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Prognostic value of non-invasive right ventricle-pulmonary artery coupling in patients with pulmonary hypertension associated with left heart disease

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Abstract

Objective This study aims to assess the prognostic significance of non-invasive right ventricle-pulmonary artery coupling in patients with pulmonary hypertension associated with left heart disease (PH-LHD) and identify the relevant clinical factors involved.

Methods A cohort of 362 patients diagnosed with PH-LHD was included in this study. Plasma N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels were measured using enzyme-linked immunosorbent assay (ELISA). Echocardiography was employed to screen routine ultrasound parameters. The tricuspid annular plane systolic excursion/pulmonary artery systolic pressure (TAPSE/PASP) and S'/PASP ratios were calculated. Participants were categorized into two groups based on the TAPSE/PASP ratio: moderate-to-severe and mild uncoupling groups. Both groups underwent routine follow-up for a period of 3 to 15 months. Clinical events included all-cause mortality, heart failure rehospitalization, and stroke. Clinical events were documented, and a multivariate Cox regression model evaluated the correlation between the TAPSE/PASP ratio and prognosis. The Kaplan-Meier survival analysis was also conducted.

Results The moderate-to-severe uncoupling group exhibited significantly higher proportions of males; individuals with a history of smoking, valvular disease, diabetes mellitus, or stroke; and elevated levels of PASP, right ventricular diameter (RVD), left ventricular diameter (LVD), left ventricular end-diastolic (LVED), and lg (NT-proBNP) compared to the mild uncoupling group ($P < 0.05$). Conversely, parameters such as age, TAPSE, S', S' /PASP, and left ventricular ejection fraction (LVEF) were significantly lower in the moderate-to-severe uncoupling group compared to the mild uncoupling group ($P < 0.05$). Multivariate Cox regression analysis revealed that TAPSE/PASP (hazard ratio [HR] = 0.150, 95% confidence interval [CI] [0.023, 0.968], $P = 0.046$) was a protective factor for the recurrence of clinical

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events. In contrast, LVED (HR = 1.301, 95% CI (1.004, 1.059), *P* = 0.024) and lg (NT-proBNP) (HR = 1.870, 95%CI [1.304, 2.682], *P* = 0.001) were independent risk factors for the recurrence of clinical events. KaplanMeier survival analysis demonstrated that the mild uncoupling group exhibited a significantly higher overall survival rate compared to the moderate-to-severe uncoupling group (Log Rank *P* = 0.024).

Conclusions The TAPSE/PASP ratio is a predictive marker for clinical outcomes in patients with PH-LHD.

Keywords Left heart disease (LHD), N-terminal pro-B-type natriuretic peptide (NT-proBNP), Prognosis, Pulmonary hypertension (PH), Right ventricle-pulmonary artery (RV-PA) coupling, Tricuspid annular plane systolic excursion/pulmonary artery systolic pressure (TAPSE/PASP) ratio

Introduction

Pulmonary hypertension (PH) is an abnormal hemodynamic state and a pathophysiological syndrome characterized by increased pulmonary vascular resistance, which can ultimately lead to right heart failure and even death. Pulmonary hypertension associated with left heart disease (PH-LHD) refers to PH caused by various left heart diseases (LHD), with or without pulmonary vascular remodeling. In recent years, the significance of the interplay between right ventricular (RV) function and pulmonary arterial (PA) circulation, known as right ventricle-pulmonary artery coupling (RV-PA coupling), has gained increasing recognition. RV-PA coupling pertains to the relationship between right ventricular (RV) contractility and RV after load. It is defined as the ratio of RV end-systolic elastance (Ees) to PA elastance (Ea) [1–5], which is the gold standard for assessing RV-PA coupling [6, 7]. This plays a crucial role in the prognosis of patients with PH [8].

The invasiveness of RV-PA coupling has been extensively evaluated in fundamental PH research. Currently, its non-invasive surrogate markers are also gaining attention for initial screening, differential diagnosis, and prognostic evaluation of PH. The tricuspid annular plane systolic excursion/pulmonary artery systolic pressure (TAPSE/PASP) ratio, a non-invasive measure of RV-PA coupling, is gradually becoming a potential surrogate for the Ees/Ea ratio [9–13].

According to research conducted by Tello et al., [14] a close correlation exists between the TAPSE/PASP ratio and the invasive assessment of RV-PA coupling. The TAPSE/PASP ratio is the optimal surrogate marker for the gold standard Ees/Ea. Multiple studies have demonstrated that the TAPSE/PASP ratio offers predictive value for the prognosis of patients with PH [9, 15–17]. However, there is limited research on the TAPSE/PASP ratio application in patients with PH-LHD. In this study, we aim to assess the predictive power of the TAPSE/PASP ratio on the short-term clinical prognosis of patients with PH-LHD.

Study participants and methods

Study participants

This retrospective study incorporated clinical data from individuals diagnosed with PH-LHD. The study participants were hospitalized in the Xuzhou Central Hospital between July 2022 and May 2023. Inclusion criteria were as follows: (1) Patients aged between 18 years and 85 years. (2) Inpatients in the cardiology or cardiovascular surgery departments. (3) Patients diagnosed with PH based on clinical evaluation and transthoracic echocardiography. Exclusion criteria were as follows: (1) Patients with incomplete TAPSE, S', and other results obtained via transthoracic echocardiography. (2) Patients with chronic liver or kidney disease. (3) Patients with severe infection or tumor. (4) Patients with PH not caused by left heart disease. This study was approved by the Ethics Committee of the Xuzhou Central Hospital. Written informed consent was obtained from all participants.

Grouping

The patients were divided into two groups based on the TAPSE/PASP ratio: the moderate-to-severe uncoupling group (TAPSE/PASP ≤ 0.32 mm/mmHg) consisted of 153 patients and the mild uncoupling group (TAPSE/PASP > 0.32 mm/mmHg) consisted of 209 patients.

Study methods

Clinical data were sourced from routinely maintained inpatient medical records and electronic medical record systems of the hospital. Clinical data compiled include gender, age, height, weight, smoking history, and history of coronary heart disease, high blood pressure, atrial fibrillation, valvular disease, diabetes mellitus, and stroke. The N-terminal pro-B-type natriuretic peptide (NT-proBNP) laboratory test results and transthoracic echocardiography results were documented. All patients underwent transthoracic echocardiography. A 2.5 MHz multiplane probe was used for the transthoracic echocardiography examination. The echocardiographic data included measurements of the right ventricle, left atrium (LA), left ventricle (LV), left ventricular ejection fraction (LVEF), TAPSE, tricuspid annular systolic velocity (S'), and tricuspid transvalvular pressure gradient. TAPSE was

measured in M-mode ultrasound at the end of diastole, by assessing the distance from the tricuspid annulus to the apex of the right ventricle. Right atrial pressure was estimated based on the width of the inferior vena cava and its inspiratory collapse rate. PASP was calculated using the formula: 4 × (maximum tricuspid regurgitation velocity)^2 + right atrial pressure. The right atrial pressure was estimated based on the width of the inferior vena cava and its inspiratory collapse rate. Clinical events included all-cause mortality, heart failure rehospitalization, and stroke. The ratios of TAPSE/PASP and S'/PASP were calculated. Characteristics of baseline clinical data and laboratory test results were compared between the two groups.

Follow-up

A telephonic follow-up was carried out in September 2023 to investigate the occurrence of clinical events post-discharge. The follow-up focused on all-cause mortality, re-hospitalization for heart failure, and incidence of stroke.

Statistical analysis

Data analysis was conducted using the SPSS 21.0 statistical software. Normally distributed measured data are expressed as mean ± standard deviation ($\bar{x}\pm$ s). For comparisons between the two groups, a two-t-sample independent test was used when variances were homogenous. When the variances were heterogeneous, a t'-test was used for comparison between the two groups. Non-normally distributed measured data are expressed as median with interquartile ranges (M [Q1, Q3]). Comparison outcomes from the two groups were tested using the Mann-Whitney U test. Enumeration data are expressed as cases (%). Comparisons between the two groups were conducted using the chi-squared test or Fisher's exact test. The event-free survival rate was analyzed using the Kaplan–Meier method. Variations in survival rates between the two groups were evaluated using the log-rank test. The hazard ratio (HR) and corresponding 95% confidence interval (CI) were calculated using the Cox proportional hazards model. A statistically significant difference was defined as a *P*-value less than 0.05 ($P<0.05$).

Results

Comparison of baseline data and laboratory test results of patients

A total of 362 patients with PH-LHD were included in this study. They were categorized into two groups based on the TAPSE/PASP ratio: the moderate-to-severe uncoupling group with a TAPSE/PASP ratio ≤ 0.32 mm/mmHg and the mild uncoupling group with a TAPSE/PASP ratio > 0.32 mm/mmHg [16]. Compared to the mild uncoupling group, the moderate-to-severe uncoupling group had significantly higher proportions of males and smokers, and a significantly younger age ($P<0.05$ for all three parameters). In comparison to the mild uncoupling group, the moderate-to-severe uncoupling group had significantly higher proportions of patients with left heart valvular disease and diabetes mellitus, and a significantly lower proportion of patients with a history of stroke ($P<0.05$ for all three parameters). Compared to the mild uncoupling group, the moderate-to-severe uncoupling group had a higher log (NT-proBNP) level, and the difference was statistically significant ($P<0.05$). The two groups exhibited no statistically significant difference in body mass index (BMI), and the proportions of patients with coronary heart disease (CHD), high blood pressure, and atrial fibrillation. (Table 1)

Comparison of transthoracic echocardiography data

Compared to the mild uncoupling group, the moderate-to-severe uncoupling group exhibited lower levels of the TAPSE/PASP ratio, S'/PASP ratio, TAPSE, S' wave, and LVEF levels, and higher levels of PASP, RVD, left atrial

Table 1 Comparison of the baseline data and laboratory test results of the two groups with PH-LHD

	Moderate-to-severe uncoupling group (≤ 0.32)	Mild uncoupling group (> 0.32)	*P* value
Case number	153	209	
Male (Case [%])	99(64.7)	113(54.1)	0.001*
Age (Years) M (Q1, Q3)	69(57,75)	73(65,78)	< 0.001*
BMI (kg/m^2) M (Q1, Q3))	24.52(22.49,26.51)	24.39(22.15,26.73)	0.738
Smoking (Case [%])	43(28.1)	47(22.5)	< 0.001*
CAD (Case [%])	69(45.1)	108(51.7)	0.967
High blood pressure (Case [%])	61(39.9)	115(55.0)	0.645
Atrial fibrillation (Case [%])	83(54.2)	103(49.3)	0.770
Left heart valve disease (Case [%])	38(24.8)	37(17.7)	< 0.001*
Diabetes mellitus (Case [%])	44(28.8)	55(26.3)	< 0.001*
Stroke (Case [%])	32(20.9)	50(23.9)	< 0.001*
lg (NT-proBNP) (pg/ml) M (Q1, Q3)	3.62(3.13,3.89)	3.15(2.71,3.68)	< 0.001*

*$P<0.05$

diameter (LAD), and LVED, with all these differences being statistically significant ($P < 0.05$) (Table 2).

Occurrence of clinical events

During the follow-up phase with an average duration of 9.0 months (interquartile range: 6.0 to 12.0 months), 131 patients (36.2%) experienced clinical events. The occurrence rate of clinical events was higher in the moderate-to-severe uncoupling group than in the mild uncoupling group (66 [43.1%] vs. 65 [31.1%], $P = 0.013$). Specifically, in the moderate-to-severe uncoupling group, 10 (6.5%) patients died, 52 (34.0%) were re-hospitalized for heart failure, and 4 (2.7%) suffered a stroke. In the mild uncoupling group, 8 (3.8%) patients died, 55 (26.3%) were re-hospitalized for heart failure, and 2 (1.0%) suffered a stroke. Although the incidence rates of these conditions were higher in the moderate-to-severe uncoupling group, the differences were not statistically significant (*P* values: 0.177, 0.072, and 0.210, respectively).

As illustrated by the Kaplan–Meier survival curve (Fig. 1), the event-free survival rate was higher in the mild uncoupling group than in the moderate-to-severe uncoupling group, with a statistically significant difference ($P = 0.024$).

Risk factors for the recurrence of clinical events

Based on the results of multivariate Cox regression analysis, LVED (HR = 1.031, 95%CI: 1.004–1.059, $P = 0.024$) and log (NT-proBNP) (HR = 1.870, 95%CI: 1.304–2.682, $P = 0.001$) are independent risk factors for the recurrence of clinical events. The TAPSE/PASP ratio (HR = 0.150, 95%CI: 0.023–0.968, $P = 0.046$) was negatively correlated to the recurrence of clinical events (Table 3).

Discussion

The epidemiological data on PH-LHD remains inconclusive. This condition involves the left and right heart systems and pulmonary vasculature. It is a complex condition characterized by a high incidence rate, poor prognosis, and high mortality rate, and severely impacts the quality of life of patients. Based on the etiology, PH-LHD is classified into several subtypes: heart failure with reduced ejection fraction (HFrEF), heart failure with preserved ejection fraction (HFpEF), heart failure with mid-range ejection fraction (HFmrEF), left heart valvular disease and congenital/acquired cardiovascular diseases leading to post-capillary PH. The predominant cause of PH-LHD is heart failure. HFrEF consists of ischemic cardiomyopathy and dilated cardiomyopathy, while HFpEF consists of hypertensive heart disease, hypertrophic cardiomyopathy, and restrictive cardiomyopathy. In this study, the TAPSE/PASP ratios of 362 patients with PH-LHD were analyzed. The following findings were observed:

(1) The TAPSE/PASP ratio is an important and clinically significant prognostic parameter for patients with PH-LHD.
(2) The TAPSE/PASP ratio decreases with an increase in the NT-proBNP, RVD, LAD, and left ventricular end-diastolic diameter (LVEDD) levels.

RV-PA uncoupling indicates that LHD has progressed to an advanced stage, rendering the course of the disease challenging to reverse. Identifying such high-risk patients is crucial to risk stratification. The application of the TAPSE/PASP ratio in left heart diseases has been investigated in several previous studies. A study involving 384 patients with HFpEF revealed that TAPSE is closely correlated with PASP in patients with HFpEF [18]. The combination of right ventricular function and pulmonary artery pressure in a single TAPSE/PASP ratio can accurately stratify the risk for patients with all types of heart failure. Another study involving 387 patients with HFpEF compared right ventricular systolic function and RV-PA coupling in patients with HFpEF with varying severities grouped by the TAPSE/PASP ratio (Group 1: the TAPSE/PASP ratio < 0.35; Group 2: the TAPSE/PASP ratio ranging from 0.35 to 0.57; Group 3: the TAPSE/PASP ratio > 0.57) [9]. Patients with a TAPSE/PASP ratio

Table 2 Comparison of transthoracic echocardiography data of the two groups with PH-LHD

	Moderate-to-severe uncoupling group (≤ 0.32)	Mild uncoupling group (> 0.32)	*P* value
Case number	153	209	
TAPSE/PASP (mm/mmHg) M (Q1, Q3)	0.27(0.24,030)	0.41(0.36,0.45)	< 0.001*
S'wave /PASP (cm/s*mmHg) M (Q1, Q3)	0.16(0.14,0.18)	0.24(0.22,0.27)	< 0.001*
TAPSE (mm) M (Q1, Q3)	14(12,16)	19(17,20)	< 0.001*
PASP (mmHg) M (Q1, Q3)	51.60(46.00,60.80)	44.40(42.00,49.60)	< 0.001*
S'wave (cm/s) M (Q1,Q3)	8.50(7.20,10.00)	11.00(10.00,12.00)	< 0.001*
RVD (mm) M (Q1, Q3)	25(23,29)	22(20,24)	< 0.001*
LAD (mm) M (Q1, Q3)	47(43,51)	42(38,48)	< 0.001*
LVED (mm) M (Q1, Q3)	58(52,65)	51.00(47.0,59.0)	< 0.001*
LVEF (%) M (Q1, Q3)	34.00(28,45)	50.00(38,57)	< 0.001*

Note: TAPSE: tricuspid annular plane systolic excursion; *$P < 0.05$

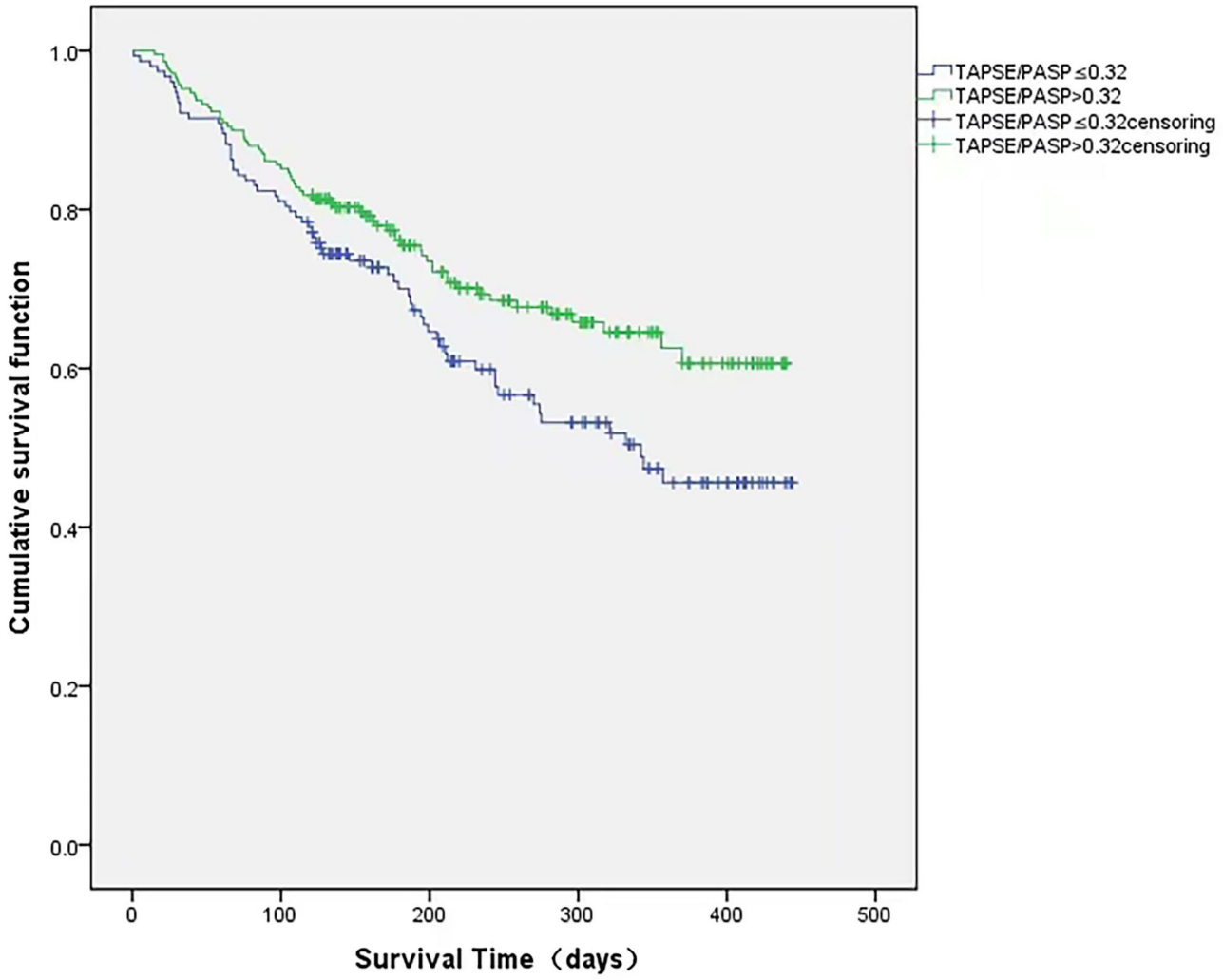

Fig. 1 Kaplan–Meier survival curve for the PH-LHD moderate-to-severe uncoupling group and the PH-LHD mild uncoupling group

Table 3 Multivariate Cox regression analysis of risk factors related to clinical event recurrence in PH-LHD patients' post-discharge

Variable	HR (95% CI)	*P* value
Male	1.005(0.988,1.024)	0.553
BMI	0.962(0.909,1.017)	0.174
Smoking	0.958(0.604,1.520)	0.856
CAD	0.767(0.510,1.156)	0.205
High blood pression	0.729(0.484,1.097)	0.130
Atrial fibrillation	0.819(0.528,1.272)	0.375
Heart valve disease	1.121(0.667,1.884)	0.667
TAPSE/PASP ratio (mm/mmHg)	0.150(0.023,0.968)	0.046*
TAPSE (mm)	0.766(0.578,1.015)	0.064
PASP (mmHg)	1.013(0.968,1.061)	0.570
RVD (mm)	1.017(0.981,1.053)	0.360
LAD (mm)	1.009(0.983,1.035)	0.506
LVED (mm)	1.031(1.004,1.059)	0.024*
LVEF (%)	1.008(0.986,1.031)	0.466
lg (NT-proBNP) (pg/ml)	1.870(1.304,2.682)	0.001*

*$P < 0.05$

less than 0.35 mm/mmHg exhibited higher PASP, higher right ventricular end-diastolic and end-systolic areas, lower TAPSE, and reduced RV fractional area change. The results showed that the TAPSE/PASP ratio is negatively correlated with the New York Heart Association functional classification. A reduced TAPSE/PASP ratio in patients with heart failure is not only associated with diminished hemodynamics but is also indicative of a higher risk of cardiovascular-related re-hospitalization and mortality. This ratio can independently predict the occurrence of adverse events.

In a prospective study, it was discovered that patients with HFpEF exhibit reduced right ventricular contractile reserve and abnormal RV-PA coupling in the early stages of the disease, and these abnormalities are reversible [19]. According to Reddy et al., the TAPSE/PASP ratio was reduced in patients with HFpEF compared to healthy individuals, suggesting that pulmonary interstitial edema may be related to abnormal RV-PA coupling [20]. An

early measurement of RV-PA coupling can predict the occurrence of pulmonary interstitial edema in patients with HFpEF. Recent research has found that the TAPSE/PASP ratio is independently associated with adverse outcomes in patients with concurrent acute HFpEF and coronary artery disease [21].

In a study on patients with HFrEF, it was discovered that a lower TAPSE/PASP ratio was associated with lower cardiac functional class, reduced exercise capacity, and diminished ventilatory efficiency [22]. It is also a predictor of adverse outcomes in patients with HFrEF.

Deaconu et al. conducted a study on 54 patients with HFrEF undergoing cardiac resynchronization therapy (CRT) [23]. They discovered that a lower TAPSE/PASP ratio was associated with a higher risk of adverse cardiovascular events. Palazzuoli et al. discovered that reduced TAPSE and TAPSE/PASP ratio levels are superior prognostic predictors in patients with HFrEF [24]. However, according to research results of Bragança et al., the TAPSE/PASP ratio is not significantly associated with all-cause mortality but is associated with surrogate markers of heart failure prognosis, such as increased E/e' ratio and elevated plasma NT-proBNP levels [12]. A recent study on patients with acute heart failure indicated that those with a lower TAPSE/PASP ratio at admission had longer hospital stays and higher incidence rates of all-cause mortality and re-hospitalization for heart failure [25]. Additionally, studies on hypertensive patients revealed that the TAPSE/PASP ratio was significantly lower in the hypertensive group than in the control group [26, 27]. However, in the current study, the proportion of patients with high blood pressure in the mild uncoupling group was higher than that in the moderate-to-severe uncoupling group, but the difference was not statistically significant.

In the aforementioned studies, the TAPSE/PASP ratio in different classifications of LHD was investigated, with most results suggesting its significance in predicting the prognosis of heart failure. This study encompasses patients from all PH-LHD classifications and those with higher pulmonary artery pressure. According to the results, LVED and NT-proBNP are independent risk factors for clinical event recurrence, and the TAPSE/PASP ratio is negatively correlated with clinical event recurrence. Patients with a reduced TAPSE/PASP ratio have a lower long-term event-free survival rate, which is consistent with the results of most previous studies.

This study has several limitations. It features a relatively small sample size and is a single-center retrospective study. Additionally, the follow-up duration is short. Future research should include prospective studies with larger sample sizes and longer follow-up durations. Moreover, this study diagnosed PH through clinical evaluation and transthoracic echocardiography, which has certain subjectivity. Future research could utilize the transpulmonary vascular gradient calculation method to assess cardiac function and conduct fluid challenge tests to determine the patient's volume responsiveness and tolerance, thereby guiding decisions on whether to continue fluid resuscitation therapy. Furthermore, this study investigated the relationship between the TAPSE/PASP ratio and prognosis by collecting TAPSE/PASP ratios at admission. The feasibility of guiding subsequent treatment needs via monitoring changes in the TAPSE/PASP ratio needs to be further investigated. The non-invasive TAPSE/PASP ratio offers a convenient method for assessing and monitoring RV-PA coupling and is expected to become a routine parameter for risk assessment, risk stratification, and prognostic evaluation in patients with PH-LHD. Lastly, the participants included in this study did not undergo right heart catheterization; therefore, we did not categorize the patients into Isolated post-capillary PH and Combined pre- and post-capillary PH groups, nor did we further investigate potential differences in pulmonary artery-right ventricle coupling between them.

Conclusion

The TAPSE/PASP ratio has been demonstrated to independently correlate with the overall event occurrence rate in patients with PH-LHD. This finding suggests that the TAPSE/PASP ratio possesses significant predictive value for clinical outcomes in this patient population.

Abbreviations

ELISA	Enzyme-linked Immunosorbent Assay
NT-proBNP	N-terminal pro-B-type natriuretic peptid
PH	Pulmonary hypertension
PH-LHD	Pulmonary hypertension associated with left heart disease
LHD	Left heart disease
RV	Right ventricular
PA	Pulmonary arterial
Ees	End systolic elastance
Ea	Arterial elastance
TAPSE	Tricuspid annular plane systolic excursion
PASP	Pulmonary artery systolic pressure
TAPSE / PASP	Tricuspid annular plane systolic excursion/ pulmonary artery systolic pressure
S'	Tricuspid systolic velocity
S'/PASP	Tricuspid systolic velocity/ pulmonary artery systolic pressure
LA	Left atrium
LV	Left ventricle
LVEF	Left ventricle ejection fraction
RVD	Right ventricle diameter
LAD	Left atrial diameter
LVED	Left ventricular end diastolic
BMI	Body mass index
HR	Hazard ratio
CI	Confidence interval
HFrEF	Heart failure with reduced ejection fraction
HFpEF	Heart failure with preserved ejection fraction
HFmrEF	Heart failure with mid-range ejection fraction

Author contributions

Ling-Zhi Dou: Data curation, Formal Analysis, Writing– original draft. Shan-Shan Li: Data curation, Formal Analysis, Writing– original draft. Sen Wang:

Data curation, Resources, Software, Visualization. He Jiang: Data curation, Investigation, Formal Analysis. Yu-Li Zheng: Data curation, Formal Analysis, Software. Meng-Meng Duan: Data curation, Formal Analysis. Yi-Gang Zhang: Formal Analysis, Software, Visualization. Bing Han: Formal Analysis, Software, Writing– review & editing. Jian-Ming Li: Conceptualization, Formal Analysis, Software, Writing– review & editing. Hong-Yun Ruan: Conceptualization, Formal Analysis, Writing– review & editing. All authors read and approved the final draft.

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Data availability
The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
This study was conducted with approval from the Ethics Committee of the Xuzhou Central Hospital (Approval Date: September 22nd, 2022). This study was conducted in accordance with the declaration of Helsinki. Written informed consent was obtained from all participants.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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