The additive value of left atrial function measured by 4D auto left atrial quantification echocardiography for distinguishing between pre-capillary and post-capillary pulmonary hypertension

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Abstract

Objective The purpose of this study was to investigate the value of left atrial (LA) volume and strain by 4D auto left atrial quantification (LAQ) for differentiating pre- and post-capillary pulmonary hypertension (PH), and compare the discriminative ability with echocardiographic pulmonary to left atrial global strain ratio (ePLAGS). **Methods** A total of ninety-eight subjects screened for intermediate to high probability of PH were prospectively enrolled in this study. Clinical history and laboratory data of all the patients were collected. All the patients underwent comprehensive transthoracic echocardiography and then LA volume and strain were measured by dedicated commercial software specially designed for LA 4D analysis. **Results** According to pulmonary arterial wedge pressure, the participants were divided into two groups: pre-capillary PH Group (n=39, age 53±24 year) and post-capillary PH Group (n=59, age 57 ± 18 year). LAVImax, LAVImin and LAVIpreA significantly increased, while LASr and LAScd obviously decreased in post-capillary PH group when comparing with pre-capillary PH group. Multivariate logistic regression analysis showed LAVImax (OR: 1.40; 95% CI, 1.05–1.87; $P = 0.021$) and LAScd (OR: 1.76; 95% CI, 1.18–2.49; $P = 0.004$) were powerful independent predictors for detecting post-capillary PH. The ROC analysis indicated that LAVImax (AUC=0.82, $p < 0.001$) and LAScd (AUC=0.78, p <0.001) had high discriminating power for predicting post-capillary PH groups, and their cutoff values were 35.69ml/m2 (sensitivity 86%, specificity 74%) and -9% (sensitivity 80%, specificity70%). **Conclusions** LAVImax and LAScd measured by 4D auto LAQ were powerful parameters for distinguishing pre-capillary PH from post-capillary PH.

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Availability of data and materials

The data that support the findings of this study are available on request from the corresponding authors, Fengjuan Yao and Hong Lin. The data are not available to the public due to the nature that the information could compromise the interest of research participants.

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Ethics approval and consent to participate

We further confirm that the protocol was approved by the Ethic Committee of SYSU. Written consent was obtained from all enrolled patients.

Abstract

Objective The purpose of this study was to investigate the value of left atrial (LA) volume and strain by 4D auto left atrial quantification (LAQ) for differentiating pre- and post-capillary pulmonary hypertension (PH), and compare the discriminative ability with echocardiographic pulmonary to left atrial global strain ratio (ePLAGS).

Methods A total of ninety-eight subjects screened for intermediate to high probability of PH were prospectively enrolled in this study. Clinical history and laboratory data of all the patients were collected. All the patients underwent comprehensive transthoracic echocardiography and then LA volume and strain were measured by dedicated commercial software specially designed for LA 4D analysis.

Results According to pulmonary arterial wedge pressure, the participants were divided into two groups: pre-capillary PH Group (n=39, age 53±24 year) and post-capillary PH Group (n=59, age 57 ± 18 year). LAVImax, LAVImin and LAVIpreA significantly increased, while LASr and LAScd obviously decreased in post-capillary PH group when comparing with pre-capillary PH group. Multivariate logistic regression analysis showed LAVImax (OR: 1.40; 95% CI, 1.05–1.87; $P = 0.021$) and LAScd (OR: 1.76; 95% CI, 1.18–2.49; $P = 0.004$) were powerful independent predictors for detecting post-capillary PH. The ROC analysis indicated that LAVImax (AUC=0.82, $p < 0.001$) and LAScd (AUC=0.78,p <0.001) had high discriminating power for predicting post-capillary PH groups, and their cutoff values were 35.69ml/m2 (sensitivity 86%, specificity 74%) and -9% (sensitivity 80%, specificity70%).

Conclusions LAVImax and LAScd measured by 4D auto LAQ were powerful parameters for distinguishing pre-capillary PH from post-capillary PH.

Keywords: echocardiography, 4D LAQ, left atrial volume, left atrial strain, post-capillary pulmonary hypertension.

INTRODUCTION

Pulmonary hypertension (PH) is a pathophysiological disorder, which may result from multiple cardiovascular and respiratory diseases. According to ESC/ERS Guidelines for PH in 2022, PH can be classified into two main subtypes: pre-capillary PH (pulmonary arterial wedge pressure (PAWP) [?]15 mmHg) and

post-capillary PH (PAWP >15 mmHg). Pre-capillary PH is usually related to pulmonary arterial hypertension, thrombo-embolic PH, or PH due to lung disease or hypoxia, while postcapillary is mainly associated with heart failure (HF) or valvular heart diseases, and the two PH subtypes require different therapeutic strategies.[1] The current guidelines on PH recommend the invasive measurement of PAWP using right heart catheterization (RHC). However, when distinguishing pre- from post-capillary PH, except for PAWP threshold, the patient phenotype and echocardiographic findings including left atrial (LA) volume, are also needed to be considered[1].

Echocardiography is an importance modality in the assessment of patients with suspected or known PH. Also, it is recommended for the non-invasive diagnostic assessment of suspected PH, especially in patients with lung disease[1]. Besides, it had been proved that echocardiography had become an effective alternative method to invasive cardiac catheterization to help evaluate hemodynamic like PAWP and pulmonary vascular resistance (PVR) [2-4]. In previous studies, echocardiographic parameters could be used to accurately differentiate pre- and post- capillary PH, such as echocardiographic pulmonary to LA ratio (ePLAR), echocardiographic pulmonary to LA global strain ratio (ePLAGS), the body surfaced area–indexed left atrial minimum volume (LAVImin) and so on[5-9]. However, the software above used for evaluating LA volume and strain were not specifically dedicated to 3D left atrial measurements.

Recently, commercial software specially used to evaluate left atrial function has been applied in clinical practice, including 4D auto LA quantification analysis (LAQ). 4D auto LAQ is a LA analysis technique that uses 3D volume data to determine the LA volume of different periods in diastole as well as LA longitudinal and circumferential strains. It was reported that it had the advantages of high sensitivity, reproducibility and accuracy[10], and it was applied to multiple clinical diseases, such as patients with arrhythmia, the high risk of thromboembolism, type 2 diabetes, heart failure and so on[11-14]. There are no studies published about LA function assessed by 4D auto LAQ for distinguishing pre- from post-capillary PH. The purpose of this study was to investigate the value of LA volume and strain by 4D LAQ for differentiating pre- and post-capillary PH, and compare with ePLAGS.

MATERIALS and METHODS

Study population

Ninety-eight adult patients screening for high probability of PH by echocardiography were enrolled from the inpatient or outpatient department of the First Affiliated Hospital of Sun Yat-sen University (SYSU) between July 2021 to April 2022. Patients with a peak tricuspid regurgitation velocity (TRV)>3.4m/s by echocardiography, or TRV>2.8m/s with additional echocardiographic signs from at least two categories (the ventricles, the pulmonary artery or inferior vena cava (IVC) and right atrium) suggestive of PH were assigned high probability of PH. Patients with TRV range from 2.8 to 3.4m/s and the absent of other echocardiographic signs, or TR¡2.8m/s with the present of echocardiographic signs of PH were suggested Intermediate probability of PH[15]. Subjects with age < 18 years, acute coronary syndrome or cardiac surgery within a period of 1 year, pacemaker rhythm, echocardiography images might interfere accurate 4D auto LAQ measurements were excluded. This was a single-center retrospective study approved by the Ethic Committee of SYSU, complied with the Declaration of Helsinki.

Clinical and Laboratory evaluation

Demographic parameters (age, gender, height and weight) and clinical variables including blood pressure and clinical diagnosis were collected. The body surface area (BSA) and body mass index (BMI) were calculated. Venous blood samples were collected in the morning after an overnight fasting and some laboratory parameters were detected, including serum NT-pro BNP, creatinine, hemoglobin and glycosylated hemoglobin (HbA1c).

Echocardiography

Comprehensive echocardiographic examinations were performed in all patients by trained experience echocardiographers using a Vivid E95 ultrasound system (General Electric Healthcare, Horten, Norway) in keeping

with the current guidelines and recommendations[16]. 2D gray-scale images were equipped with a 2.5 MHz matrix array transducer (M5Sc) and acquired at 50–80 frames/s over 3 heart cycles. Data from 3 to 5 beats was averaged in atrial fibrillation cases. Left ventricular ejection fraction (LVEF) was obtained by Simpson method from apical 4-and 2-chamber views. LV mass (LVM) was calculated using the Devereux formula[17]. And the index of the left ventricular diameters at the end of systole and diastole (LVEDI, LVESI) and LV mass (LVMI) were equal to LVED, LVES and LVM divided by BSA respectively. The Doppler imaging were performed to evaluate the peak early (E) and late (A) diastolic velocities of the mitral inflow, the peak early diastolic velocity of the medial mitral annular (e'), the peak systolic velocity of tricuspid annular (S') and the tricuspid regurgitation peak velocity (TRV). Then, the ratio of E/A and E/e' were calculated respectively. Tricuspid annular plane systolic excursion (TAPSE) was tracked in the right ventricular focus apical four-chamber view using M-mode echocardiography. Pulmonary artery systolic pressure (PASP) was calculated by the modified Bernoulli formula: PASP =4xTRV^2 + estimated right atrial pressure (RAP), while the estimated RAP was based on inferior vena cava diameter and collapsibility index. The PAWP was estimated by (43 - 0.1xTRV- 0.5x LVEF+1.0x RVFAC+0.3x LAVi + 0.7x E/ e' + 0:9x IVC) x PAMP/100 [4]. PAWP [?]15 mmHg was defined as pre-capillary PH, and PAWP >15 mmHg was defined as post-capillary PH.

The 4D Auto LAQ

4V probe (4Vc) was used for imaging acquisition in the apical chamber view with the image frame rate >30 frames/s, and the parameters of LA 4D volume and strain were acquired by software of 4D Auto LAQ. When 4D Auto LAQ analysis mode were selected, the sub-mode sequentially entered. Firstly, the sampling point was placed at the center of mitral valve annulus level, then the 'review' function was selected to obtain the parameters of LA volume and strain (**Figure 1**). The indices of left atrial volume between the various stages, including LAVImax, LAVIpreA, and LAVImin were measured simultaneously. LA longitudinal strain parameters were also evaluated using this technique including LA reservoir strain (LASr), LA conduit strain (LAScd), and LA contraction strain (LASct). Meanwhile, ePLAGS was calculated as TRV/LASr. LA function in different phases, including storage, channel and active systolic function were calculated as following:

$$\text{LA storage function: diastolic ejection index (DEI)} = (LAVi_{max} - LAVi_{min}) / LAVi_{max}] \times 100\ \%$$

$$\text{LA channel function: passive ejection index (PEI)} = [(LAVi_{max} - LAVi_{preA}) / LAVi_{max}] \times 100\ \%$$

$$\text{LA active systolic function: active ejection index (AEI)} = [(LAVi_{preA} - LAVi_{min}) / LAVi_{preA}] \times 100\ \%$$

Measurement variability

To assess reproducibility, the measurements of LA volume and strain by 4D Auto LAQ were repeated by the same observer on the same echocardiographic images in 10 randomly selected patients at least 1 weeks apart. These parameters were also analyzed by another independent observer blind to the patient grouping to ensure interobserver variability.

Statistical analysis

Statistical analysis was performed by SPSS 25.0 (IBM SPSS Statistics, Chicago, IL, USA). Normality was assessed with a normal probability (Q-Q) plot and with a Shapiro-Wilk test. Continuous variables were expressed as mean ± standard deviations, mean ± standard errors, median (inter-quartile range) or frequencies (percentages) as appropriate. Chi-square test or Fisher's exact test were used to compare categorical variables. Independent t-test was performed for continuous variables. Non-normally distributed values were compared using the Mann–Whitney U test. The Pearson or Spearman correlation coefficients were used to evaluate the linear relationship between the variables. Univariate and multivariate logistic regression analyses were performed to determine factors associated with post-capillary PH. The factors with p [?] 0.10

were selected as related variables for multivariate analysis. Receiver operating characteristic (ROC) curve analysis was used to compare the discriminative ability of the independent parameters and to determine the optional cutoff value. A two-sided p value of < 0.05 was considered statistically significant.

RESULTS

General clinical characteristics

According to the estimated PAWP, forty-one patients had pre-capillary PH, and fifty-seven patients had post-capillary PH. Clinical characteristics of the patients were detailed in **Table 1** . In line with the NICE classification[1], most of patients with pre-capillary PH belonged to group 1, 3, and 4, while patients with post-capillary PH could be predominantly classified into group 2. There were significantly higher with NT-Pro BNP, hemoglobin and HbA1c in post-capillary PH group comparing with pre-capillary PH group (p <0.05). However, BMI, BSA, heart rate, systemic blood pressure and serum Hb did not differ between the two groups (p >0.05).

Echocardiographic analysis (**Table 2**)

Although the diameter of pulmonary artery (PA) and the areas of right atrial (RA) were enlarged in both groups, there were no significantly differences in structure and function of the right heart chamber between the two groups, including PA, RA areas, RVFAC, S', TAPSE and TAPSE/PASP (p >0.05). For the left ventricular, the LVEDI, LVESI, LVMI and E/e' were obvious higher in patients with post-capillary PH, while the LVEF was lower than pre-capillary PH (p <0.001).

LA volume indices were significantly increased in post-capillary PH compared to pre-capillary PH (LAVImax: 54.89+-22.04 vs. 29.54+-13.06 mL/m^2, LAVImin: 36.75+-17.65 vs. 16.26+-8.57 mL/m^2, LAVIpreA: 46.55+-20.49 vs. 23.25+-11.48 mL/m^2, $p < 0.0001$), while DEI (0.34+-0.12 vs. 0.45+-0.11, $P < 0.001$), PEI (0.15+-0.10 vs. 0.22+-0.11, $P = 0.0001$) and AEI (0.21+-0.11 vs. 0.30+-0.12,$P = 0.05$) were decreased (**Figure 2)** . LASr (11.30+-6.92 % vs. 17.50+-6.70 %, $P < 0.001$) and LAScd (-6.45+-3.75 % vs. -11.38+-5.78 %, $P <$ 0.001) obviously reduced in post-capillary PH group compared with pre-capillary PH group. Besides, there were obvious decreased with LA strain in patients of post-capillary PH, as a result, the post-capillary PH group had higher ePALGS. (**Figure 3**)

Regression analysis

Logistic regression analysis was used to determine which of the parameters of echocardiography could be used to distinguish pre- from post-capillary PH. The parameters would be put into multivariate analysis if p <0.10 in univariate analysis. Thus, the volume and the function of LA in different phases, LASr, LAScd, LVEDi and LVEF were chosen as inputs for multivariate logistic regression model. However, only LAVImax (OR: 1.40; 95% CI, 1.05–1.87; $P = 0.021$) and LAScd (OR: 1.76; 95% CI, 1.18–2.49; $P = 0.004$) were considered as the most powerful independent predictors for detecting post-capillary PH (**Table 3**). ROC analysis showed that LAVImax (AUC=0.82, $p < 0.001$) and LAScd (AUC=0.78, p<0.001) had a high discriminating power in distinguishing between pre-capillary and post-capillary PH groups, and their cutoff values were 35.69ml/m2 (sensitivity 86%, specificity74%) and -9% (sensitivity 80%, specificity70%) (**Figure 4A**). Considering LAVImin and ePLAGS were useful to discriminate between pre- and post-capillary PH in previous studies, both the parameters were also taken into ROC analysis in our studies. It was demonstrated that they had high differentiation capability (LAVImin: AUC=0.84, p<0.001; ePLAGS: AUC=0.72, p <0.001) as well (**Figure 4B**).

Observer variability Intra-observer variability for LAVImax, LAVImin, LAVIpreA, LASr, LAScd and LASct by inter-class correlation were 0.992 ($p < 0.001$), 0.983 ($p < 0.001$), 0.994 ($p < 0.001$) and 0.960 ($p <$ 0.001), 0.901 (p< 0.001),0.878 ($p = 0.001$) respectively. Inter-observer variability for LAVImax, LAVImin, LAVIpreA, LASr, LAScd and LASct by inter-class correlation were 0.985 ($p < 0.001$), 0.991 ($p < 0.001$), 0.935 ($p < 0.001$) and 0.963 ($p = 0.001$), 0.848 ($p = 0.001$); 0.802 (p= 0.001) respectively.

DISCUSSION

In this study, we have showed that BSA-index of left atrial maximum volume (LAVImax) and left atrial conduit strain (LAScd) measured by 4D auto LAQ were useful noninvasive parameters in distinguishing pre- and post-capillary PH: LAVImax and LAScd were higher in post-capillary PH group, and their cutoff values were 35.69ml/m^2(sensitivity 86%, specificity74%) and -9% (sensitivity 80%, specificity 70%).

In our studies, most patients in post-capillary PH group were belong to group 2 PH according to the NICE classification, along with higher serum NT-Pro BNP, hemoglobin and HbA1c, which were in line with previous studies[1, 6-8, 18]. It was indicated that the clinical diagnosis and grouping were reliable, although the PASP and PAWP were estimated by echocardiography in our studies. Both groups had similarly structure and function of right heart chamber, with enlarged PA and RA, right ventricular-pulmonary artery uncoupling and decreasing RV systolic function. However, the LVEF was lower, while LVMI and E/e' were higher in post-capillary PH group, which indicating that the LV systolic and diastolic function were depressed. These findings supported that post-capillary PH predominantly classified into group 2 PH in our study.

As we know, LA size is a maker of LV filling pressure and diastolic function. The LA and the pulmonary veins and venules are the proximal part of the pulmonary circulation. Therefore, regardless of any cause in LA pressure rising, it would be reflected on the pulmonary venous circulation pressure, and following on the PAWP. Continuous increasing of LA pressure could cause LA and LV enlargement, myocardial stretch and significant rise of stiffness[19, 20]. Consequently, LA volume and strain were important in differentiating pre- and post-capillary PH except for PAWP. Recent studies had showed that LA maximum area access by CT, LA maximum volume index evaluated by MRI and echocardiography were useful parameters for distinguishing pre- and post-capillary PH[8, 21, 22]. These were consistent with our results, which demonstrated that LAVImax measured by 4D auto LAQ was a valuable indication. However, Csaba et al. showed that LAVImin measured by transthoracic 3DE discriminated better than LAVImax between pre- and post-capillary PH[6]. In that paper, the software of 3DE were not specifically dedicated to 3D left atrial measurements, and the strain of LA wasn't taken into for analysis, which may explain the reason inconsistency with our study. Besides, when analysing the ability of LAVImin for differentiating pre- and post-capillary PH, the AUC was also high by ROC analysis (AUC=0.844, P <0.001), yet LAVImin wasn't an independent factor for differentiating both groups when adding the LA strain parameters into multivariate logistic regression analysis.

4D auto LAQ is specially designed for LA 3D analysis which could determine the LA volume of different periods in diastole as well as LA strains conveniently and highly reproducibly. In our study, it was demonstrated that LAScd was lower, while ePLAGS were higher in post-capillary PH, and they were also useful parameters for distinguishing pre- and post-capillary PH. Ashwin et al. also found that ePLAGS assessed by 2D echocardiography accurately differentiated pre-capillary from post-capillary PH[7], and this was in line with our study. On the basis of Frank Starling law, the enlargement of LA is associated with myocardial thinning, restrained contraction function and hence compromised deformation. We found that LASr and LAScd were obviously decreased in patients of post-capillary PH in our study, which could be seen as directly reflecting LA myocardial dysfunction, in adhering with previous study that LA Strain was the strongest predictor of cavity pressure.[23] Nevertheless, LAScd was one of the most independent factors for differentiating pre- and post-capillary PH by regress analysis. Maybe because the LA conduit strain connected reservoir strain and LA contraction strain, and it can also be reflected the LV filling pressure as well as LASr. In addition, LA storage and channel function (DEI and PEI) were higher in post-capillary PH group, but LA active systolic function (AEI) was not in this study, which could be evidenced this suppose.

Nevertheless, there are a few limitations. Firstly, this was a single-center study with a relatively small sample size. Secondly, the PASP and PAWP were measured from echocardiography and not obtained by invasively, while these noninvasive parameters were significantly correlated with invasive measurements[2]. Finally, we didn't analyse the variability of parameters of LA structure, function and stain between 4D auto LAQ and 2D echocardiography. LA myocardial function assessed by 2D strain analysis is much more complex than that of the thicker LV, so LA volume and function should be calculated with another software.

CONCIUSION

In conclusion, our results showed that LAVImax (35.69ml/m^2, sensitivity 86%, specificity74%) and LAScd (-9%, sensitivity 80%, specificity 70%) measured by 4D auto LAQ were powerful parameters for distinguishing pre-capillary from post-capillary pulmonary hypertension.

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Table 1 Clinical characteristics of the patients with pre-capillary and post-capillary PH

Age (year)	
Male, n (%)	
BSA (kg/m2)	
BMI(kg/m^2)	
HR (1/min)	
Systolic Blood Pressure (mmHg)	
Diastolic Blood Pressure (mmHg)	
Atrial fibrillation, n (%)	
Classification (NICE) n (%)	
Group 1	
Group 2	
Group 3	
Group 4	
Group 5	
NT Pro-BNP (pg/mL)	
hemoglobin (g/L)	
creatinine(umol/L)	
HbA1C (%)	
PAWP (mmHg)	

BSA:body surface area ;BMI:body mass index; HbA1C: glycosylated hemoglobin; PAWP: pulmonary arterial wedge pressur

Table2 Echocardipgraphy parameters of the patients with pre-capillary and post-capillary PH

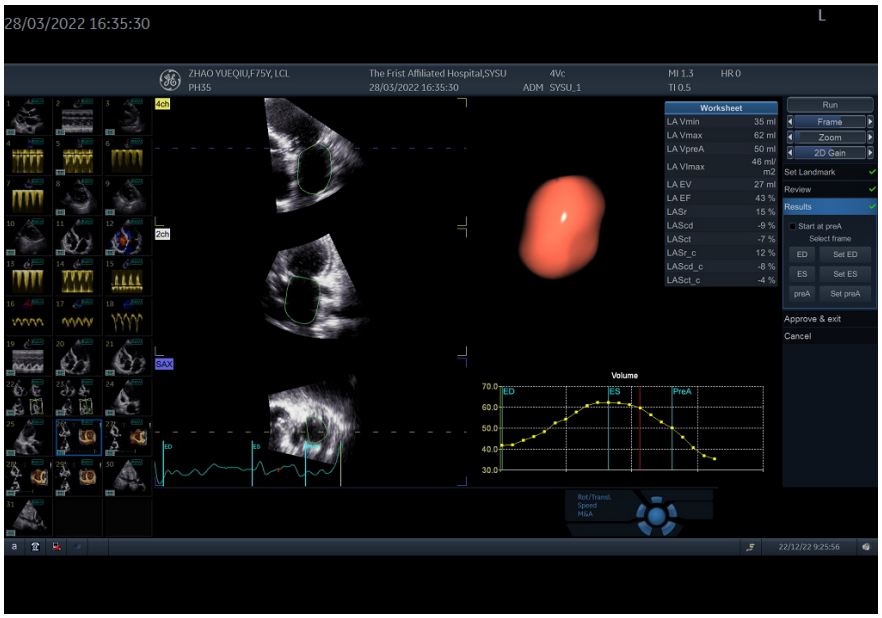
Right heart chambers
Pulmonary Artery (mm)
RVFAC (%)
S' tricuspid valve (cm/s)
PASP (mmHg)
TRV (m/s)
PAMP (mmHg)
Right Atrial Area (cm^2)
TAPSE (mm)
TAPSE_PASP
Left Ventricular
LVEDI (mm)
LVESI (mm)
LVEF (%)
LVMI (g/m^2)
E/e'
Left Atrial with 4D LAQ
LAVImax(mL/m^2)
LAVImin(mL/m^2)
LAVIpreA(ml/m^2)
DEI (%)
PEI (%)
AEI (%)
LASr (%)
LAScd(%)
LASct (%)
ePLAGS(m/s/%)

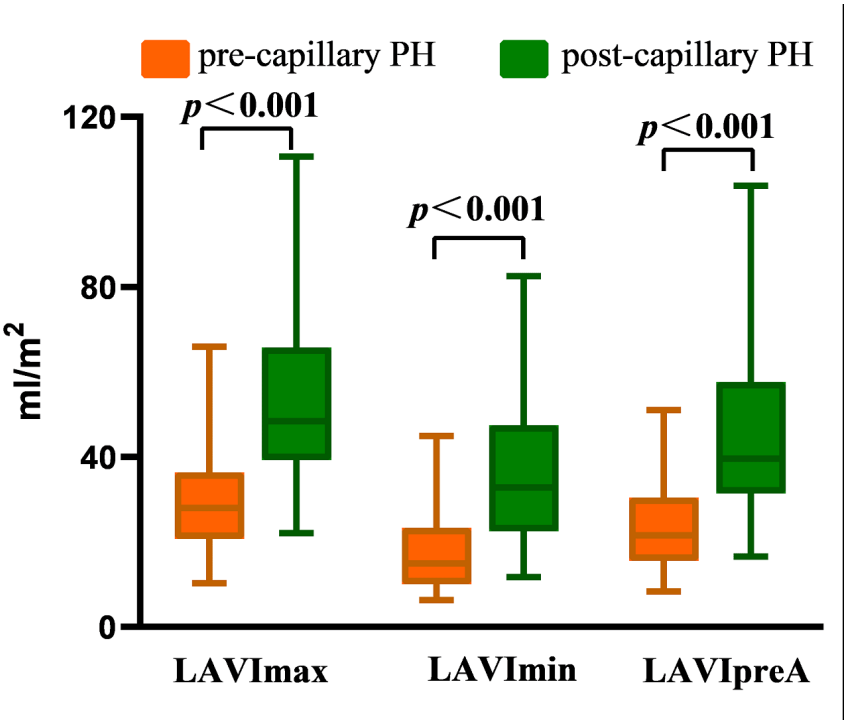
RVFAC:right ventricular fractional of area change; TRV: the maximum velocity of Tricuspid valve regurgitation; TAPSE: tr

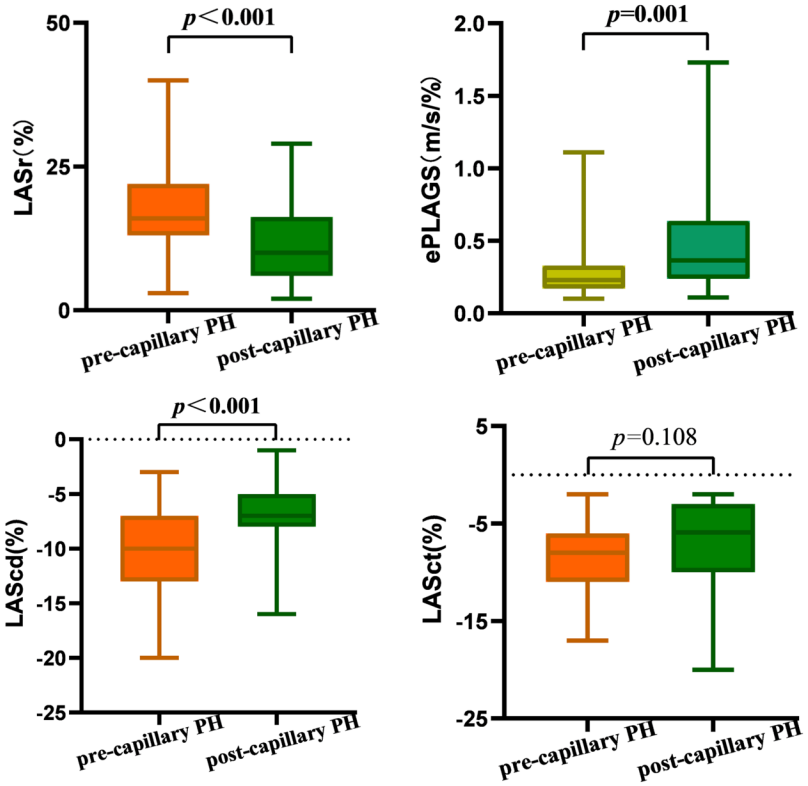
Table3 Univariate and multivariate modelling of parameters differentiatng pre-capillary from post-capillary PH

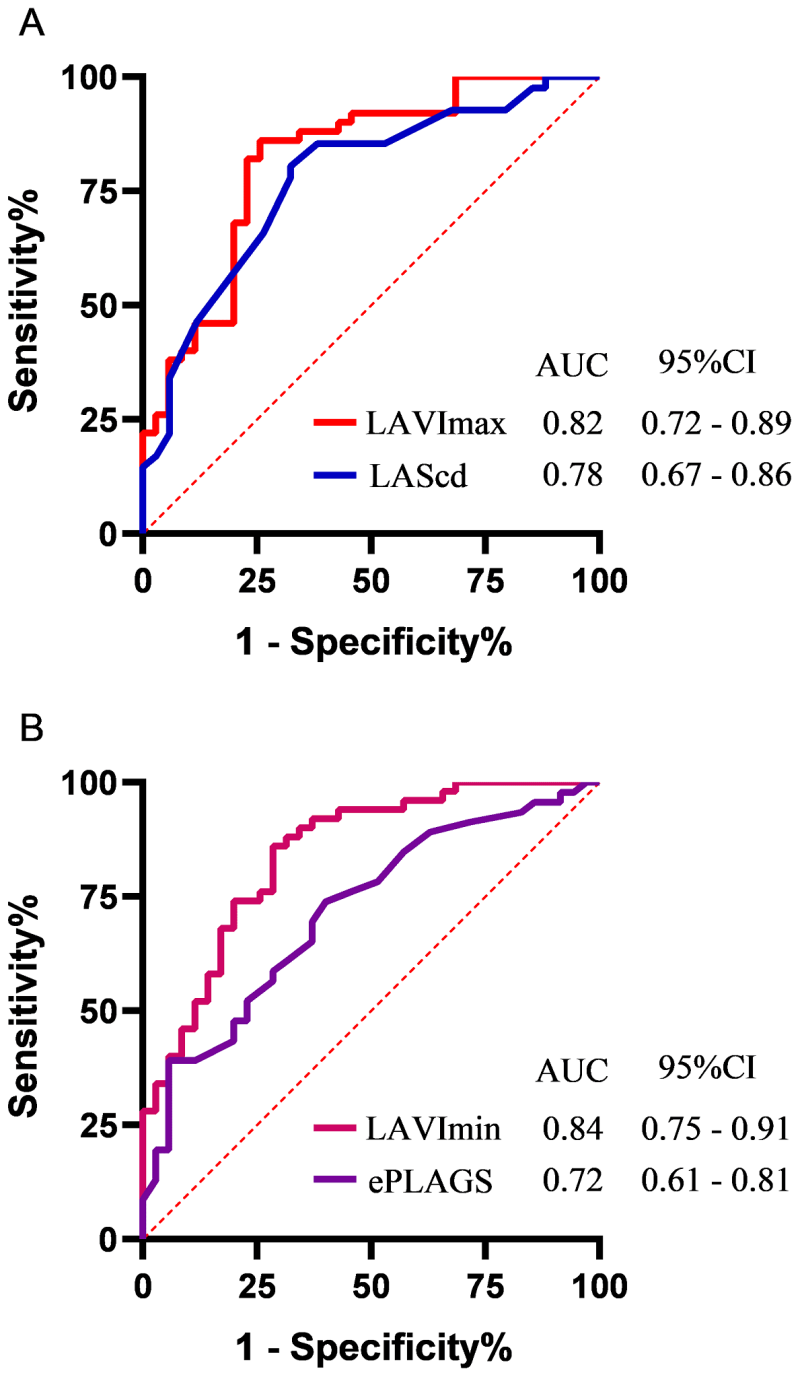
Variable
LAVImin
LAVImax
LAVIpreA
LASr
LAScd
LASct
ePLAGS
DEI
PEI
AEI
LVEDI
LVEF

LAVImax, LAVImin and LAVIpreA: The indices of left atrial maximum volume, minimum volume and volume at pre-ejecti









Abbreviations

AEI: LA active systolic function (active ejection index)

DEI: LA storage function (diastolic ejection index)

ePLAGS: echocardiographic pulmonary to left atrial global strain ratio

LAQ: left atrial quantification

LAVImax: The indices of left atrial maximum volume

LAVIpreA: The indices of left atrial volume at pre-ejection

LAVImin: The indices of left atrial minimum volume.

LASr: LA reservoir strain

LAScd: LA conduit strain

LASct: LA contraction strain.

PAMP: pulmonary arterial mean pressure

PAWP: pulmonary arterial wedge pressure

PEI: LA channel function (passive ejection index)

PH: pulmonary hypertension