A Simple and Novel Noninvasive Method of Estimating Markedly Elevated Pulmonary Vascular Resistance in Patients with Pre-capillary Pulmonary Hypertension

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Abstract

Background: Several echocardiographic methods to estimate pulmonary vascular resistance (PVR) in patients with pulmonary hypertension (PH) have been proposed. So far, most studies have focused on relatively low PVR. We aimed to clarify the clinical usefulness of our new echocardiographic index of evaluating markedly elevated PVR in pre-capillary PH patients.

Methods: We studied 129 consecutive patients with pre-capillary PH. We estimated the mean pulmonary artery pressure using echocardiography ($mPAP_{Echo}$) and measured LV internal diameter at end diastole (LVIDd). The ratio of $mPAP_{Echo}$ / LVIDd was then correlated with invasive PVR. Using receiver operating characteristic curve analysis, a cutoff value for the index was generated to identify patients with PVR > 15 Wood units (WU).

Results: $mPAP_{Echo}$ / LVIDd correlated well with PVR (r = 0.70, P < 0.0001). There was a better correlation between PVR and $mPAP_{Echo}$ / LVIDd in patients with PVR > 15 WU compared with TRV^2 /TVI_{RVOT} and $sPAP_{Echo}$ / LVIDd. A cut-off value of 1.14 had an 80.0% sensitivity and 74.7% specificity to determine PVR > 15 WU (AUC=0.840, p<0.0001).

Conclusions: The index of $mPAP_{Echo}$ / LVIDd could be a valuable noninvasive and simple method of estimating markedly elevated PVR in pre-capillary PH patients.

Background

Pulmonary vascular resistance (PVR), calculated as the transpulmonary gradient divided by pulmonary blood flow, is the important parameter of hemodynamic evaluation in the management of pulmonary hypertension (PH). Assessment of PVR usually requires right heart catheterization (RHC), which is invasive and difficult to popularize and continuously monitor patients.

Several echocardiographic methods to estimate PVR have been proposed previously. Abbas et al. in 2003 found a good correlation (r = 0.93) between the invasively measured PVR and the ratio of the tricuspid regurgitation velocity (TRV) to the velocity time integral of the right ventricular outflow tract (TVI_{RVOT}) [1]. In 2013 Abbas et al. demonstrated a more robust association between PVR and TRV^2/TVI_{RVOT}, including patients with a PVR > 6 WU [2]. However, we noticed that their study population consisted of patients with various cardiac and pulmonary pathologies and relatively low PVR (80% ≤ 6 WU), and do not take right atrial pressure into account.

It has been reported that echocardiographic methods are useful for estimating the mean pulmonary artery pressure (PAP) [3]. And it is consistent with the formula being used for the RHC. PVR increased in patients with reduced pulmonary blood flow, and left ventricular volume can reflect pulmonary blood flow. Studies have confirmed that left ventricular end-diastolic volume (LVEDV) is reduced in idiopathic pulmonary arterial hypertension (IPAH) in proportion to reduced pulmonary flow [4–5]. Therefore, we use

estimating mPAP ($mPAP_{Echo}$) and LV internal diameter at end diastole (LVIDd) surrogate for transpulmonary pressure and pulmonary blood flow respectively. Our hospital admits patients with various types of PH, with a wide range of PVR, especially patients with high PVR. A large proportion of patients with high PVR are chronic thromboembolic pulmonary hypertension patients who evaluate the risk of pulmonary endarterectomy. Measurement of patient's haemodynamic status including PVR is crucial. We hypothesized that we could establish a simpler and more accurate noninvasive method to estimate PVR.

The main objective of our study was to investigate whether the new simple method $mPAP_{Echo}$ / LVIDd would provide better estimation of PVR in situations of markedly elevated PVR.

Methods

Study Population

A total of 430 consecutive patients referred for transthoracic echocardiography and RHC evaluation of known or suspected PH between June 2015 and December 2020 were included. A subsequent of 163 patients were excluded due to an interval over 3 days between RHC and echocardiography. Patients with congenital heart disease were not included. Of the remaining 258 patients, 224 were diagnosed with PH. Pre-capillary PH was defined as pulmonary arterial pressure (mPAP) of ≥25 mmHg at rest, pulmonary arterial wedge pressure ≤15 mmHg and pulmonary vascular resistance (PVR)>3 Wood units [6]. 11 patients with PAWP > 15mmHg and 84 patients without pulmonary regurgitation were excluded for a final study cohort of 129 pre-capillary PH patients (Figure 1). Table 1 described the diagnosis of all the participants according to 2015 ESC Guidelines [7]. This study was approved by China-Japan Friendship Hospital's Human Research Ethics Committee.

Right Heart Catheterization

A 7F Swan-Ganz catheter Philips Allura X-PER FD20 flat-plate angiography system (Baxter Inc) was used to measure systolic, diastolic, and mean pulmonary arterial pressure (PAP), mean right atrial pressure (RAP), and mean pulmonary capillary wedge pressure (PCWP). Cardiac output was measured using the Fick method, which calculated the cardiac index (CI). The transpulmonary gradient (TPG) was calculated by subtracting the mean PAP from the PCWP. Pulmonary vascular resistance (PVR) (Wood units, WU) was calculated by dividing the TPG by the cardiac output.

Echocardiography

Within 3 days of RHC, two-dimensional and Doppler echocardiography were performed using the Vivid E95 ultrasound system (General Electric Healthcare, Vingmed, Horten, Norway) with a M5S transducer. The subjects were placed in the left lateral position, and at least three consecutive beats were stored.

Two-dimensional (2D) and Doppler echocardiography were performed in accordance with current guidelines [8]. Analysis of the images was performed offline using the EchoPac software version 201 (General Electric Healthcare, Vingmed, Horten, Norway). LV internal diameter at end-diastole (LVIDd) was acquired in the parasternal long-axis view by M-mode. The ultrasound beam is aligned so that it is perpendicular to the interventricular septum and posterior wall at a level of the mitral leaflet tips (Figure 2). TVI_{RVOT} was obtained by placing a 1-mm to 2-mm pulsed wave Doppler sample volume in the proximal right ventricular outflow tract when imaged from the parasternal short-axis view. The average of three measurements was used for LVIDd and TVI_{RVOT}. The peak tricuspid regurgitant velocity (TRV) was measured as the highest of the velocities obtained from the lower parasternal and apical multiple views. The early diastolic pulmonary regurgitation velocity (PRV) was measured as the highest of the velocities obtained from the parasternal short-axis view (Figure 2).

Noninvasive estimation of RAP was based on the size and collapse index of the IVC and was scored as either 3 mmHg, 8mmHg, or 15mmHg [8]. Doppler echocardiographic determination of mean PAP ($mPAP_{echo}$) was estimated as $4\times(\text{early PRV})^2$ + estimated RAP. Doppler echocardiographic determination of systolic PAP ($sPAP_{echo}$) was estimated as $4\times TRV^2$ + estimated RAP.

The first method was based on the index of $mPAP_{Echo}$ / LVIDd. The second method was based on the ratio of $sPAP_{Echo}$/ LVIDd. The TRV^2/TVI_{RVOT} ratio was also calculated, as described by Abbas et al[2].

Statistical Analysis

Continuous data are presented as the mean ± standard deviation, and categorical data are presented as percentages. Correlations between variables were assessed using Pearson's correlation coefficient. Receiver operating characteristics (ROC) curve were performed to determine echocardiographic cutoff values for detecting PVR > 6 WU and 15 WU. Intra-observer and inter-observer reproducibility were assessed in randomly selected 30 subjects. Inter-observer reproducibility was tested by two independent observers. Inter-observer and intra-observer reproducibility were evaluated by means of intraclass correlation coefficient (ICC). Statistical analyses were performed using SPSS 17.0 software (SPSS Inc, Chicago, USA).

Results

The main clinical, hemodynamic and basic echocardiographic characteristics of the studied patients are presented in Table 1.

Table 1

Baseline Characteristics of Study Population

Variable	Pre-capillary PH (n = 100)
Demographic characteristics	
Age (years)	48±14
Male (%)	52(40%)
BSA (m^2)	1.7±0.8
Aetiology of PH	
PAH	51
CTEPH	69
Lung disease	3
Others	6
WHO functional class	
I/II	61
III/IV	68
Elevated BNP or NT-proBNP (%)	80(80%)
Right heart caheterization	
Systolic PAP (mmHg)	81±24
Mean PAP (mmHg)	46±14
Mean RAP (mmHg)	3.3±5.1
PAWP (mmHg)	7.1±5.0
PVR (WU)	14.6±7.5
CI (L/min/m^2)	2.1±0.9
Echocardiography	
LVIDd (mm)	39.3±5.4
LVEF (%)	69±6
RA minor-axis dimension (mm)	50.9±9.4
RV basal diameter (mm)	47.4±7.0
RV/LV basal diameter ratio	1.4±0.3
HR (beats/min)	78±15
TRV (m/s)	430±67

TRPG (mmHg)	75.9±22.5
PREDG (mmHg)	34.2±12.3
TVI_{RVOT} (cm)	11.1±3.8
TRV^2/TVI_{RVOT}	8.6±3.7
$mPAP_{Echo}$ / LVIDd	1.1±0.4
$sPAP_{Echo}$/ LVIDd	2.2±0.8
TAPSE (mm)	15.6±3.5
S' (cm/s)	10.0±2.4
RV FAC (%)	28.8±8.3

BSA, body surface area; PAH, pulmonary arterial hypertension; CTEPH, chronic thromboembolic pulmonary hypertension; CTD-PAH, connective tissue disease induced PAH; BNP, brain natriuretic; NT-proBNP, N-terminal fragment of pro-B-type natriuretic peptide; PAP, pulmonary artery pressure; RAP, right atrial pressure; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance; WU, wood units; CI, cardiac index; LVIDd, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; RA, right atrial; RV, right ventricular; HR, heart rate; TRV, tricuspid regurgitation velocity; TRPG, tricuspid regurgitation pressure gradient; PREDG, pulmonary regurgitation early-diastolic gradient; IVC, inferior vena cava; TVI_{RVOT}, velocity time integral of the right ventricular outflow tract; $mPAP_{Echo}$, echocardiographic determination of mean PAP; $sPAP_{Echo}$, echocardiographic determination of systolic PAP; TAPSE, tricuspid annular plane systolic excursion; RVFAC, right ventricular fractional area change;

Linear regression analysis between PVR and TRV^2/TVI_{RVOT} revealed a weak correlation ($r=0.47$, $P<0.001$; Figure 3A). $sPAP_{Echo}$/ LVIDd significantly correlated with PVR ($r = 0.56$, $P <0.0001$; Figure 3B). There was a better correlation between PVR and $mPAP_{Echo}$/ LVIDd ($r = 0.70$, $P < 0.0001$; Figure 3C)

For patients with PVR ≤ 15WU, there were similar correlations with both $TRV^2/TVI_{RVOT}$and $mPAP_{Echo}$/ LVIDd and $sPAP_{Echo}$/ LVIDd ($r = 0.43$, $P < 0.05$; $r = 0.52$, $P < 0.0001$; $r = 0.52$, $P < 0.0001$, respectively; Figures 3D~F). However, in patients with PVR > 15 WU, the correlation markedly improved with $mPAP_{Echo}$/ LVIDd compared with $TRV^2/TVI_{RVOT}$and $sPAP_{Echo}$/ LVIDd ($r = 0.60$, $P < 0.0001$; $r = 0.21$, $P > 0.05$; $r = 0.37$, $P < 0.05$, respectively; Figures 3G~I).

In the ROC curve analysis, the $TRV^2/TVI_{RVOT} \geq 5.18$ had an 87.2% sensitivity and 100.0% specificity to determine PVR > 6 WU. Its area under the curve (AUC) is 0.942 ($P < 0.01$, 95% CI, 0.86–1.00), which is higher than the AUC of $mPAP_{Echo}$/ LVIDd (0.831) and the AUC of $sPAP_{Echo}$/ LVIDd (0.836).

As shown in Figure 4, the $mPAP_{Echo}$/ LVIDd ≥ 1.14 had an 80.0% sensitivity and 74.7% specificity to determine PVR > 15 WU. Its AUC is 0.840 ($P < 0.0001$, 95% CI, 0.76–0.92), which is higher than the AUC of

TRV^2 /TVI_{RVOT} (0.772) and the AUC of $sPAP_{Echo}$/ LVIDd (0.827).

Reproducibility

The inter-observer ICC was 0.83 for TVI_{RVOT} and 0.97 for LVIDd, and the intra-observer ICC was 0.88 and 0.99 for TVI_{RVOT} and LVIDd. LVIDd demonstrated better inter-observer and intra-observer reproducibility than TVI_{RVOT}.

Discussion

This study demonstrates that the index of $mPAP_{Echo}$ / LVIDd represents a simpler and better method of estimating markedly elevated PVR in pre-capillary PH patients.

A number of echocardiographic methods have been proposed for the noninvasive estimation of PVR [1–2, 9–12]. However, most methods acquired formulas containing various empirical constants, which would affect the accuracy of the estimating PVR results. The guidelines of the American Society of Echocardiography recommended the noninvasive estimation of PVR should not be used as a substitute for invasive evaluation of PVR[3]. However, pulmonary vascular resistance still needs to be evaluated in PH patients, especially continuous preoperative and postoperative monitoring in IPAH and CTEPH patients. PVR higher than 1200 $dyn{\cdot}s{\cdot}cm^{-5}$ (15WU) is considered to be severe and is correlated with an increased risk of post-operative mortality [13–14]. We proposed a simple method to help clinically identify patients with extremely high PVR values (> 15 WU) instead of generating a regression equation compared to previously reported methods.

Our results showed that both Abbas et al [2] and our new methods correlate similarly for patients with lower PVR values (PVR ≤ 15 WU). However, for PVR > 15 WU, the correlation appeared stronger with $mPAP_{Echo}$ / LVIDd compared with TRV^2/TVI_{RVOT}. Moreover, the AUC of $mPAP_{Echo}$ / LVIDd is higher than the AUC of TRV^2 /TVI_{RVOT} to determine PVR > 15 WU. The new method has its own advantages. The underlying explanations are as following:

The echocardiographic estimation of mean PAP is more consistent with PVR formula. The mean PAP reflects the driving pressure that is required for pulmonary blood flow more accurately than systolic PAP. PR is reported to occur in almost 75% of the population [15]. Dilation of the annulus and main pulmonary artery are usually accompanied by PH patients. PR secondary to PH is common, thus it is easy to obtain the complete PR Doppler signal. It has been reported that the early-diastolic PA-RV pressure gradients derived from the peak early-diastolic PR velocity is useful for estimating the mean PA pressure [3, 16–17]. In our study, TR could be obtained in 117 of 129 patients (90%). Among these patients, 10 had severe TR, 41 had not well-defined TR signal quality, which may lead to overestimation or underestimation of pulmonary arterial pressure [18–20]. Abbas et al. method [1–2] and Haddad et al. method using TRV to calculate systolic PAP and Lindquist et al. method[9] using TRV to calculate mean PAP may be inaccurate

in patients under these circumstances. Extremely severe PR is rare in patients with PH. Therefore, we consider that the mean PAP estimated by PR Doppler signal is more reliable when PR is present. TRV can be measured to estimate systolic PAP when PR is absent.

Compared to the method of Abbas et al [2] and Kaga et al [10], the new method also takes into account the contribution of RAP to estimate mPAP. Current guidelines have suggested that RAP predicts prognosis of PAH [7]. For patients with PVR > 15 WU, RAP will also be higher. So, the estimated RAP will contribute more to $mPAP_{Echo}$ in patients with PVR > 15 WU. Although Haddad et al. [12] took RAP into account, according to the size and collapse index of the IVC, RAP was estimated to be 10 mmHg, 15mmHg, or 20mmHg, which would lead to overestimation of RAP.

PH results in the reduced of pulmonary blood flow, which also causes the reduced of the blood flow back to the left atrial and ventricular. In addition, there is a leftward displacement of the interventricular septum during diastole of LV in sever PH patients, due to the presence of right ventricular pressure overload [21–22], which will further lead to the compression of the LV cavity. Grzegorz et al. [5] reported that LVEDV in IPAH patients correlated inversely with PVR and LVEDV is reduced in PH patients in proportion to reduced pulmonary flow. Therefore, LVEDV represents pulmonary blood flow in pre-capillary PH and is significantly reduced in patients with extremely high PVR. LVIDd, as an alternative indicator of LVEDV, is easier to obtain and more suitable for routine applications. Moreover, LVIDd had better repeatability and accuracy than TVI_{ROVT}. In patients with PH, the dilatation of main pulmonary artery caused pulmonary valve to move forward. When obtaining the flow velocity in the RV outflow tract, the Doppler sampling line had a larger angle with the direction of blood flow, which would affect the accuracy of the measurement of TVI_{ROVT}. In addition, when the velocity of the RV outflow tract was low, the contour of the spectrum was not clearly displayed, which would affect the repeatability of the measurement.

Our novel index has utility for predicting patients with markedly elevated PVR, which is of great value in etiological diagnosis, disease severity and continuous monitoring of PVR before and after treatment.

Limitations

There are several limitations in this study. Although the clinical condition of the patients was stable during each examination, RHC and echocardiography were not performed simultaneously, which affected the accuracy of the comparison. Second, this study was only applicable to patients with pre-capillary PH. However, we usually pay more attention to the PVR of pre-capillary PH patients rather than post-capillary PH patients in clinical practice. Third, this study was a single-center retrospective study. Further prospective multicenter studies involving larger patient populations are required to confirm the results.

Conclusion

The novel, simple and noninvasive index, $mPAP_{Echo}$ / LVIDd, can be clinically used in the routine echocardiographic evaluation for PH and can be a valuable noninvasive and simple method of

estimating markedly elevated PVR in pre-capillary PH patients. As compared with conventional methods, the ratio of $mPAP_{Echo}$ / LVIDd > 1.14 showed good sensitivity and specificity for identifying markedly elevated PVR (> 15 WU).

Declarations

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Author contributions

Ai-Li Li created the idea and designed the study. Ai-Li Li and Ya-Nan Zhai performed research, collected data, analyzed the results and wrote the manuscript. Xin-Cao Tao provided the data of RHC. Wan-Mu X

ie, Qian Gao helped in collecting the cases. Yu Zhang, Ai-Hong Chen helped organizing data. Jie-Ping Lei helped analyzed the statistical data. Min Liu, Zhen-Guo Zhai and Jin-Gang Zheng gave support of the study. All authors have given approval to the final version of the manuscript.

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Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The study protocol was approved by China-Japan Friendship Hospital's Human Research Ethics Committee (2020-95-K59). All patients gave informed written consent before inclusion.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests

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Figures

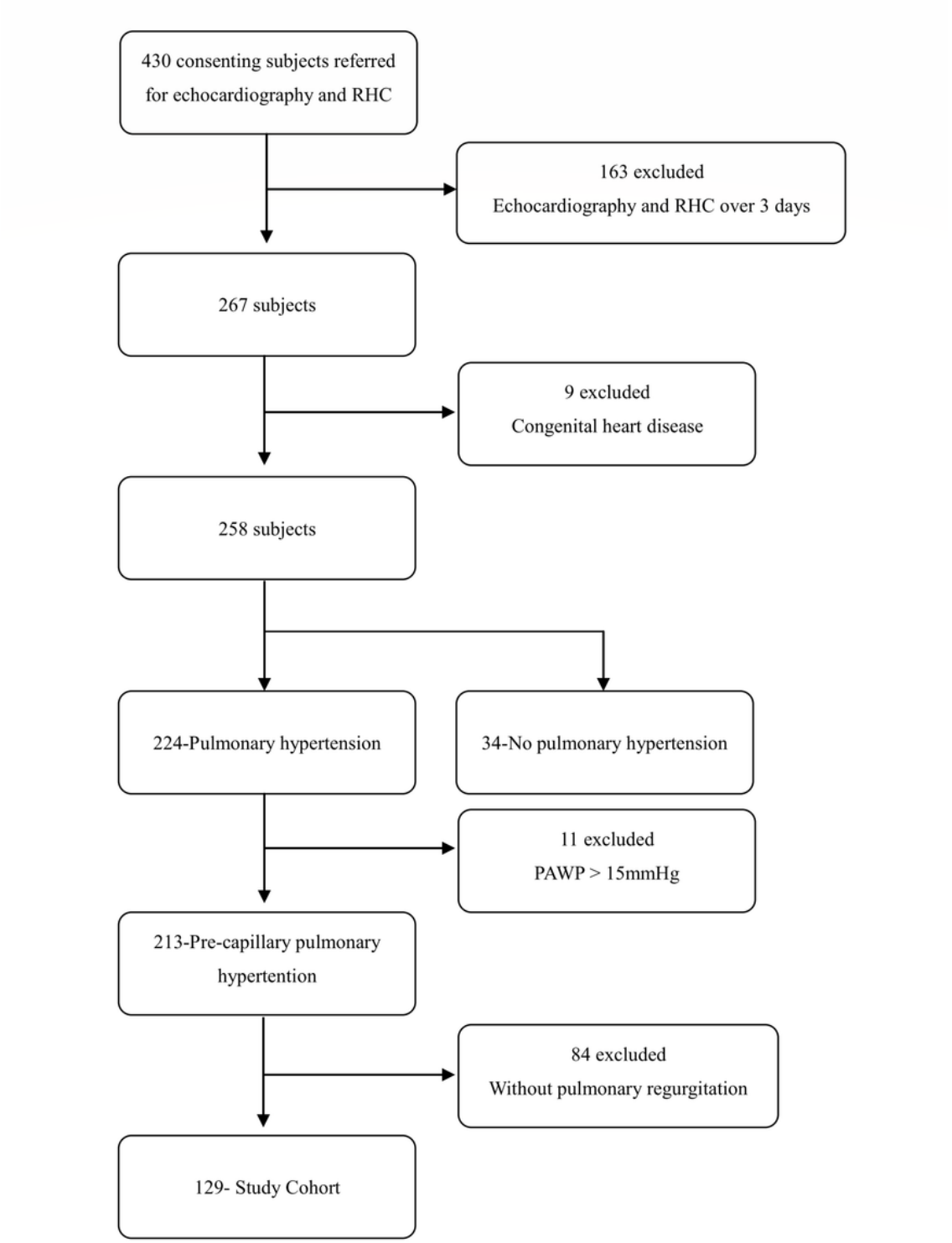

Figure 1

Study flow diagram.

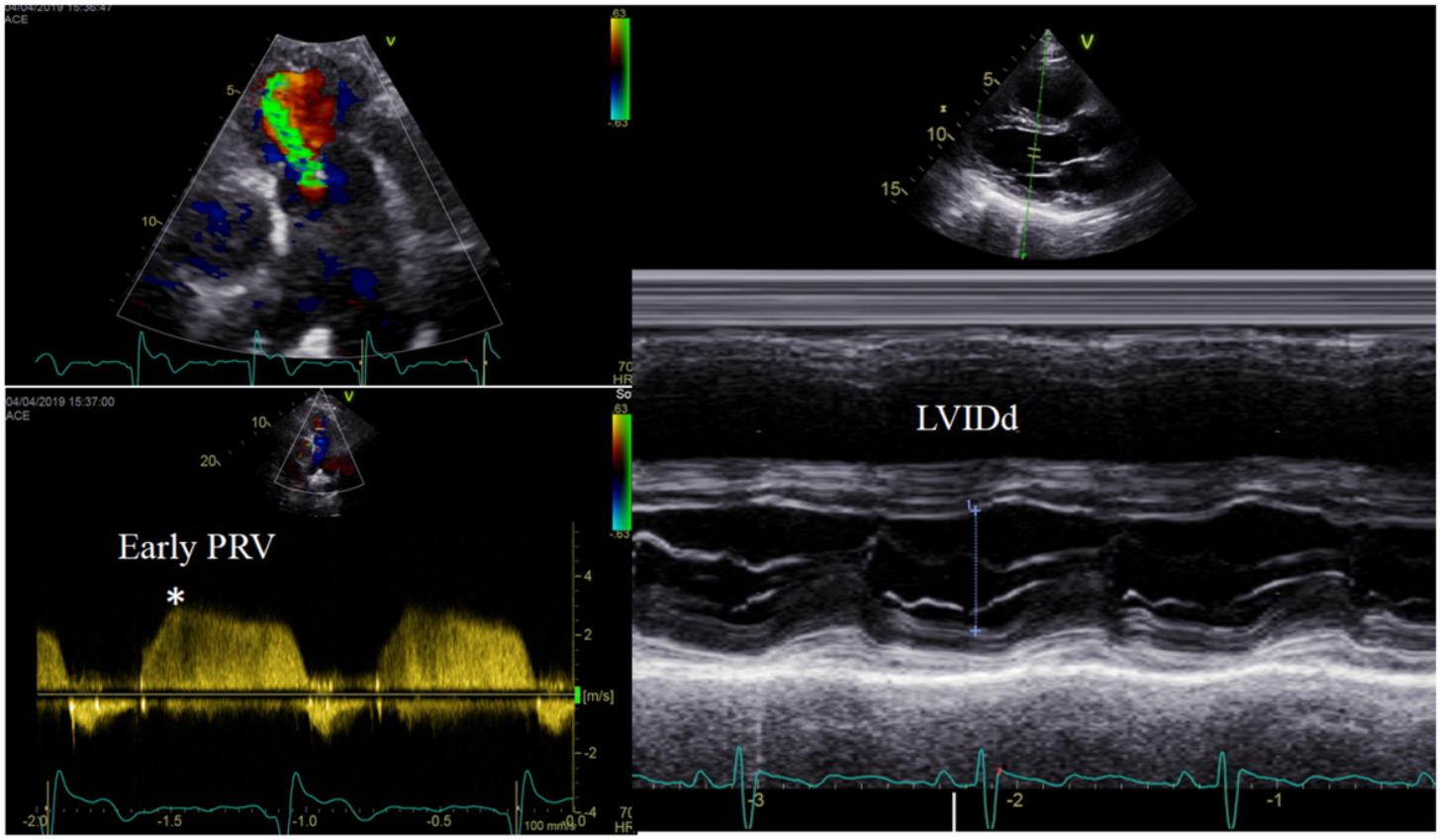

Figure 2

A. The early diastolic pulmonary regurgitation velocity (PRV) was measured to calculate mean pulmonary artery pressure. B. LV internal diameter at end-diastole (LVIDd) was acquired in the parasternal long-axis view at a level of the mitral leaflet tips by M-mode.

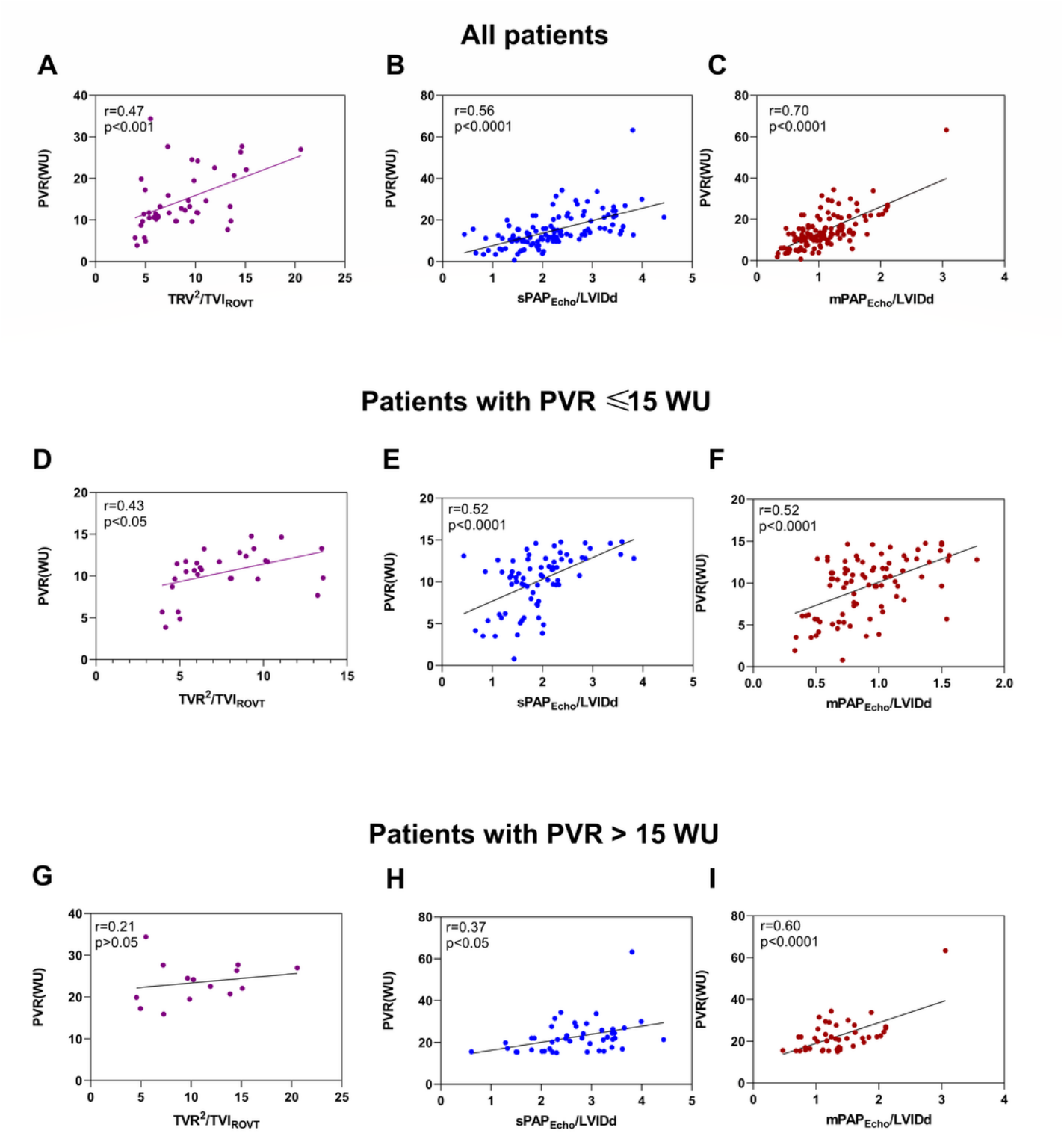

Figure 3

Linear regression analysis between PVR and TRV2 /TVIRVOT , sPAPEcho / LVIDd and mPAPEcho / LVIDd in the entire study cohort (A~C), in patients with PVR ≤ 15 WU (D~F), and in patients with PVR > 15 WU (G~I).

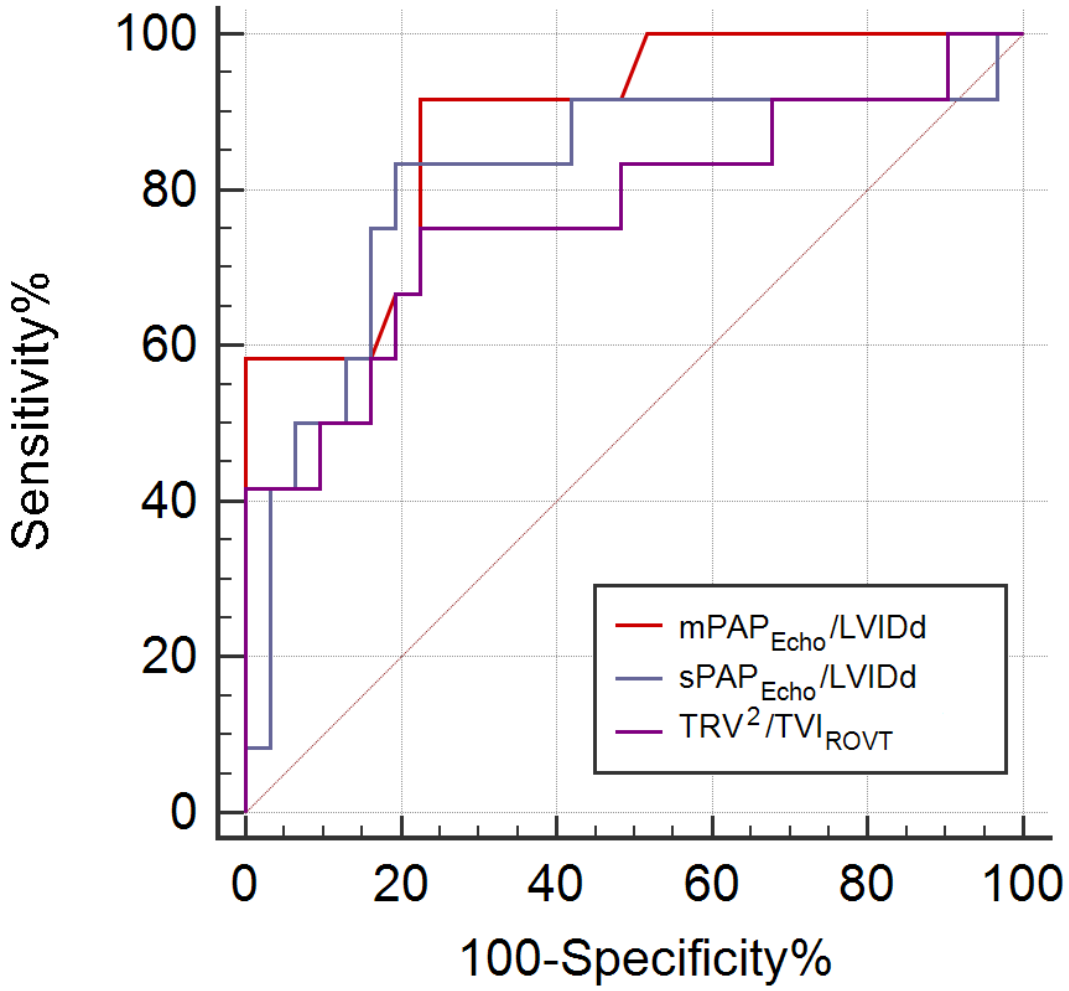

Figure 4

Receiver operating characteristic curves for TRV2 /TVIRVOT, sPAPEcho / LVIDd and mPAPEcho / LVIDd to distinguish PVR > 15 WU.