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Original Article

Assessment of right ventricular systolic function in heart failure with preserved, reduced and mid-range ejection fraction

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ABSTRACT

Background: Few studies have evaluated the right ventricle systolic function in different categories of heart failure despite its effect on outcomes.

Methods and results: Single-centre, cross-sectional study included 150 patients, 50 patients in each category of HF: group I, preserved; group II, mid-range; group III, reduced ejection fraction. Left ventricular systolic function was assessed by 3D echo, and right ventricular systolic function was assessed by fractional area change (FAC), tricuspid annular plane systolic excursion (TAPSE), tissue Doppler image (TDI), and global longitudinal strain (GLS). There was no significant difference among the three groups regarding sex, the prevalence of risk factors, but patients in group III were significantly older ($p < 0.001$) and had a higher prevalence of coronary artery disease ($p = 0.004$) than were found in the other two groups. In group I, the prevalence of RV systolic dysfunction was 18%, 22%, 14% and 26% by TAPSE, FAC, S wave velocity, and GLS, respectively. Their prevalence was higher in group II and much higher in group III than in group I. There were significant positive correlations among TAPSE, S wave velocity, GLS, and ejection fraction in groups II and III ($p < 0.001$).

Conclusion: The prevalence and severity of RV systolic dysfunction were positively correlated with LV systolic dysfunction, and the degree of RV dysfunction in mid-range was closer to reduce than preserved ejection fraction.

Study registration at clinical trial.gov: NCT03641599.

1. Introduction

Previous European Society of Cardiology (ESC) heart failure (HF) guidelines established two categories of HF: HF with reduced ejection fraction (HFrEF), in which the left ventricular (LV) ejection fraction (LVEF) is below 50%; and HF with preserved ejection fraction (HFpEF), in which the LVEF exceeds 50%. However, the many clinical trials that have evaluated the outcomes of different therapeutic strategies in HFrEF have usually included patients with a LVEF less than 40%. Therefore, a borderline area has arisen consisting of patients who are not well represented in clinical trials of HFrEF and do not have a normal LVEF.

HF with borderline ejection fraction was first defined in 2013 in the American College of Cardiology/American Heart Association guidelines as the presence of typical symptoms of HF and a LVEF of 41%–49%. In 2016, the ESC specified that HF with mid-range ejection fraction (HFmrEF) was defined as an LVEF of 40%–49%.[1–13]

Four elements are simultaneously required for a positive diagnosis of HF: (i) symptoms with or without signs of HF, (ii) LVEF of 40–49% for mid-range group, (iii) elevated natriuretic peptides (BNP ≥35 pg/mL or NT-proBNP ≥125 pg/mL), and (iv) relevant structural heart disease, such as LV hypertrophy (LV mass index ≥115 g/m^2 in males and ≥95 g/m^2 in females), left atrial enlargement (>34 mL/m^2), or diastolic dysfunction ($E/e' \geq 13$ and a mean e' septal and lateral wall <9 cm/s).[2]

HFmrEF has a prevalence of 10–20% of HF patients. Compared with HFrEF and HFpEF, HFmrEF has distinct but intermediate clinical, structural, and functional characteristics as well as intermediate outcomes.[3]

Previous studies have demonstrated that right ventricular (RV) dysfunction is common in patients with reduced and preserved EF and associated with poor outcomes.[4,5] However, the prevalence of RV dysfunction and the characteristics of RV function in HFmrEF have not been well studied; increasing our knowledge of these parameters might help us to better understand this group of HF.

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2. Aim

The aim of this study was to assess the prevalence and severity of RV systolic dysfunction in patients with HF and the correlations between RV and LV systolic function in HFpEF, HFrEF, and HFmrEF.

3. Patients and methods

3.1. Study design

This single-centre, prospective, cross-sectional study evaluated 150 patients, including 50 patients with each category of HF (preserved, reduced, and mid-range ejection fraction) who sought medical advice at the outpatient clinic or were admitted to the cardiology department from January 2017 to June 2018. All patients provided signed informed consent, and the study was approved by the local ethical committee.

3.2. Inclusion criteria

Adult patients of both sexes were included if they fulfilled the following criteria: (i) symptoms with or without signs of HF, (ii) elevated natriuretic peptides (BNP $\geq$ 35 pg/mL or NT-proBNP $\geq$ 125 pg/mL), and (iii) relevant structural heart disease: LV hypertrophy (LV mass index $\geq$115 g/m^2 in males and $\geq$95 g/m^2 in females), left atrial enlargement (>34 mL/m^2) or diastolic dysfunction (E/e′ $\geq$ 13 and a mean e′ septal and lateral wall <9 cm/s).[2] The patients were then classified according to EF into HFpEF >50%, HFrEF <40%, and HFmrEF between 40% and <50%.

3.3. Exclusion criteria

Patients with chronic obstructive pulmonary disease, organic valvular heart disease, rhythm other than sinus rhythm, history of pulmonary embolism, or respiratory failure were excluded.

3.4. Methods

3.4.1. Echocardiography

All patients were examined while in the left lateral position using a PHILIPS (EPIC 7C) machine with a multi-frequency transducer. Standard views for two-dimensional and M-mode were used for tissue Doppler image (TDI). Measurements were obtained according to the recommendations of the American Society of Echocardiography for assessment of RV systolic function,[6] which included the following parameters:

- RV fractional area change (FAC) was calculated as follows: (RV end-diastolic area − RV end-systolic area)/RV end-diastolic area (normal value $\geq$35%);
- Tricuspid annular plane systolic excursion (TAPSE) was measured in the apical four-chamber view using the two-dimensional maximal amplitude of lateral tricuspid annular movement from the end-diastolic frame to the end-systolic frame (normal valve $\geq$16 mm);
- Tricuspid S wave velocity was measured at peak systolic velocity by TDI of the lateral tricuspid annulus (normal value $\geq$9.5 cm/s);
- Pulmonary artery systolic pressure (PASP) was estimated by adding the pressure gradient between the RV and the right atrium according to the peak continuous-wave Doppler velocity of the TR jet (obtained using a modified Bernoulli equation) to the estimated right atrial pressure, which was estimated from inferior vena caval size and collapsibility with respiration;
- Global longitudinal systolic strain (GLS) was measured as follows: speckle tracking was evaluated by recording three consecutive end-expiratory cardiac cycles using the frame rate (70–80 frames/s), and harmonic imaging was acquired in the apical four-chamber view for quantification of peak systolic strain by automated function imaging speckle tracking analysis (normal value $\geq$−20%).

3.4.2. 3D assessment of LV systolic function

Apical 3D full volume was determined as follows: 4R wave-triggered sub-volumes were acquired for four consecutive cardiac cycles during breath-holding to form a larger pyramidal volume including the entire LV. The 3D dataset was then stored for offline analysis. The software displayed the apical 4, 2, and 3 chambers and short-axis views. In each image, manual adjustment of the axis was used to obtain the best orientation of the apical views and avoid LV fore-shortening. After manual identification of the mitral valve plane and the apex with two reference points on the end-diastolic and end-systolic frames, the software identified the endocardial border in each frame, an LV 3D model was then generated, and LV volumes and LEVEF were then calculated.

3.5. Statistical methods

Data management and statistical analyses were performed using SPSS software ver. 25. Numerical data are summarized as means and standard deviations. Categorical data are summarized as numbers and percentages. Comparisons among the three groups with regard for normally distributed numeric variables were performed using ANOVA. Categorical variables were compared using the Chi-square test. Pearson correlations were performed. "*r*" is the correlation coefficient and it ranged from −1 to +1, with −1 indicating a strong negative correlation, +1 indicating a strong positive correlation, and 0 indicating no correlation. All *p*-values were two-sided. *p*-values less than 0.05 were considered significant. The *p*-values were adjusted for multiple comparisons.

4. Results

This study included 150 patients, with 50 patients in each category:

Group I included 50 patients with HFpEF.
Group II included 50 patients with HFmrEF, and
Group III included 50 patients with HFrEF.

4.1. Demographic data, symptoms, risk factors, and comorbidities

There were no significant differences among the three groups regarding sex, symptoms, the prevalence of risk factors (diabetes, hypertension, smoking, and obesity), or chronic renal disease; however, patients in group III were significantly older (*p*-value <0.001) and had a higher prevalence of coronary artery disease (CAD) than were found in the other two groups (*p*-value, 0.004) (Tables 1, 2 and 3).

4.2. Right ventricular systolic function

Four measurements were used to assess RV systolic function: TAPSE, FAC, S velocity, and GLS. All of these parameters gradually declined from group I to group III, and the difference among the groups was significant with an overall *p*-value of <0.001 (Table 2).

Table 1
Demographic, risk factors, comorbidity, and symptoms of study population.

Age (years) mean ± SD		Group I ($n = 50$)		Group II ($n = 50$)		Group III ($n = 50$)		*P* value
		50 ± 7[a]		52 ± 8[a]		63 ± 6[b]		<0.001
		N	**%**	***N***	**%**	***N***	**%**	
Sex	Male	37	74.0	31	62.0	39	78.0	0.184
	Female	13	26.0	19	38.0	11	22.0	
DM		9	18.0	12	24.0	17	34.0	0.178
HTN		14	28.0	11	22.0	9	18.0	0.485
Smoking		14	28.0	12	24.0	14	28.0	0.873
Obesity		10	20.0	12	24.0	11	22.0	0.89
Renal		4	8.0	2	4.0	9	18.0	0.056
CAD		7	14.0	13	26.0	22	44.0	0.004
NYHA	II	28	56.0	25	50.0	22	44.0	0.864
	III	20	40.0	18	36.0	17	34.0	
	IV	2	4.0	7	14.0	11	22.0	

One-way ANOVA was used for age, chi-square test was used for gender, different letters indicate significant pair. All post hoc comparisons were Bonferroni adjusted.

Table 2
RV systolic function in heart failure groups.

	Group I ($n = 50$)			Group II ($n = 50$)			Group III ($n = 50$)			*P* value
	Mean	±SD	Prevalence of dysfunction *N* (%)	Mean	±SD	Prevalence of dysfunction *N* (%)	Mean	±SD	Prevalence of dysfunction *N* (%)	
TAPSI	16.7[a]	2.5	**9** (18%)	15.4[b]	1.9	18 (36%)	14.3[b]	2.9	25 (50%)	<0.001
FAC	35[a]	5	11 (22%)	31[b]	4	36 (72%)	28[c]	6	38 (76%)	<0.001
PASP	27[a]	5	7 (14%)	31[b]	8	10 (20%)	31[b]	9	22 (44%)	0.006
TDI S	11.2[a]	1.9	13 (26%)	9.2[b]	1.2	20 (40%)	8.5[b]	1.4	32 (64%)	<0.001
GLS	−19.8[a]	2.1	13 (26%)	−18.7[a]	2.6	20 (40%)	−16.1[b]	3.6	34 (68%)	<0.001

One-way ANOVA was used. Post hoc analysis was done, and different letters indicate significant pair. All post hoc comparisons were Bonferroni adjusted.

The prevalence of RV systolic dysfunction was significantly low in group I, in which the prevalence of RV systolic dysfunction was 18%, 22%, 14%, and 26% by TAPSE, FAC, S velocity, and GLS, respectively. The prevalence of these parameters were higher in group II, at 36%, 72%, 40%, and 40%, respectively, and much higher in group III, at 50%, 76%, 64%, and 68%, respectively (Table 2, Figs. 1, 2 and 3).

The prevalence was 7% in group I, 15% in group II, and 20% in group III when the four parameters were used together for the assessment of RV dysfunction (*p*-value, 0.014).

4.3. Right ventricular systolic function and PASP

PASP was within the normal range in group I but slightly increased in groups II and III. The difference was significant overall (*p*-value <0.001) and between groups I and II (*p*-value 0.02) and groups I and III (*p*-value 0.047) but insignificant between groups II and III (*p*-value 0.999).

Additionally, there was a significant negative correlation between PASP and all parameters related to RV systolic function (TAPSE, FAC, S velocity, and GLS; *p*-value <0.001).

Table 3
Correlation between RV systolic function parameters and LV EF%.

		Group I ($n = 50$)	Group II ($n = 50$)	Group III ($n = 50$)
TAPSI	*r*	−0.144	0.746**	0.776**
	P value	0.317	<0.001	<0.001
FAC	*r*	−0.125	0.507**	0.155
	P value	0.386	<0.001	0.281
PASP	*r*	0.016	−0.407**	−0.331*
	P value	0.912	0.003	0.019
TDI S	*r*	−0.137	0.591**	0.687**
	P value	0.342	<0.001	<0.001
GLS	*r*	−0.198	0.715**	0.766**
	P value	0.168	<0.001	<0.001

** Significant correclation.

4.4. Correlation between RV systolic function parameters and EF%

There were no significant correlations between the parameters related to RV systolic function and LV systolic function in group I, but there was a significant positive correlation among TAPSE, S velocity, GLS, and EF in group II (*p*-value <0.001). In group III, there was a significant positive correlation among TAPSE, FAC, S velocity, GLS, and EF (*p*-value <0.001) (Table 3, Fig. 2).

4.5. Left ventricular systolic function and PASP

There was a negative correlation between EF and PASP that was significant in groups II (*p*-value, 0.003) and III (*p*-value = 0.019) but insignificant in group I, where the *p*-value was 0.912 (Fig. 3).

5. Discussion

Only a few studies have evaluated RV systolic function in the three categories of HF with regard for the importance of understanding changes in RV function and their effects on clinical presentation and outcomes; it is essential to define the prevalence and severity of RV dysfunction among the three groups and the degree of correlation between RV and LV systolic functions.

RV function has not been well studied in HFrEF; while it was recently studied in HFpEF, with the development of the new classification of HF (into preserved, mid-range, and reduced), the definition and orientation of the mid-range group is unclear.

Andreea et al.[3] asked whether HF with mid-range ejection fraction was a new category of HF or still a grey zone. There may be substantial heterogeneity among patients with HFmrEF, as this group may include patients with *de novo* HF, HF patients with previously reduced LVEF who have since recovered their systolic function, or patients with deteriorated EF.

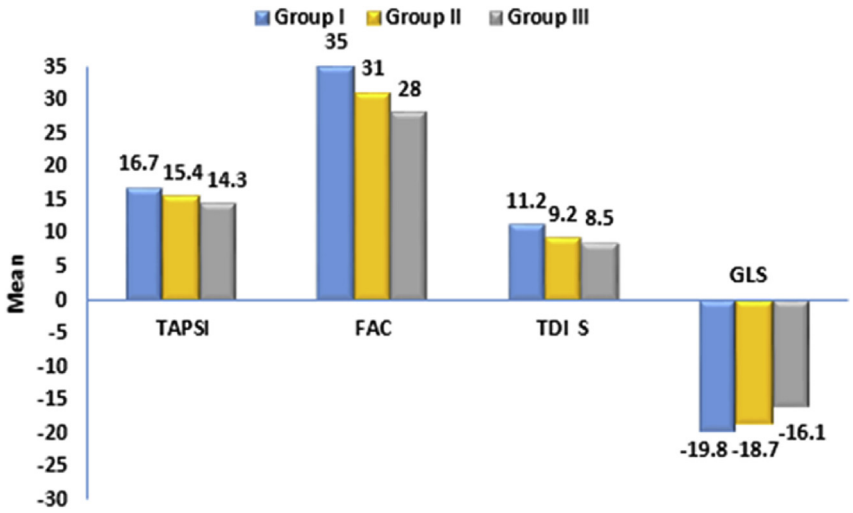

Fig. 1. The prevalence and severity of RV dysfunction in HF categories.

Consequently, a gap has arisen in our knowledge of LVEF between 40% and 49%. Recent studies focussing on these patients have presented the same conclusions or sometimes presented contradictory findings. Extensive research is recommended to improve our knowledge about this group of patients, and this study focused on the assessment of systolic function in the RV, which is sometimes called the forgotten chamber.

The main findings of this study are as follows: (i) the prevalence and severity of RV systolic dysfunction is correlated with LV systolic function, (ii) all parameters measured for RV systolic function (TAPSE, FAC, S velocity, and GLS) were positively correlated with EF in groups II and III, (iii) significantly negatively correlated between EF and PASP in groups II and III, and (iv) significantly negatively correlated between PASP and all parameters for RV systolic function.

The three groups of patients were comparable with regard for sex and the prevalence of risk factors and comorbidities except for CAD, which was more prevalent in group III than in groups I and II, and age, with patients older in group III than in groups I and II.

Our previous results show that RV systolic dysfunction gradually declined with EF; however, the results in group II were closer to those in group III than group I. As mentioned previously, the results of earlier reports are conflicting. Here, we review the results of some studies of HFmrEF:

Jeffrey et al.[7] found that patients with HFmrEF had clinical profiles and prognoses that were closer to those of patients with HFpEF than those of HFrEF, with certain distinctions. In contrast, Nauta et al.[8] found that HFmrEF more closely resembled HFrEF than HFpEF.

Andreea et al.[3] found that background aetiology and risk factors were similar among patients with different types of HF. However, Kapoor et al.[9] showed that patients with HFmrEF were older and more likely to be female and have a high comorbidity burden (diabetes, atrial fibrillation, chronic obstructive pulmonary disease, and renal insufficiency), making this population highly similar to the HFpEF population. However, similar to HFrEF, HFmrEF was strongly associated with ischaemic heart disease. Nadruz et al.[10] concluded that HFmrEF seemed to have intermediate clinical characteristics between those of HFrEF and HFpEF.

In this study, AF patients were excluded for proper 3D assessment of LV function and measurement of GLS. However, AF was more common in HFpEF than in HFmrEF and more common in HFmrEF than in HFrEF and was associated with similarly increased risks of death, HF hospitalization, and stroke or TIA among all ejection fraction groups.[11]

Few reports have evaluated RV function in different categories of HF:

Robaeys et al.[12] studied pulmonary function tests, RV diameter, TAPSE, and PASP in 168 patients with different categories of HF and found that pulmonary and RV dysfunction were frequently present in HF irrespective of LVEF.

However, another study found that correlations with RV dysfunction were different between the HFrEF group and the HFpEF and HFmrEF groups. Regardless of the extent of LV dysfunction, the TAPSE/PASP ratio was a powerful independent predictor of prognosis in all HF patients. The authors concluded that the correlates were different but the prognostic implications for RV dysfunction similar between HF patients with reduced or preserved ejection fraction.[13]

6. What is new?

Few studies have evaluated the right ventricle (RV) systolic function in the three categories of heart failure (HF) despite its effect on presentation and outcomes.

The unique finding reported in this study is the methodology used for the assessment of RV and LV systolic function. In the LV, 3D echo replaced the conventional 2D method to overcome its limitations (it applies to only two sections of the LV, assumes a symmetric shape of the LV, and is inaccurate in remodelled or aneurismal LVs and apical foreshortening), and 3D echo allowed a more accurate and reproducible assessment of the LVEF without geometric assumptions, similar to those measured by cardiac magnetic resonance imaging.

With regard for the RV, four different methods were used, including 2D (FAC), M-Mode (TAPSE), TDI (S velocity), and 2D strain (GLS), in a trial to incorporate their different parameters, each of which has its own advantages and limitations.

7. Study limitations

This study included a small number of patients, lacked an invasive assessment of RV function, and lacked a prospective assessment of the effect of RV dysfunction on outcomes.

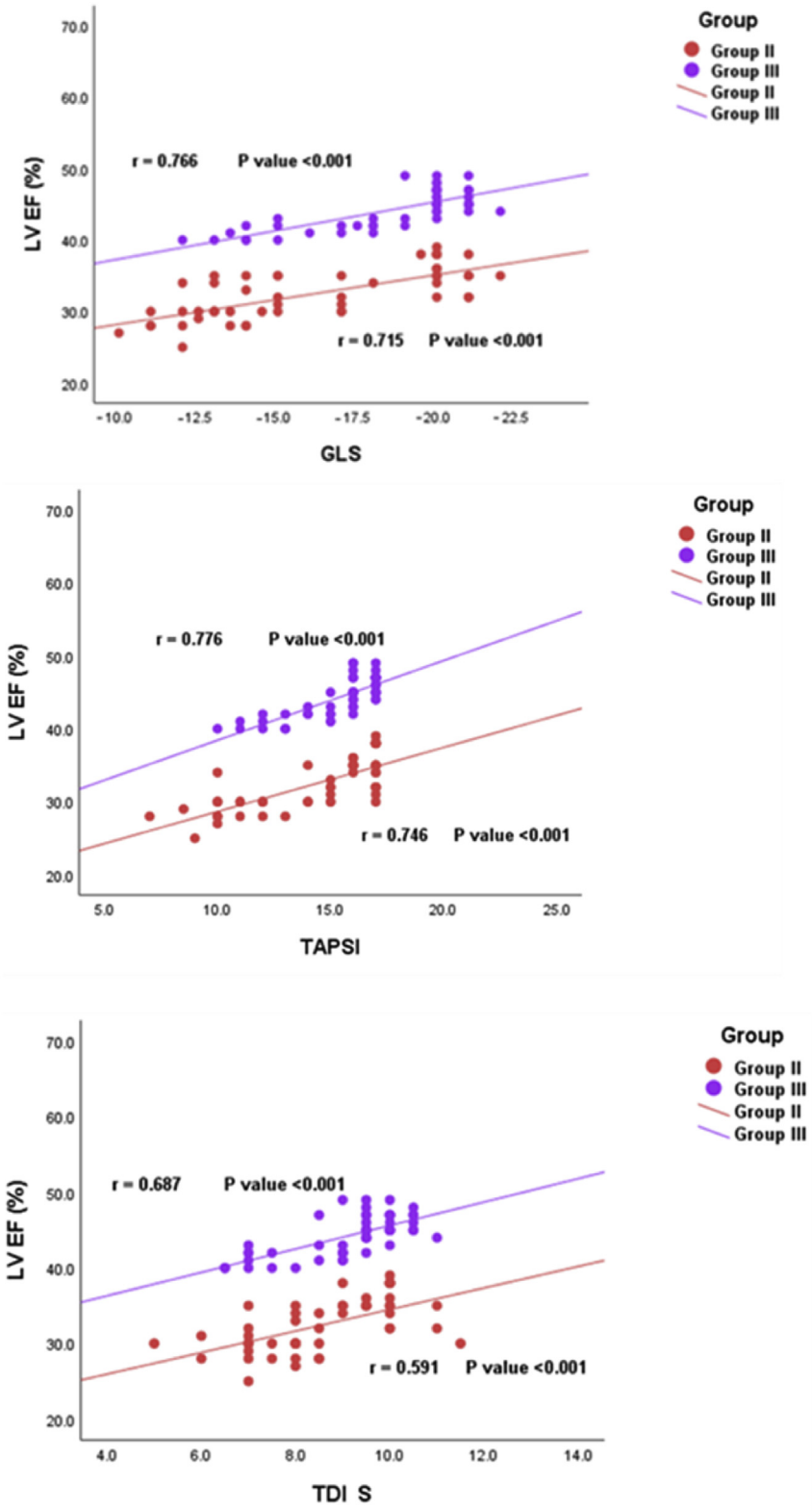

Fig. 2. Correlation between TAPSE, TDI S velocity, GLS, and EF%.

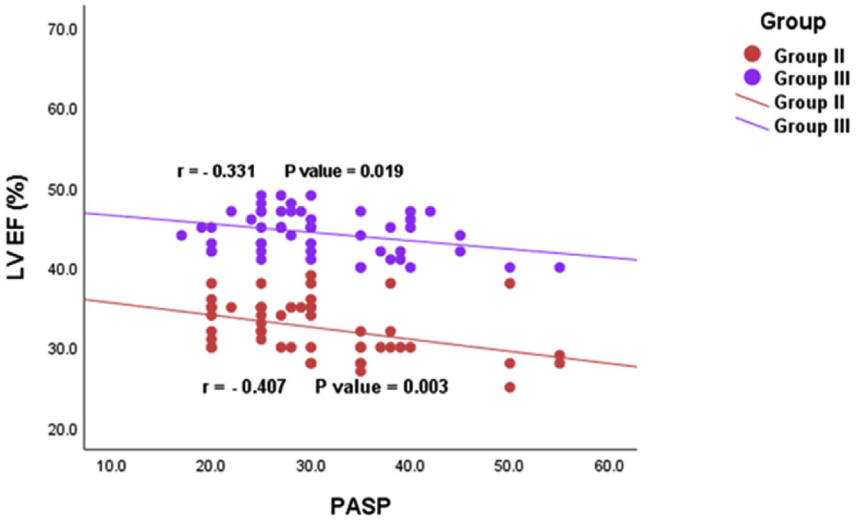

Fig. 3. The correlation between LVEF and PASP.

8. Conclusion

The prevalence and severity of RV systolic dysfunction are positively correlated with LV systolic dysfunction, and the degree of RV dysfunction in HFmrEF was closer to that in HFrEF than HFpEF.

Declaration of competing interest

The author has no conflict of interest to declare.

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