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Diagnosing pulmonary hypertension due to left heart disease using diastolic echo markers: The National Echo Database of Australia (NEDA) PH-LHD predictive formula

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Chapter 3. Original Research Article (Paper 2)

Differentiating Pre-Capillary and Post-Capillary Pulmonary Hypertension by Doppler Echocardiography in a Large Real-world Database

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1. Introduction

Pulmonary hypertension (PH) is defined by mean pulmonary artery pressure (mPAP) ≥ 25mmHg at rest (1, 6). It is a potentially fatal, debilitating pathology with poorly understood epidemiology (2, 7-9). The clinical classification of PH consists of 5 different groups (10) according to the underlying pathophysiology (10, 11). Management and prognoses of PH patients vary greatly depending on the underlying aetiology. The majority of PH is secondary to left heart diseases (2, 12, 13) and these patients need to be differentiated from patients with pulmonary arterial hypertension, who will benefit from modern vasodilator therapy. Right heart catheterization (RHC) can provide useful haemodynamic parameters to differentiate the underlying pathologies. However, RHC is not readily available, is operator dependent, and can be associated with potentially serious risks.

Because of the complexity in diagnosis and the low level of awareness, PAH patients are often misdiagnosed or the diagnosis is significantly delayed, leading to a worse prognosis (14, 15). The symptoms of early PAH may be subtle and non-specific. The first objective evidence of PH is usually provided by Doppler echocardiography. Pulmonary artery systolic pressure (PASP) can be estimated by applying modified Bernoulli equation to the maximal tricuspid regurgitation velocity (TRV) and adding the assumed right atrial pressure (16). A PASP of over 40mmHg is commonly used as the echocardiographic cut-off to define PH but this is non-specific and does not localise the site or mechanism of the problem. Although the former can usually be defined by RHC,

it is not feasible or appropriate for all patients with elevated estimated PASP by echo to undergo invasive investigation.

Haemodynamically, PH can be classified into pre-capillary PH (prePH) and post-capillary PH (postPH) based on the pulmonary capillary wedge pressure (PCWP) obtained by RHC (1, 6). Patients with prePH have pulmonary vascular disease manifesting as a normal PCWP (≤15mmHg) and a high pulmonary vascular resistance (PVR) (>3 Wood units, WU) (6). PostPH is characterised by a high PCWP (>15mmHg), usually caused by increased left heart filling pressure (e.g. systolic or diastolic heart failure). Within the PostPH group, some patients develop pulmonary vascular disease, resulting in a high PVR, causing an out-of-proportion rise in the PAP (PVR>3WU). Therefore, a complex picture may emerge requiring measurement of the PAP, PVR and PCWP (1, 6).

The original formula for PVR_{echo} (TRV/TVI_{RVOT} x 10) was described by Abbas et al. in a study involving 44 patients (17) who had simultaneous echos and RHC. The original formula provided correlation coefficient (r) of 0.929 in the original study. However, the formula was revised to TRV^2/TVI_{RVOT} x 5 in 2013 after the meta-analysis on the data of 150 patients from five validation studies. The revised formula had better correlation than the original formula (r=0.79 vs 0.76) to invasively measured PVR, when applied to the meta-analysis data of 150 patients (18).

The ePLAR was recently proposed as a surrogate echo marker of TPG and as a non-invasive marker of PVR in patients with PH (19). The ePLAR is a simple ratio of the

maximal velocity of tricuspid regurgitation (TRV) and the ratio of early mitral filling velocity and the mitral annular velocity (E/e'), thus the ePLAR=TRV/(E/e'). TRV is routinely used to estimate pulmonary artery systolic pressure (PASP) (16) and mitral E/e' is a validated marker of left atrial pressure (20-22).

2. Study Objectives

We aimed to investigate the ability of the ePLAR (19), to differentiate between prePH and postPH, in a real-world database containing RHCs and echos. We also aimed to test the performance of ePLAR against the previously published PVR_{echo} by Abbas at el. (17, 18, 23).

3. Methods

A retrospective cohort study was conducted at the Royal Perth Hospital, a referral centre for PH patients. Human Research Ethics Committee approvals from both the University of Notre Dame and Royal Perth Hospital were obtained. The data from all RHCs performed for various indications, between January 2010 and February 2015 was automatically extracted from the hospital database (AXIOM Sensis XP information system, version VC11D). The echos of patients in the RHC database were then extracted from the National Echo Database Australia (NEDA). The closest corresponding echo and RHC was extracted and the two databases were merged. Data analysis was performed using IBM SPSS Statistics software version 24.

The cases with calculable ePLAR were categorised into normal pulmonary pressure and PH groups using the mean pulmonary artery pressure (mPAP) values (mPAP≥25mmHg to define PH) from the RHC data. The PH group was further classified into prePH and postPH according to the pulmonary capillary wedge pressure (PCWP>15 to define postPH). The postPH group was further classified into in-proportion (isolated postPH) and out-of-proportion (combined pre-and postPH) using the diastolic pulmonary gradient (DPG) since pulmonary vascular resistance (PVR) was only available in a small number of cases. DPG is calculated as the difference between the diastolic pulmonary artery pressure and PCWP. DPG is less sensitive to changes in cardiac output and left atrial pressure. It has become the preferred measurement over the TPG and recommended in recent guidelines to detect the pulmonary vascular remodelling in PH-LHD(1). However, the studies that investigate the prognostic value of DPG have been showing mixed results (24-26). The TRV was recorded using continuous wave Doppler while E wave was recorded using pulsed wave Doppler. The septal e' wave by tissue Doppler was used to calculate ePLAR for consistency.

3.1. National Echo Database Australia (NEDA)

National echo database Australia (NEDA) is a large, longitudinal, non-interventional study collecting comprehensive echo measurements and text interpretation information from multiple participating echocardiography laboratories around Australia, both prospectively and retrospectively (27). NEDA is headed by 2 principal investigators and a steering committee of eminent cardiologists and researchers. It is a real-world database study aiming to take advantage of big data collection as well as increasing sophistication

of modern echocardiography practice. The linkage of NEDA with health outcome data such as national death index will provide unique ability to analyse the population data and investigate valuable echocardiographic markers that predict the risks associated with multiple cardiovascular pathologies such as pulmonary hypertension, valvular heart disease and heart failure. Currently, NEDA study has been approved in 20 large Australian Hospitals and the database is growing. It has collected the echo data from 435,122 individuals to date (28).

The vender-neutral data extraction tool was developed by the team of NEDA engineers which can be applied to the imported data from individual echo laboratories. The imported data is then transformed into standardized database using the NEDA data dictionary, given the differing variable names with each echocardiography vendor. The NEDA data transfer and transformation process are illustrated in figure 1 and 2 in the appendix session (page 56).

4. Statistical Analysis

Continuous variables were skewed and are reported as median and interquartile range (IQR), with statistical significance assessed by Mann Whitney U test. The categorical variables are reported as number and percentages. Chi-square tests were used to compare categorical variables.

The accuracy of echocardiography to detect PH by RHC criteria (mPAP≥25mmHg) was calculated using cross tabulation and ROC curve analyses. The sensitivity, specificity

and predictive values of various ePLAR cut-offs to detect postPH were calculated by cross tabulation and ROC curve analyses. Correlations of ePLAR to RHC variables (DPG, TPG and PVR) were also calculated using Pearson's correlation coefficient. Binominal logistic regression was used to examine the performance of ePLAR to predict postPH, in comparison with other echo variables and markers (left ventricular ejection fraction, Mitral E velocity and age). ROC curve analysis was used to compare the accuracy of ePLAR and PVRecho. The correlation between components of TPG (mPAP and PCWP) and ePLAR (TRV and E/e') were also examined by linear regression.

5. Results

During the study period, 997 RHCs were recorded on a total of 836 patients. Using identifiers from the RHC database, 887 echos on a total of 732 patients were found within the NEDA. The databases were merged into a single database for further analyses. The median time difference between the two procedures was 7 (interquartile range 1-62) days.

5.1. Agreement between Echo and RHC to diagnose PH

Pulmonary artery systolic pressure (PASP) was recorded in 73% (n=649) of echos. Fifty four percent (n=476) had pulmonary hypertension by echocardiographic criteria (PASP≥40mmHg). Sixty eight percent of RHC (n=601) had mPAP≥25mmHg. The sensitivity and specificity of echocardiography to detect pulmonary hypertension using

RHC as gold standard was 82% and 49% (r=0.63, p=<0.001) using the cut-offs of PASP≥40mmHg for echo and mPAP≥25mmHg for RHC to define PH.

5.2. ePLAR cohort

The ePLAR could be calculated in 21% (n=184) of patients, of which 32% (n=59) did not have PH (mPAP<25mmHg). The median ePLAR (IQR) of these cases without PH was 0.16 (0.11-27) m/s. The breakdown on the ePLAR cohort is illustrated in figure 1. One hundred and twenty-five cases with PH (mPAP≥25mmHg) and measurable ePLAR were divided into pre-capillary (PCWP<15mmHg, n=18) and post-capillary (PCWP≥15mmHg, n=105) physiologies. Two RHCs had no recorded PCWP. Despite similar mPAP, prePH patients had a median ePLAR (IQR) of 0.35 (0.13-0.50) m/s vs 0.17 (0.12-0.23) m/s (P=0.003) for postPH patients. The comparison of demographic, RHC and echo variables between the two groups is summarized in Table 1. Similar comparison was also made for isolated postPH and combined pre-and post-capillary PH patients (table 2). The ePLAR cut-offs value of <0.25m/s and <0.28m/s had positive predictive values (PPV) of 93% and 94% respectively for postPH (figure 2), with reasonable sensitivity and specificity (78% and 67% for <0.25m/s and 83% and 67% for <0.28m/s) (Appendix 3).

The correlations between the ePLAR and DPG, TPG and PVR were also examined. PVR was only calculable in 47 out of 184 cases in the ePLAR cohort due to cardiac output (CO) being infrequently measured in our database. In this subgroup, Pearson's correlation coefficients (r) of ePLAR to DPG, TPG and PVR were 0.19 (p=0.097), 0.02

(p=0.44) and -0.05 (p=0.37) respectively (Appendix 3). Pearson's correlation coefficient (r) between TRV and mPAP was modest at 0.58 (p value = <0.001) while r between the PCWP and E/e' was weak at 0.25 (p = < 0.001). Binominal logistic regression was performed to test the impact of the ePLAR, left ventricular EF, mitral E velocity and age on the likelihood of individuals having postPH. Increasing ePLAR value, EF and age were associated with reduction in likelihood of postPH while increasing mitral E velocity was associated with higher likelihood of postPH. ePLAR performed better than any other covariates (regression coefficient=-6.46, p=0.017) (Appendix 3).

5.3. ePLAR against PVR_{echo} in differentiating prePH and post PH

To compare ePLAR against other non-invasive echo markers used to separate postPH from prePH, we applied two commonly used formulae to our data. PVR was calculable using Abbas' formulae (17, 18) in 24% (n=209) of the combined echo and RHC cohort. Of these individuals 146 had a RHC that was consistent with PH (mPAP≥25mmHg). The mean PVR_{echo} value for 33 cases with prePH was similar to that of 113 cases with postPH: 3.7+/-2 WU vs 3.9+/-2 WU (p=0.67). ROC curves confirm that ePLAR (both cut-off values of 0.25 and 0.28) is a better discriminator of postPH than the Abbas PVR_{echo} formulae (using a cut-off <3 to define postPH), figure 3.

6. Discussion

The current study confirms that the ePLAR is a useful non-invasive method to help differentiate prePH from postPH. Patients with postPH who have lower TPG and DPG

were found to have low ePLAR values, indicating the usefulness of ePLAR in highlighting patients with PH-LHD (Group 2 PH). Certainly, in the current study the clear majority of patients with PH had evidence of an isolated post-capillary mechanism and in these patients, RHCs might have been avoided if there was a well validated non-invasive surrogate to RHC – such as ePLAR. On the other hand, PH patients with higher ePLAR have prePH physiology (higher TPG and DPG) and they may require further testing including RHC to further clarify the underlying pathologies.

The main strength of ePLAR is its simplicity. Its calculation only requires two Doppler variables (TRV and E/e') which are easily measurable. It should not take extra time or effort for one to measure ePLAR while performing a routine echocardiography. Instead of using pulmonary artery systolic pressure estimation which requires the estimation of right atrial pressure which can be a further source of error, the formula uses TRV on its own. The correlation between E/e' ratio and left atrial pressure has also been well validated in previous studies, even in the presence of atrial fibrillation(22, 29, 30). In theory, the ratio between the pulmonary pressure represented by TRV to left atrial pressure represented by E/e' should correlate well with transpulmonary gradient (TPG) which is calculated as the mean pulmonary artery pressure minus the pulmonary capillary wedge pressure (PCWP) representing the left atrial pressure. Although the calculation of ePLAR does not include a measurement that represents blood flow or cardiac output, it performed better than the commonly used PVR_{echo} formulae in differentiating two major PH physiologies.

6.1. Prior Studies

Previous investigators had examined a variety of non-invasive surrogate markers of PVR (17, 18, 23) to differentiate the underlying aetiologies of PH. Some of these markers have been validated in subsequent studies and proved to be useful; however, most of these studies had small sample sizes. A combined clinical and echo risk scoring system was also proposed to identify PH-LHD and reduce the number of unnecessary RHCs (31). In its foundation study involving 133 PH patients who had RHC, ePLAR was found to have good accuracy in differentiating prePH and postPH (19).

6.2. Strengths and limitations

The data for this study were extracted automatically from large databases, minimising the risk of any human error. In addition, our study has the advantage of testing the usefulness of the ePLAR in a 'real-world' dataset. Our study is also larger than previous studies despite the low percentage of patients with calculable ePLAR. It does, however, also have some limitations. The most important of these is that the RHC and echo data were not acquired simultaneously. This may explain the modest correlation between the two modalities in terms of defining PH, though previous data have shown similar associations even during simultaneous measurements (32). Although ePLAR has provided a good discriminatory power between two PH physiologies, its accuracy needs further improvement. In the current study, the optimal ePLAR cut-off of <0.28 gives sensitivity of 83% which means there are still considerable chance of having false negative test results. To be clinically useful as a non-invasive tool, ePLAR should have very high sensitivity and low false negative rate, given the dire consequence of missing

PAH patients which has proven specific therapy.

Another inherent weakness of the ePLAR, as well as the PVR_{echo} formulae, is that both require measurement of TRV which cannot be accurately estimated in some patients. The TRV was not available in 45% of echos in our study in keeping with previous data suggesting that approximately 1 in 3 echos do not have evaluable TR velocities (2). Although we lacked clinical data in our study, the primary purpose was to compare invasive and non-invasive methods of estimating pulmonary vascular resistance rather than diagnosing the final cause of pulmonary hypertension. Moreover, cardiac output was infrequently measured during RHC and subsequently PVR_{RHC} was not calculable in most of the patients in the database. Only 4 % (n=35) of cases have both measurable PVR_{echo} and PVR_{RHC}. Furthermore, some components of ePLAR and PVR_{echo} were either not routinely measured or recorded in our database; contrary to our expectation.

Despite these limitations, ePLAR appears to be a useful non-invasive tool to help differentiate prePH from postPH. A prospective study, involving simultaneous measurements of echo and RHC parameters, in a group of patients with different haemodynamic classes of PH, is needed to further investigate the performance of ePLAR. This will also increase the percentages of studied subject with calculable ePLAR.

7. Conclusions

We have investigated the performance and feasibility of ePLAR in a large single centre, real world database containing RHC and echo data. Although ePLAR was only

calculable in 21% of the cohort, it provided good discriminatory power between pre-and postPH, and was superior in this respect to previous echocardiographic formulae. Further work is required to validate the discriminatory potential of the ePLAR prospectively and to clarify its ability to identify those individuals who will benefit from RHC and potentially from disease specific therapy.

Figure 1. ePLAR flow chart

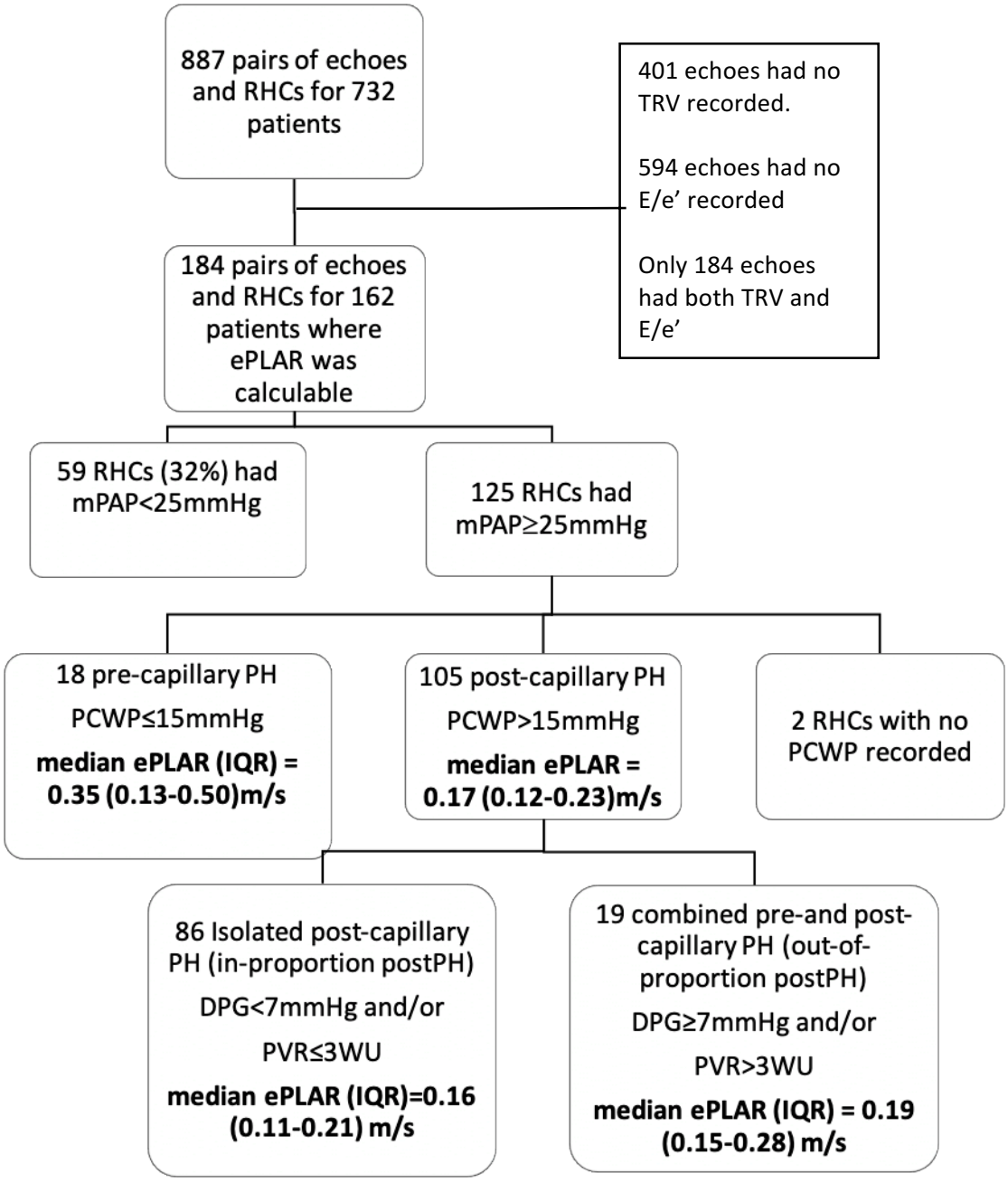


Table 1. Comparison of demographic, RHC and echo variables between the pre- and post-capillary pulmonary hypertension patients in whom ePLAR can be calculated.

Variable	Pre-capillary PH		Post-capillary PH		P value
	N	Median (IQR)	N	Median (IQR)	
Age (years)	18	70 (54-86)	105	71 (51-84)	0.983
Female (percentage)	18	61%	105	44%	0.17#
BMI (kg/m^2)	16	23 (21-27)	67	26 (24-31)	0.014
Mean pulmonary artery pressure (mmHg)	18	35 (28-48)	105	36 (30-43)	0.912
Pulmonary capillary wedge pressure (mmHg)	18	13 (9-14)	105	22 (18-29)	0.000
Diastolic Pulmonary Gradient (mmHg)	18	10 (4-17)	105	1 (-3-4)	0.000
Transpulmonary gradient (mmHg)	18	21 (16-37)	105	11 (8-17)	0.000
Cardiac output (L/min)	4	4.6 (4.3-5.4)	24	4.0 (3.1-4.9)	0.211
Pulmonary vascular resistant (WU)	4	6.4 (4.8-7.1)	24	8.6 (6.6-10.5)	0.057
Ejection Fraction (%)	18	68 (61-73)	100	51 (34-64)	0.000
Mitral E:A	16	0.9 (0.7-1.2)	79	1.7 (0.8-2.9)	0.011
LA volume (indexed) (cm^3)	3	29 (27-.)	31	57 (43-71)	0.008
Tricuspid Regurgitation Velocity (m/s)	18	3.5 (2.9-4.2)	105	3.2 (2.8-3.5)	0.035
Mitral E/e'	18	10 (9-22)	105	19 (14-27)	0.004
ePLAR (m/s)	18	0.35 (0.13-0.50)	105	0.17 (0.12-0.23)	0.003
Abbas' original $PVR_{echo,}$ (WU)	14	2.6 (1.9-3.8)	52	3.2 (2.5-4.9) (n=52)	0.147
Abbas' sharpened PVR_{echo} (WU)	14	5.4 (2.9-7.7)	52	4.9 (3.5-8.8) (n=52)	0.556

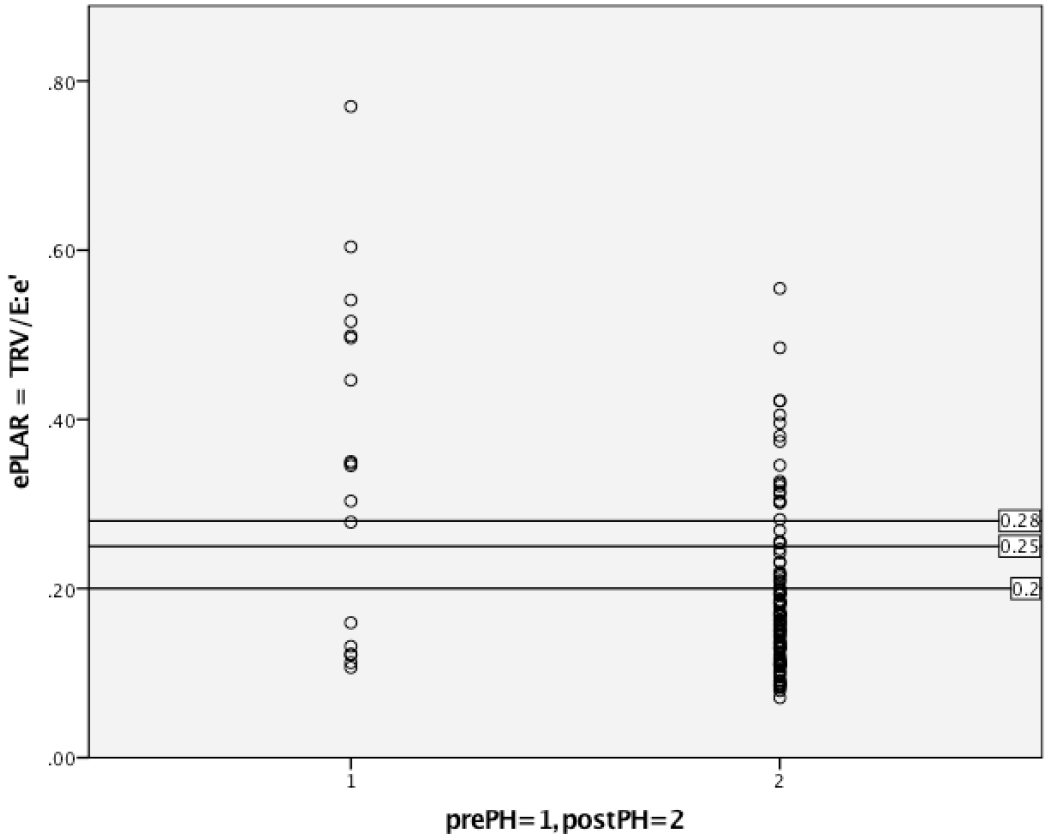
# p value obtained by Pearson chi-square test
IQR= interquartile range, ePLAR= echocardiographic pulmonary to left atrial ratio, N= number of patients

Table 2. Comparison of demographic, RHC and echo variables between the isolated post capillary and combined pre-and post-capillary pulmonary hypertension patients in whom ePLAR can be calculated.

Variable	Isolated postPH		Combined pre-and postPH		P value
	N	Median (IQR)	N	Median (IQR)	
Age (years)	86	72 (51-84)	19	64 (51-83)	0.641
BMI (kg/m^2)	56	26 (23-31)	11	30 (26-31)	0.134
Mean pulmonary artery pressure (mmHg)	86	33 (29-41)	19	42 (37-49)	0.000
Pulmonary capillary wedge pressure (mmHg)	86	24 (19-29)	19	18 (17-22)	0.001
Diastolic Pulmonary Gradient (mmHg)	86	0 (-4-3)	19	10 (9-16)	0.000
Transpulmonary gradient (mmHg)	86	10 (7-13)	19	22 (17-31)	0.000
Cardiac output (L/min)	21	4.0 (3.1-5)	3	4.5 (3.1-.)	0.793
Pulmonary vascular resistant (WU)	21	8.3 (6.3-10.2)	3	10.2 (7.1-.)	0.359
Ejection Fraction (%)	81	50 (30-63)	19	58 (36-69)	0.098
Mitral E:A	61	1.7 (0.9-3)	18	1.1 (0.7-2.6)	0.183
LA volume (indexed) (cm^3)	27	57 (45-71)	4	44 (32-66)	0.239
Tricuspid Regurgitation Velocity (m/s)	86	3.1 (2.7-3.4)	19	3.8 (3.1-4.1)	0.009
Mitral E/e'	86	19 (15-28)	19	19 (13-22)	0.312
ePLAR (m/s)	86	0.16 (0.11-0.21)	19	0.19 (0.15-0.28)	0.042
Abbas' original PVR_{echo} (WU)	41	3.0 (2.4-5.2)	11	3.9 (3.1-4.6)	0.226
Abbas' sharpened PVR_{echo} (WU)	41	4.3 (3.4-8.7)	11	7.1 (4.1-9.1)	0.165

IQR= interquartile range, ePLAR= echocardiographic pulmonary to left atrial ratio, N= number of patients

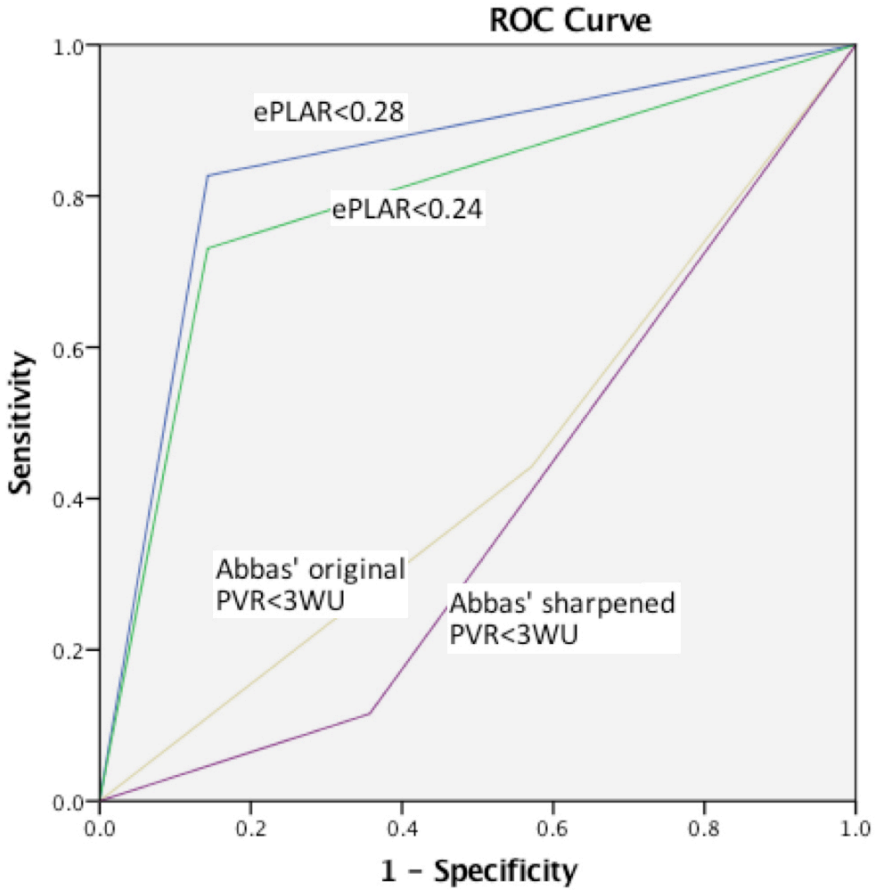
Figure 2. Scatter plot showing distribution of ePLAR values in two major physiology groups: pre-capillary PH and post-capillary PH, with the table showing sensitivity, specificity and predictive values of each ePLAR cut-off to predict postPH



e P L A R value	Sensitivity	Specificity	PPV	NPV
0.20	67%	67%	92%	25%
0.25	78%	67%	93%	34%
0.28	83%	67%	94%	40%
0.30	84%	61%	93%	40%

PPV= positive predictive value, NPV=negative predictive value

Figure 3. ROC analysis on 2 different ePLAR cut-offs compared with PVRecho formulae by Abbas et al. to detect post capillary PH



Area Under the Curve

Test Result Variable(s)	Area
ePLAR <0.28	.842
ePLAR<0.24	.794
Abbas' original < 3WU	.435
Abbas' sharpened <3WU	.379