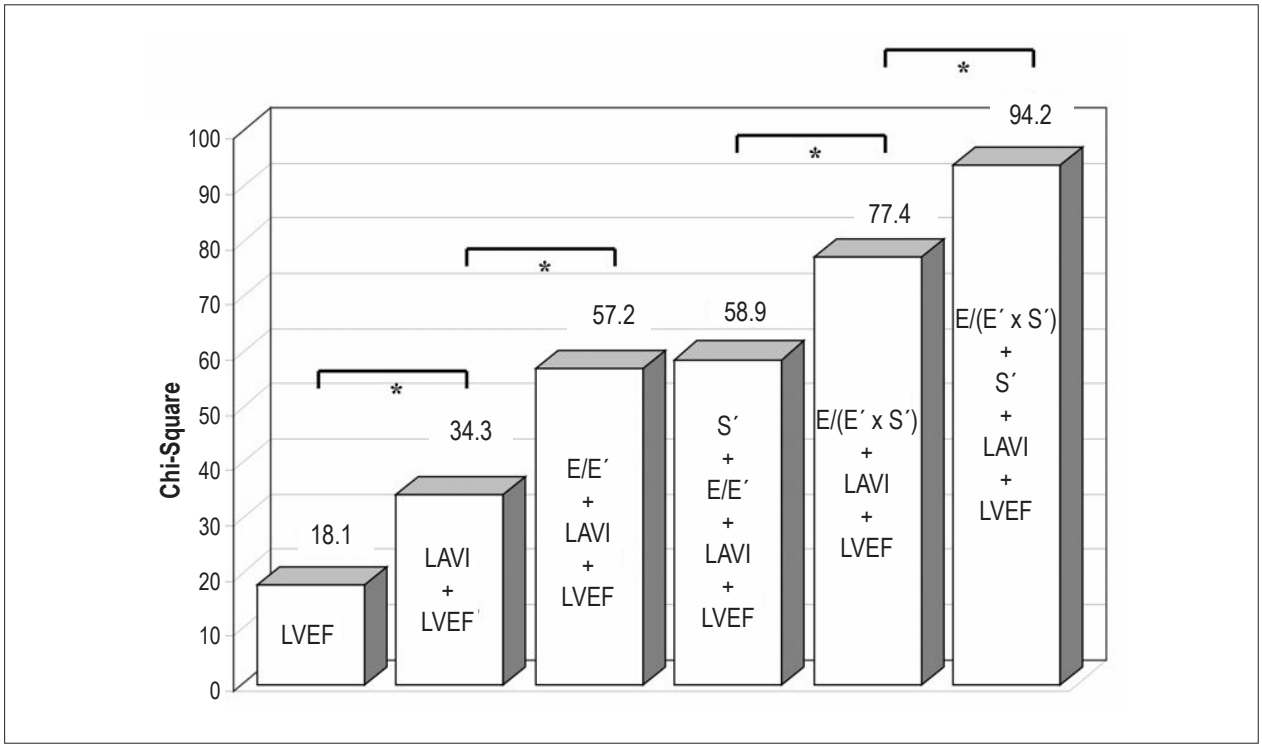


**Figure 3 -** *The additional benefit of E/(E'×S') at hospital discharge to predict cardiac death. The addition of E/(E'×S') markedly improved the prognostic utility of the model containing left ventricular ejection fraction (LVEF), left atrial volume index (LAVI), E/E' ratio and S' wave. E: maximal early diastolic transmitral velocity; E': maximal early mitral annular diastolic velocity using the average of the medial and lateral site of mitral annulus; S': maximal systolic mitral annular velocity using the average of the medial and lateral site of mitral annulus.* *p < 0.05

E/(E'×S') ratio over the combined index LVEF ≤ 40% and E/E' > 15 can be attributed to the capacity of reduced S' velocity to identify LV dysfunction in subjects with normal LVEF[24]. The survival rate was significantly higher in patients with E/(E'×S') ≤ 2.83 at discharge than in group with E/(E'×S') > 2.83, regardless of LVEF. The subgroup of patients with an initial E/(E'×S') ratio > 2.83 and its worsening after one month presented the worst prognosis. This result may have implications for the risk stratification of this patient population.

In our study, differently from what is observed in the literature, plasmatic NTproBNP level was not a good predictor of death. However, in these studies were included patients

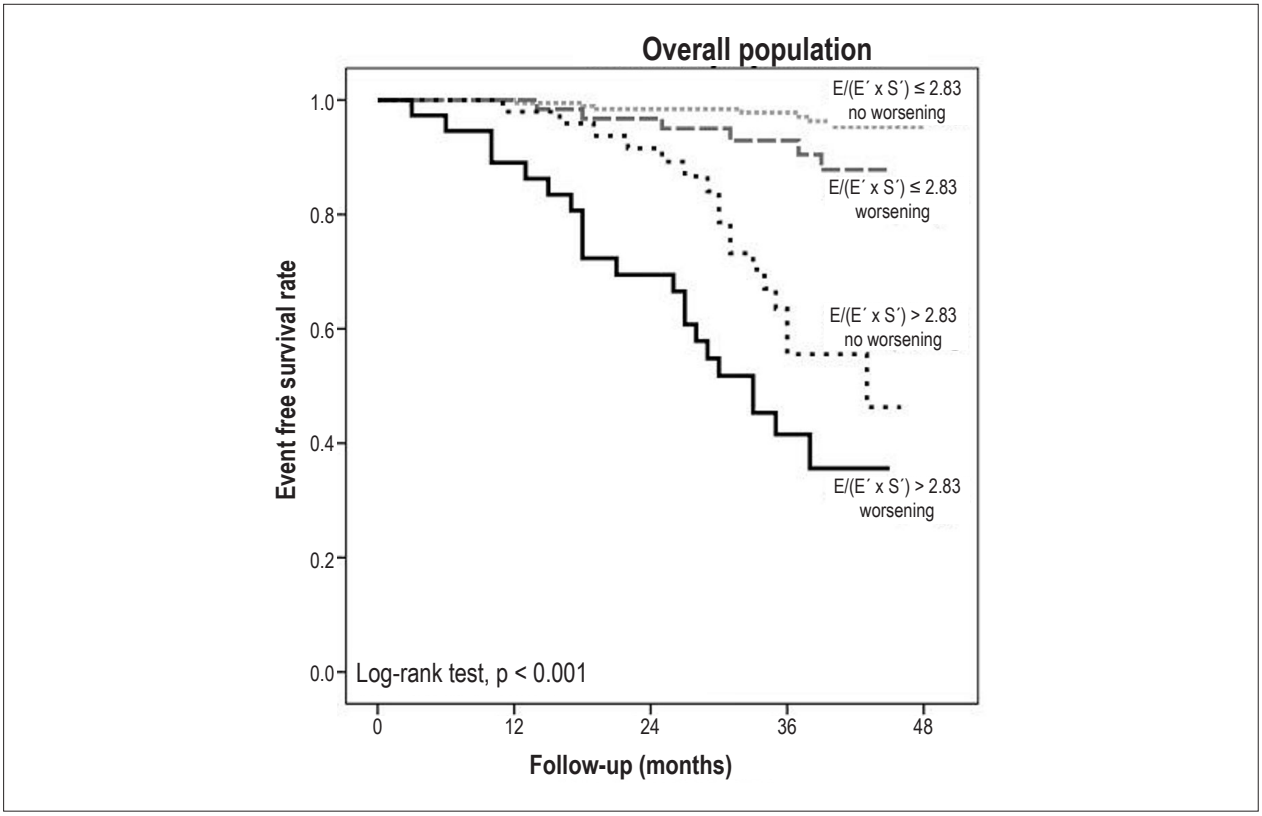


**Figure 4 -** *Kaplan-Meier survival curves of patients classified according to the initial E/(E'×S') value and to E/(E'×S') worsening one month after hospital discharge. The percent of survival was 96.3% in patients with initial E/(E'×S') ≤ 2.83 and no worsening, 90.3% in patients with E/(E'×S') ≤ 2.83 and worsening after one month, 66% in patients with E/(E'×S') > 2.83 and no worsening, and 43.2% in those with initial E/(E'×S') > 2.83 and worsening at one month, respectively. E: maximal early diastolic transmitral velocity; E': maximal early mitral annular diastolic velocity using the average of the medial and lateral site of mitral annulus; S': maximal systolic mitral annular velocity using the average of the medial and lateral site of mitral annulus.*

presenting to the emergency department with dyspnea[25], consecutive patients with acute or chronic HF[26,27] or LV systolic dysfunction[28]. In our population, we performed echocardiography and NTproBNP determination after appropriate medical treatment. Statistical analysis of our data supports the observation that NTproBNP has prognostic value but it is inferior to E/(E'×S') index.

Coronary artery disease was highly prevalent in the present series and one cannot rule out the occurrence of ischemic events contributing to the death of the patients. In our study, the presence of coronary artery disease was not a predictor of cardiovascular death.

Our results should be considered in the context of several limitations. The number of patients in this study was relatively small; however, we were able to reach several significant observations. We deliberately did not use sophisticated Doppler parameters that are more difficult to record and thus are not suitable for daily practice. We have limited TDI measurements at two sites (medial and lateral mitral annulus) and we did not examine anterior and posterior velocities that might have provided additional information. The study centre functioned as a tertiary invasive centre and therefore the study population may not reflect a general population of patients with HF. Our study is a single-center study and its reproduction in other centers or by multicenter studies may argue for its validity. Future studies are also necessary to compare the prognostic value of E/(E'×S') ratio with that of the newer parameters analyzing myocardial deformation, like LV longitudinal strain, strain rate and/or torsion determined by two- or three- dimensional echocardiography.

## Conclusion

Our findings indicate that in patients with HF, in sinus rhythm, the novel TDI derived index, E/(E'×S'), is an important independent long-term prognostic index of cardiac death. Regardless of LVEF, an E/(E'×S') value > 2.83 at hospital discharge can identify patients at high risk of cardiovascular death, particularly if it is associated with worsening after one month.

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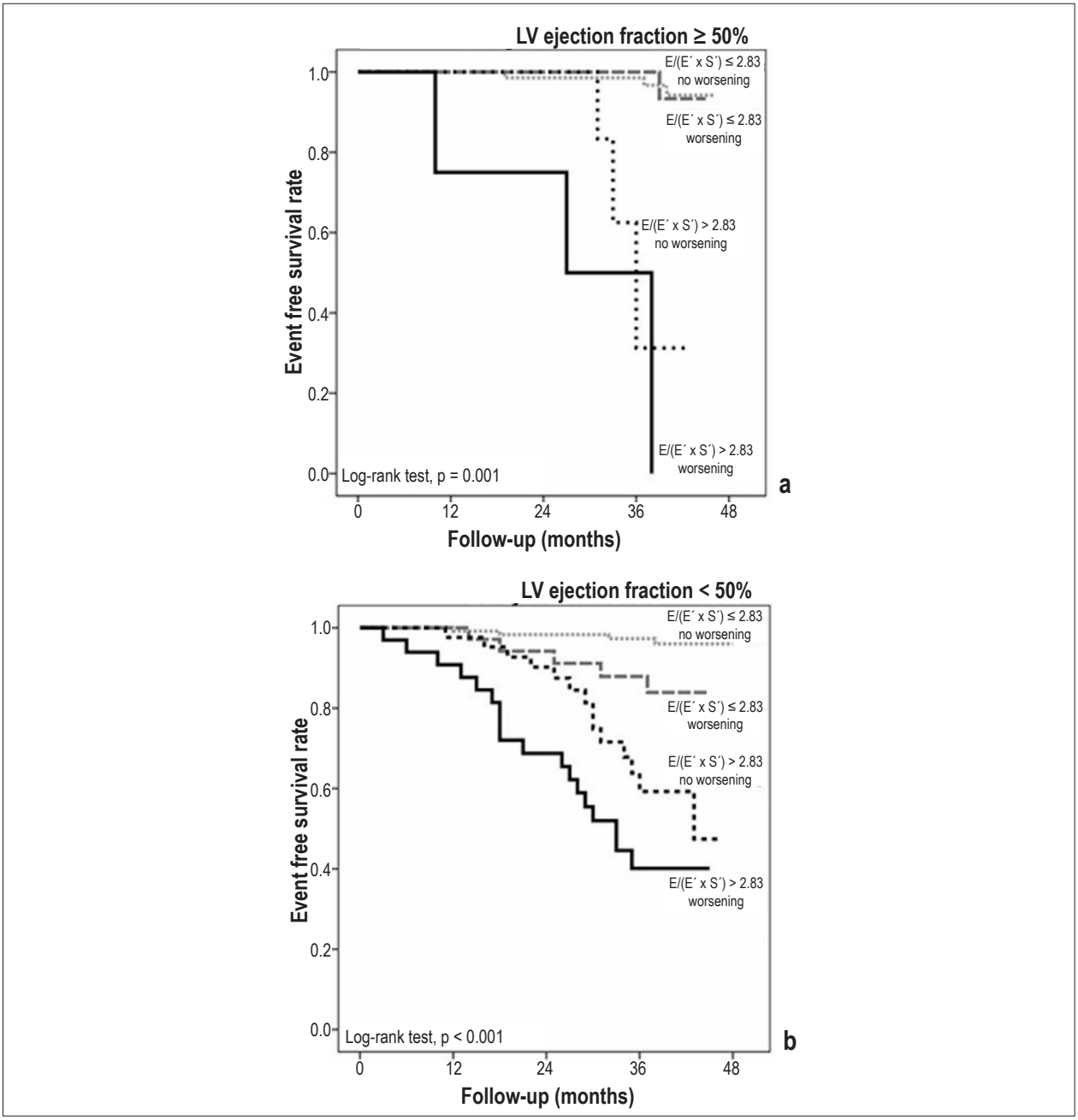


**Figure 5 -** *Kaplan-Meier survival curves of patients classified according to the initial E/(E'×S') value and to E/(E'×S') worsening one month after hospital discharge:* **a)** *in patients with left ventricular ejection fraction ≥50%, the percentage of survival was 95.7% in those with initial E/(E'×S') ≤2.83 and no worsening, 96.3% in patients with E/(E'×S') ≤2.83 and worsening after one month, 62.5% in patients with E/(E'×S') >2.83 and no worsening, and 25% in those with initial E/(E'×S') >2.83 and worsening at one month, respectively;* **b)** *in patients with left ventricular ejection fraction <50% the percentage of survival was 95.7% in those with initial E/(E'×S') ≤2.83 and no worsening, 85.7% in patients with E/(E'×S') ≤2.83 and worsening after one month, 66.7% in patients with E/(E'×S') >2.83 and no worsening, and 45.5% in those with initial E/(E'×S') >2.83 and worsening at one month, respectively. E: maximal early diastolic transmitral velocity; E': maximal early mitral annular diastolic velocity using the average of the medial and lateral site of mitral annulus; S': maximal systolic mitral annular velocity using the average of the medial and lateral site of mitral annulus.*

## Author contributions

Conception and design of the research: Mornos C, Petrescu L, Cozma D, Ionac A. Acquisition of data: Mornos C, Petrescu L, Cozma D. Analysis and interpretation of the data: Mornos C, Petrescu L, Cozma D, Ionac A. Statistical analysis: Mornos C, Cozma D. Writing of the manuscript: Mornos C, Petrescu L, Cozma D, Ionac A. Critical revision of the manuscript for intellectual content: Mornos C, Petrescu L, Cozma D, Ionac A. Supervision / as the major investigator: Mornos C, Petrescu L, Ionac A.

### Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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### Study Association

This study is not associated with any post-graduation program.

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