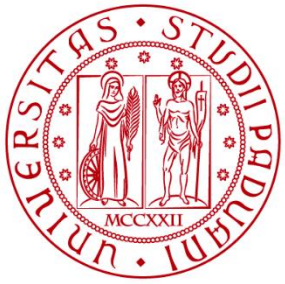

UNIVERSITÀ DEGLI STUDI DI PADOVA

University of Padova

Department of Cardiac, Thoracic, Vascular Sciences and Public Health

Ph.D. COURSE: ***Translational Specialistic Medicine "G.B. Morgagni"***

CURRICULUM: ***Cardiovascular Sciences***

SERIES: ***XXXV°***

TITLE: *ECHOCARDIOGRAPHY AND EVALUATION OF CARDIAC PHYSIOLOGY*

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Table of Contents

Abbreviations

AN = Absolute number

Afib = Atrial fibrillation

AUC = Area under the curve

BP = Blood pressure

Ch = Chamber

CMR = Cardiovascular magnetic resonance

Cn = Net atrioventricular compliance

CoV = Coefficient of variation

DCM = Dilated cardiomyopathy

DD = Diastolic dysfunction

ED = End-diastole

EOA = Effective orifice area

ES = End-systole

FP = Filling pressure

HR = Heart rate

ICC = Intraclass correlation coefficient

LAEI = Left atrial expansion index

LAmaxVol = Maximal left atrial volume

LAminVol = Minimal left atrial volume

LAP = Left atrial pressure

ln = logarithm of

LV = Left ventricular

LVEDV = Left ventricular end-diastolic volume

LVEDP = Left ventricular end-diastolic pressure

LVEF = Left ventricular ejection fraction

MAC = Mitral annular calcification

MR = Mitral regurgitation

MV = Mitral valve

MG = Mean gradient

PASP = Pulmonary arterial systolic pressure

PCWP = Pulmonary capillary wedge pressure

RAmaxVol = Maximal right atrial volume

RAminVol = Minimal right atrial volume

RAEI = Right atrial expansion index

RAP = Right atrial pressure

RHC = Right heart catheterization

ROC = Receiver operating characteristic

RVEDV = Right ventricular end-diastolic volume

SD = Standard deviation

SGC = Swan-Ganz catheter

TR = Tricuspid Regurgitation

TRmaxVel = Tricuspid regurgitation maximal velocity

TTE = Transthoracic echocardiography

Thesis studies list

Study 1

Left atrial expansion index for non-invasive estimation of pulmonary capillary wedge pressure: a cardiac catheterization validation study[1]

Study 2

Non-invasive evaluation of pulmonary capillary wedge pressure using the left atrial expansion index in mitral valve stenosis, prosthesis, and repair

Study 3

Cardiovascular magnetic resonance left atrial expansion index estimates pulmonary capillary wedge pressure in dilated cardiomyopathy

Study 4

Right atrial expansion index for echocardiographic estimation of right atrial pressure: a cardiac catheterization validation study

Abstract

Introduction: Pulmonary capillary wedge pressure (PCWP) and right atrial pressure (RAP) assessment are fundamental for cardiac disease diagnosis and management. Right heart catheterization (RHC) provides accurate PCWP and RAP measurement, but it is invasive and impractical for widespread use. The left atrial expansion index (LAEI), measured by either transthoracic echocardiography (TTE) or cardiovascular magnetic resonance (CMR), and the right atrial expansion index (RAEI), measured by TTE, estimate the LA and RA compliance by describing the relative LA and RA volume increase during the atria reservoir phase. This thesis aimed to assess and validate LAEI and RAEI as non-invasive parameters for PCWP and RAP estimation. *Methods:* We performed four observational, cross-sectional, single-center studies. The 1st study retrospectively enrolled 649 patients with various chronic cardiac diseases divided into derivation (n=509) and validation (n=140) cohorts. The 2nd study retrospectively enrolled 167 patients with mitral valve (MV) stenosis, prosthesis, and repair. In the 3rd study, we included 126 patients with dilated cardiomyopathy (DCM) divided into derivation (n=92, retrospective) and validation (n=34 prospective) cohorts. Finally, in the 4th study, we included 586 patients with various chronic cardiac diseases divided into derivation (n=406, retrospective) and validation (n=180, prospective) cohorts. All patients underwent clinically indicated RHC and either TTE (1st, 2nd, 4th study) or CMR (3rd study) within 24 hours. PCWP and RAP were measured during RHC, whereas TTE/CMR parameters were measured offline, blinded to RHC results. *Results:* In the 1st study, we found that TTE-measured LAEI had a strong logarithmic association with PCWP (lnLAEI-PCWP:r=-0.73, p<0.001); lnLAEI showed an independent and added predictive value for PCWP estimation over clinical and diastolic dysfunction (DD) parameters. In the validation cohort, lnLAEI<4.02 identified PCWP>12mmHg with higher accuracy than 2016 DD algorithm (88% vs. 74%) and PCWP=38.3-6.2xlnLAEI predicted invasively measured

PCWP (0.4±5.4mmHg). In the 2nd study, TTE-measured LAEI maintained the logarithmical association with PCWP (lnLAEI-PCWP:r=-0.616; p<0.001). lnLAEI was an independent determinant of PCWP and provided added predictive value over clinical and TTE parameters. Moreover, lnLAEI discriminated elevated PCWP better than other TTE parameters, and PCWP=36.8-5.5xlnLAEI could estimate invasive PCWP (0.0±6.1mmHg). In the 3rd study, CMR-measured LAEI was also logarithmically associated with PCWP (lnLAEI-PCWP:r=-0.81, p<0.001), and lnLAEI provided added and independent predictive value over clinical and CMR parameters for PCWP estimation. In the validation cohort, lnLAEI≤3.85 identified PCWP≥15mmHg with 85.3% accuracy and PCWP=52.33-(9.17xlnLAEI) predicted PCWP (-0.1±5.7mmHg). In the 4th study, TTE-measured RAEI was logarithmically correlated to RAP (lnRAEI-RAP:r=-0.64, p<0.001), and lnRAEI provided independent and added predictive value for RAP assessment over clinical and TTE parameters, including inferior vena cava (IVC) diameter and collapsibility index. In the validation cohort, lnRAEI<3.57 was more accurate than IVC assessment for the identification of RAP≥10mmHg (81.7% vs. 71.7%), and RAP=18.9-3.2xlnRAEI predicted invasive RAP (0.31±2.9mmHg) more accurately than guidelines recommended IVC assessment (1.73±4.4mmHg). *Conclusions:* TTE-measured LAEI outperformed the 2016 DD algorithm for PCWP estimation in a large cohort of patients with various cardiac diseases and also allowed non-invasive PCWP assessment in patients with MV stenosis, prosthesis, and repair. Furthermore, CMR-measured LAEI resulted in an accurate and straightforward parameter for PCWP assessment in DCM patients. Finally, TTE-measured RAEI resulted in a novel and fast parameter more accurate than IVC assessment for RAP estimation.

Introduction

Left atrial pressure

Hemodynamic significance

Pulmonary capillary wedge pressure (PCWP), which corresponds to the left atrial pressure (LAP) in the absence of pulmonary veins stenosis[2,3], plays a pivotal role in the hemodynamic evaluation of patients with cardiac diseases. PCWP normal values range between 4-12 mmHg, and PCWP increase is the hemodynamic hallmark of left heart failure (HF). PCWP had been defined as elevated using 12 mmHg [4] or 15 mmHg [5] cut-offs. The European Society of Cardiology (ESC) 2016 guidelines defined HF as "a clinical syndrome characterized by typical symptoms (i.e., breathlessness, ankle swelling, and fatigue) that may be accompanied by signs (i.e., elevated jugular venous pressure, pulmonary crackles, and peripheral edema) caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/or elevated intracardiac pressures at rest or during stress" [6]. The more recent ESC 2021 guidelines remarked previous HF definition as "a clinical syndrome consisting of cardinal symptoms (i.e., breathlessness, ankle swelling, and fatigue) that may be accompanied by signs (i.e., elevated jugular venous pressure, pulmonary crackles, and peripheral edema). It is due to a structural and/or functional abnormality of the heart that results in elevated intracardiac pressures and/or inadequate cardiac output at rest and/or during exercise."[7] HF is a leading cause of cardiovascular hospitalization and death,[8] and approximately 50% of patients with HF have only mildly reduced or preserved left ventricular ejection fraction (LVEF) [9]. The elevation in PCWP is the fundamental hemodynamic criterion for left HF, the responsible for pulmonary congestion and cardiac dyspnea, and is a strong determinant of cardiac outcome[10,11]. Therefore, correctly identifying elevated PCWP is paramount for diagnosing and treating HF patients. Implantable devices for invasive PCWP measurement allowed a more tailored

therapy that reduced HF hospitalization compared to the standard of care in HF patients.[12] Furthermore, evaluation of PCWP allows to differentiate cardiogenic shock from other types of shocks (as hypovolemic and distributive) and could guide critically ill patients management [13]. PCWP allows evaluating the hemodynamic impact of left heart valve diseases[14] and provides essential information in diagnosing pulmonary hypertension and assessing potential left HF contribution to a primitive pulmonary arterial disease.[15]

Invasive and non-invasive estimation

Right heart catheterization (RHC) is the gold-standard reference technique for accurate and direct PCWP measurement. However, RHC is impractical, requires a catheterization laboratory or an intensive care unit room, is invasive, and carries a small but non-negligible risk.[16-18] Furthermore, RHC still failed to demonstrate its clinical benefit when used for monitoring critically ill patients [19-21] and is unfeasible for evaluating patients during follow-up visits, when repeated PCWP assessment would be desirable. Therefore, RHC is reserved in clinical practice only for a selected group of patients.

In contrast, transthoracic echocardiography (TTE) is inexpensive, safe, immediately available bedside, and easily repeatable. For these reasons, TTE would be the ideal tool for non-invasive PCWP estimation,[22] and it is routinely used in clinical practice for PCWP estimation following the American Society of Echocardiography (ASE)/European Association of Cardiovascular Imaging (EACVI) 2016 diastolic dysfunction (DD) guidelines algorithm [23] (Figure 1), that updated the previous 2009 version.[24] LV DD is one of the leading causes of elevated PCWP[25], and LV DD evidence during TTE is one of the diagnostic criteria required for diagnosing HF with preserved EF [4,6]. Moreover, TTE DD parameters provided prognostic information in addition to conventional clinical and LV volumetric measurements in patients with acute myocardial infarction, [26-29] HF with reduced [30], and preserved LVEF.[31]

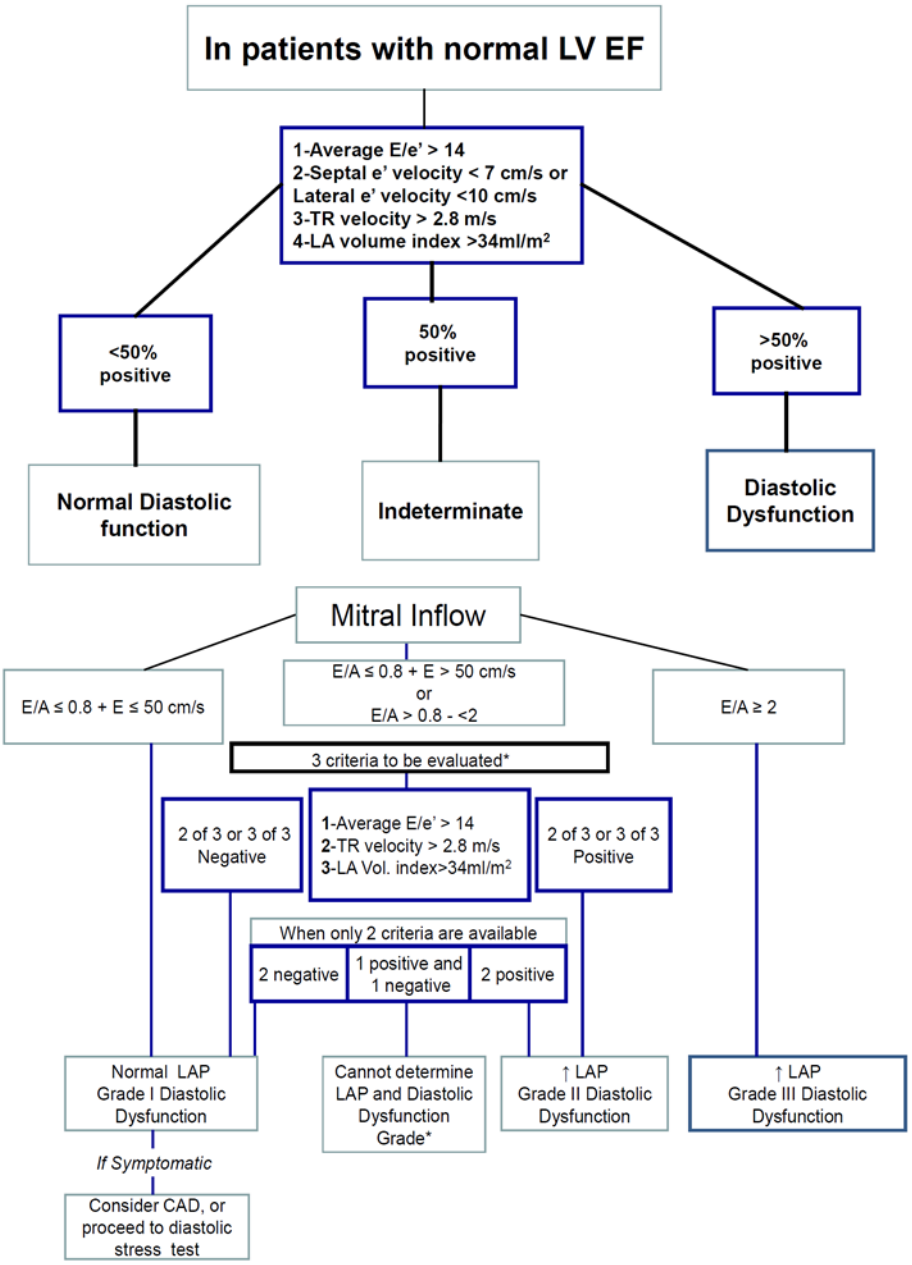


Figure 1. ASE/EACVI 2016 DD guideline algorithm tried to simplify the 2009 DD guidelines approach and required the evaluation of LAmaxVol, E/A, E/e', and TRmaxVel. (Top) Algorithm for DD evaluation in patients with preserved LVEF. (Bottom) Algorithm evaluating DD grade and filling pressure (FP) in patients with reduced LVEF and preserved LVEF with evidence of cardiac disease. S. F. Nagueh *et al.*, Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* **29**, 277-314 (2016).[23]

Despite being invaluable for clinical practice, the algorithm accuracy in subsequent studies was inconsistent and suboptimal [32-35]. For example, the accuracy varied significantly among different studies, ranging from 87% to approximately 70% in multicenter studies [32,33] and 75% to 72% in single-center studies [34,35]. Furthermore, the algorithm could not classify up to 15% of patients. [33,36] The suboptimal accuracy might rely on the limitations of each

parameter included in the 2016 TTE DD algorithm. Interestingly, each parameter showed, at best, a weak to moderate linear correlation with PCWP [32,33]. In patients with both reduced and preserved LVEF the following linear correlation coefficient (r) with PCWP were found in different large studies[32,33]: E/A r= 0.46 to 0.53; E/e' r= 0.34 to 0.52; tricuspid regurgitation maximal velocity (TRmaxVel) r=-0.15 to 0.58; left atrial maximal volume (LAmaxVol) r=0.23 to 0.28. Of note, r-values were even worse when only the subgroup with preserved LVEF was considered (E/A r=0.23; E/e' r=0.17; TRmaxVel r=-0.11; LAmaxVol r=0.10). LAmaxVol is a chronic and late marker of increased pressure but is unable to describe acute hemodynamic changes. Moreover, the left atrium could dilate without DD, for example, in patients with bradycardia, high-output states, heart transplants with biatrial technique, Afib, significant mitral valve (MV) diseases, and athletes. Mitral inflow parameters (i.e., E velocity and E/A) depend on the cardiac flow and are altered in the presence of MV disease or prosthesis. E/A has a U-shaped relation with LVDD (0.8<E/A<2 both in DD grade II and normal diastolic function), which makes it challenging to differentiate normal from pseudonormal filling (particularly in patients with preserved LVEF) without additional variables. E/A is not applicable in AFib patients (because of A wave absence) or in patients with tachycardia and first-degree AV block (because of E and A fusion). Finally, mitral inflow parameters reference values change with age[23]. E/e' is also altered by changes in cardiac flow, MV disease, and prosthesis. Medial and lateral e' are altered if there is severe LVEF impairment [37], regional myocardial scar, or severe mitral annulus calcification (MAC) and pericardial disease (i.e., pericardial constriction). E/e' poorly predict LV filling pressure (FP) in HF with preserved EF [38]. Also, E/e' is not accurate in healthy subjects, and there is a ''gray zone value'' in which PCWP would result indeterminate (8< E/e'<13). TRmaxVel potentially describes the burden of LVFP elevation on pulmonary vasculature, but it is flow dependent and provides an indirect estimation of PCWP only when the pulmonary arterial resistances are normal[15]. Another limitation of the 2016 guidelines was the dichotomized

approach to PCWP, defined as low or elevated, without trying to quantitate the PCWP values. This approach overlooks valuable information on the potential entity of the LVFP elevation.

Furthermore, PCWP assessment could be even more difficult in cardiac categories where the 2016 DD algorithm cannot be directly applied, such as atrial fibrillation (Afib) or significant mitral regurgitation (MR) [23]. For example, PCWP estimation in patients with AFib is limited to small studies and must rely on other indirect parameters (i.e., E deceleration time)[39-41]. The estimation of PCWP in patients with MR was explored in small and criticized studies [42,43]. Besides, E/e' was a reliable estimate of PCWP only in subjects with secondary but not primary MR [44]. Evaluation of PCWP using conventional DD parameters for MAC has also been controversial. Indeed, differences in mitral pulsed and tissue Doppler parameters were identified [45,46], and DD parameters recently showed only an even weaker correlation with LVFP in this category. [47,48] Moreover, the 2016 DD algorithm cannot be applied in patients with mitral valve (MV) stenosis, prosthesis, and surgical repair. The TTE guidelines [49-51] to evaluate these conditions do not provide dedicated parameters for PCWP assessment. As a consequence, despite the non-invasive PCWP evaluation would be fundamental in these conditions,[7] in patients with MV stenosis [51], prosthesis, and surgical repair [49,50] it is not routinely performed since mitral filling and annulus relaxation parameters cannot be applied in these settings[52,53], and alternative approaches proposed [54] showed limitations. [55,56]

More recently, LA reservoir function has been assessed using LA strain. Indeed, the LA strain recently showed its value for LVFP estimation [34,57,58]. However, LA strain calculation requires dedicated training for the operators, expensive and dedicated software packages that are not available in every echocardiography laboratory, and post-processing analysis,

which might be time-consuming and unfeasible during the busy clinical routine. Finally, LA strain still suffers from significant inter-vendor variability. [59]

As concerning other cardiovascular imaging modalities, cardiovascular magnetic resonance (CMR) has become the gold-standard imaging technique for quantifying the size, mass, and global and regional LV and RV function and accurately assessing myocardial scar and fibrosis [60,61]. Therefore nowadays, CMR is the leading imaging technique for cardiomyopathies evaluation[62]. However, despite the importance of PCWP as the hemodynamic hallmark responsible for HF decompensation [63] and its association with outcomes[10,64], CMR does not currently provide dedicated parameters for PCWP estimation. Small studies demonstrated the feasibility of assessing echocardiographic equivalent DD parameters with CMR [65-69]. However, despite promising[70], CMR-performed DD evaluation did not enter clinical practice because cumbersome and impractical; as a consequence, PCWP evaluation is currently not performed during routine CMR exams.

Left atrial expansion index

LA echocardiographic evaluation historically relies on LA static dimensions (LA diameters and LAmaxVol, Figure 2) despite the left atrium being a dynamic structure. LAmaxVol[71] demonstrated a role as a prognostic factor[72] and LV DD chronic marker [73]. However, recent studies provided evidence that LAminVol had a greater prognostic value than LAmaxVol.[74,75]

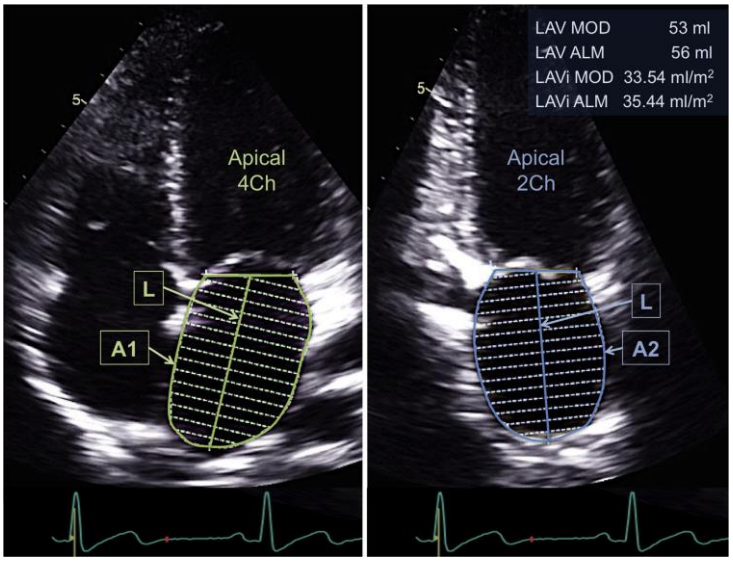


Figure 2. LAmaxVol is calculated during standard 2D TTE using either the area-length or disks-summation methods from LA area tracings obtained from a dedicated 4Ch view and 2Ch view acquisitions. Surkova E, Badano LP, Genovese D, et al. Clinical and Prognostic Implications of Methods and Partition Values Used to Assess Left Atrial Volume by Two-Dimensional Echocardiography. J Am Soc Echocardiogr. 2017;30(11):1119-1129.[73]

The left atrium modulates LV filling, and the LA function could be separated into LA reservoir, conduit, and contractile phases. LA reservoir function occurs during ventricular systole when the MV is closed, and the left atrium receives and stores blood from the pulmonary veins. The determinants of this phase are PWCP, LA active relaxation, LA compliance [76], and MV annulus descending induced by LV contraction [77]. LA conduit function accounts for the rapid and late passive LV filling that lasts from MV opening to atrial contraction. During this phase, the left atrium works as a conduit, and blood passively flows from the atrial cavity and pulmonary veins to the left ventricle, following the existing pressure gradient between

the two chambers. In this phase, LV DD determinants play a fundamental role. The LA contractile function corresponds to LA active contraction and is modulated by intrinsic LA contractility ad LV DD [78]. LA contraction accounts for 20-30% of LV stroke volume in healthy individuals and is fundamental for maintaining an adequate LV stroke volume in patients with impaired LV relaxation.

The LA function evaluation could be precisely studied through invasively derived pressure-volume curves, but this is not performed in clinical practice[79] (Figure 3). Therefore, LA function could be non-invasively evaluated through either volumes-time curves (both 2D and 3D volumetric analysis) or strain-time curves (speckle-tracking analysis).[80]

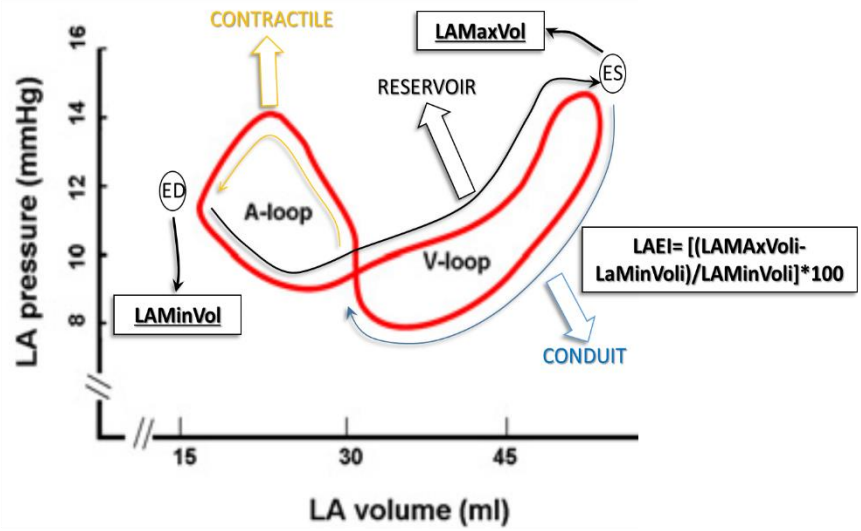


Figure 3. LA pressure-volume loop is composed of two linked loops (right). The right circle (V loop) runs clockwise, its ascending portion represents LA reservoir function, and the descending portion describes the LA conduit function. The left circle (A-loop) runs counterclockwise and represents LA pump function. More specifically, the pressure-volume curve starts at the end-diastole (ED) with the point located more on the left of the A-loop. During the reservoir phase, there is an increase in both LA volume and pressure; the slope of this portion represents LA compliance (Δvolume/Δpressure) and ends at the end-systole (ES) with the point located more on the right of the V-loop. The conduit phase, which starts with the point located more on the right of the V-Loop, determines a reduction in LA volume and pressure. The LA contraction starts where the two cycles join and determines a further reduction in LA volume and an increase in LA pressure related to the active contraction. Rosca M, Lancellotti P, Popescu BA, Piérard LA. Left atrial function: pathophysiology, echocardiographic assessment, and clinical applications. Heart (British Cardiac Society). 2011;97(23):1982-1989. [79-81]

Volumetric evaluation of LA phasic function is derived from measurements of LAmaxVol, LAminVol, and LA volume immediately before atrial contraction (LApreaVol) and described as follows: LA reservoir function by LA expansion index (LAEI)=[(LAmaxVol-LAminVol)/LAminVol]x100; LA conduit function by LA passive emptying

fraction=[(LAmaxVol-LApreAVol)/LAmaxVol]x100; LA contractile function by LA active emptying fraction=[(LApreaAVol-LAminVol)/LApreAVol]x100.

LA reservoir function recently gained attention for its diagnostic and prognostic role in cardiac diseases [80,82]. As briefly anticipated, the LA reservoir phase begins with the MV closure and ends with the MV opening. During this time, the blood flows from the pulmonary veins into the left atrium, producing an increase in LA volume accompanied by LA pressure rise. The ratio between LA volume and pressure changes during the reservoir phase corresponds to LA compliance [79]. Therefore, the left atrium transforms the continuous pulmonary veins flow into phasic LV volume diastolic filling through its reservoir function, allowing cyclic blood storage into the left atrium during systole (LA reservoir volume). LA pressure remains low in healthy subjects since LA compliance is high. In cardiac diseases causing chronic LA pressure increase, the atrium dilates following the Frank-Starling law to maintain adequate LA reservoir volume [77,79,83]. When compensatory mechanisms are depleted, LA compliance decreases, LA reservoir function progressively reduces, and LA reservoir volume becomes progressively less. Therefore, the active LA contribution to LV diastolic volume filling becomes slight, and the left atrium acts more and more as a passive conduit [58,84]. In this condition, pulmonary veins blood could only minimally be stored in the LA during systole, and LV diastolic volume filling is mainly due to the pulmonary veins blood moving from the left atrium to the left ventricle during diastole [85,86].

LAEI describes LA compliance through the relative LA volume increase during the LA reservoir phase. Since LA volume and its changes are related to LA pressure by LA volume-pressure curves [79](LA compliance=ΔLA volumes/ΔLA pressure), LAEI might be used as a non-invasive parameter for PCWP estimation. LAEI could be easily obtained from 2D or 3D TTE/CMR measurement of LA volumes at ED (when the LA volume is the smallest, LAminVol) and ES (when the LA volume is the biggest, LAmaxVol), and then calculated as LAEI=[(LAmaxVol-LAminVol)/LAminVol]x100

Previous studies demonstrated that LAEI could estimate FP in patients with ischemic heart diseases [87,88], and MR [89]. In addition, LAEI might help with LAmaxVol and age in predicting future Afib episodes and in-hospital mortality in patients who underwent coronary artery bypass. [90] Also, LAEI demonstrated a prognostic role in HF[91,92] and acute coronary sydromes[88] along with age, pulmonary arterial systolic pressure (PASP), LVEF, and previous admission for HF. Lastly, LAEI could help optimize the management of patients with HF with reduced LVEF. [93]

Knowledge gap driving our studies

The knowledge gap driving the 1st study originated from the limitations of the 2016 DD algorithm for PCWP evaluation. DD algorithm requires a cumbersome multiparametric approach that provides a modest accuracy, with indeterminate results in 15% of cases, and cannot be applied in different cardiac conditions as in patients with Afib and significant MR. We, therefore, hypothesized that TTE-measured LAEI might improve PCWP evaluation over DD parameters in patients with various chronic cardiac conditions.

The knowledge gap driving the 2nd study originated from the absence of dedicated parameters for PCWP assessment in patients with MV stenosis, prosthesis, and surgical repair, despite the crucial role of an accurate PCWP evaluation in these patients. Therefore, we hypothesized that TTE-measured LAEI might be a novel and suitable parameter for PCWP evaluation in these challenging patient subgroups.

The knowledge gap driving the 3rd study originated from the absence of dedicated CMR parameters for PCWP evaluation, although CMR has become the gold-standard cardiac imaging technique. Therefore, we hypothesized that CMR-measured LAEI might estimate PCWP in a cohort of patients with dilated cardiomyopathy (DCM).

R*ight atrial pressure*

Hemodynamic significance

Right atrial pressure assessment (RAP), which corresponds to central venous pressure (CVP), plays a pivotal role in the hemodynamic evaluation of patients with cardiac diseases as much as PCWP. RAP normally ranges between 0 to 8 mmHg, and RAP increase is the hemodynamic hallmark of right HF[7]. RAP had been conventionally defined as elevated using 10 mmHg cut-off[71,94]. The elevation in RAP is the fundamental hemodynamic criterion for right HF diagnosis and is responsible for systemic venous congestion. Indeed, RAP elevation represents the cumulative cardiac burden in HF [95].

Moreover, describing right heart preload provides indications on volume status, directly influencing management and therapeutic strategies in critically ill patients[96]. Increased RAP is independently related to all-cause mortality in patients with cardiovascular disease[97,98]. In addition, RAP estimation is needed, along with TRmaxVel, for TTE estimation of the right ventricular systolic pressure (RVSP), which is equivalent to the PASP in the absence of RV outflow gradient (i.e., pulmonary stenosis)[99].

Invasive and non-invasive assessment

RHC or a central venous catheter with the distal tip at the right atrium level represent the gold-standard for accurate direct invasive RAP measurement. However, the same limits already aforementioned for invasive PCWP assessment applies also for this scenario (invasive procedure with procedural risk, impractical, requirement of a catheterization laboratory or an intensive care unit room, unfeasible for evaluating patients during follow-up visits). Therefore invasive RAP measurement is performed in clinical practice only for a selected group of patients.

RAP is routinely estimated non-invasively using TTE inferior vena cava (IVC) assessment from the subcostal view (Figure 4). The IVC assessment is based on the IVC max diameter and IVC degree of collapse during rapid inspiration or sniffs [71,94,100,101].

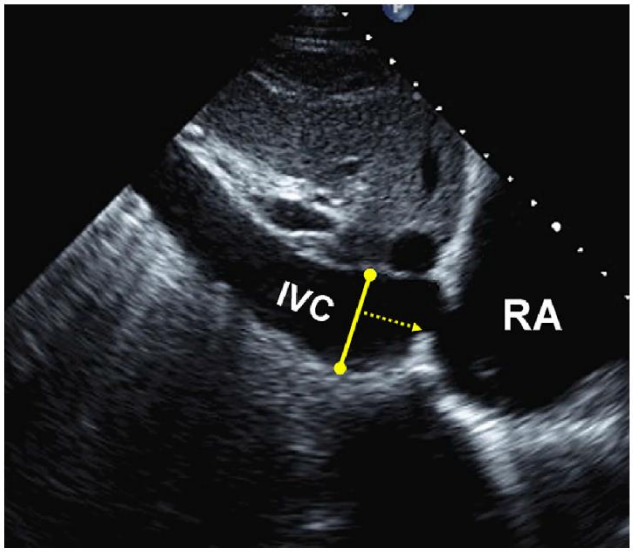


Figure 4. 2D TTE IVC assessment is performed from the subcostal view by assessing IVC diameter at 1 centimeter from the right atrium and the IVC collapsibility during rapid inspiration. Rudski, L. G., et al. (2010). "Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography." J Am Soc Echocardiogr 23(7): 685-713.

Guidelines[71,94] proposed three ranges of RAP from IVC assessment: normal RAP (3 mmHg; range from 0 to 5 mmHg) with IVC diameter ≤2.1 cm and IVC collapse during sniff >50%. Intermediate RAP (8 mmHg, range from 5 to 10 mmHg) with IVC diameter ≤2.1 cm and IVC

collapse during sniff <50% or IVC diameter >2.1 cm and IVC collapse during sniff >50%. Elevated RAP (15 mmHg, range from 10 to 20 mmHg) with IVC diameter >2.1 cm and IVC collapse during sniff <50%. The interpreter, however, may upgrade or downgrade the intermediate RAP value based on secondary indices such as RA enlargement, RV hypertrophy, diastolic predominance in the hepatic veins, restrictive filling pattern in the trans-tricuspid inflow, or tricuspid E/e' >6. However, these additional secondary parameters did not increase RAP estimation accuracy [102,103]. Moreover, the arbitrary use of secondary indices based on potential operator preferences might increase the inter-observer RAP variability. Finally, since the elevated RAP category cannot overcome 15 mmHg with IVC assessment, RAP could be underestimated in specific clinical scenarios (i.e., severe RV dysfunction, severe TR). In fact, despite IVC size and collapsibility assessment having been used for RAP estimation for almost 40 years [104,105], this approach has several limitations. For example, IVC assessment is unreliable for RAP estimation in patients mechanically ventilated [106] and in young athletes [107]. Moreover, BSA differences might be a confounding factor for IVC diameters assessment, and IVC might need to be corrected for BSA [108]. Furthermore, IVC resents intraabdominal pressure, whereas the right atrium resents intrathoracic pressure, which might modify IVC diameter simply by moving patients from the supine to the left lateral decubitus.[109] Furthermore, IVC collapse requires collaborative patients, and the sniff maneuver is difficult to standardize in routine clinical practice where the patients' efforts might differ from one subject to another. Then, IVC might translate outside the TTE imaging plane during the rapid inspiration, showing false IVC collapse when there is not. Finally, in about 10% of patients, the subcostal view has an insufficient quality for IVC assessment, hampering RAP estimation in these patients.

Of note, the other parameters proposed for RAP evaluation as the hepatic venous flow [110] or tricuspid E/e' ratio [111], correlated weakly to RAP early after surgery and in patients with normal RV function [112]. In addition, performing a multiparametric assessment including IVC,

RA size, hepatic veins flow, and tricuspid E/e' provided only modest precision and was not more precise than IVC assessment alone. [102,103]

Right atrial expansion index

RA echocardiographic evaluation relies on RA static dimensions (RA diameters RAmaxArea and RAmaxVol) despite the right atrium being a dynamic structure. RA dilatation is a chronic marker of elevated RAP and could be potentially used for RAP assessment along with IVC [113], although the additional benefit seems not clinically relevant over IVC assessment alone [102]. In addition, the RA size was found to correlate with RV end-diastolic pressure (EDP) in patients with congenital heart diseseas[114] and acute HF [113].

Studies found RA reservoir function impaired in patients with pulmonary arterial hypertension[115], likely due to RV failure and overload, resulting in RA volume to predict clinical worsening [116,117]. Moreover, RA function assessment predicted outcomes in patients with pulmonary arterial hypertension [118-120] and HF with preserved EF [121].

The right atrial expansion index (RAEI) describes RA compliance by calculating the relative RA volume increase during the RA reservoir phase and could be easily calculated as RAEI=[(RAmaxVol-RAminVol)/RAminVol]x100 (Figure 5), providing potential insight for RAP estimation. However, to our knowledge, RAEI had never been previously tested as a non-invasive parameter for RAP assessment.

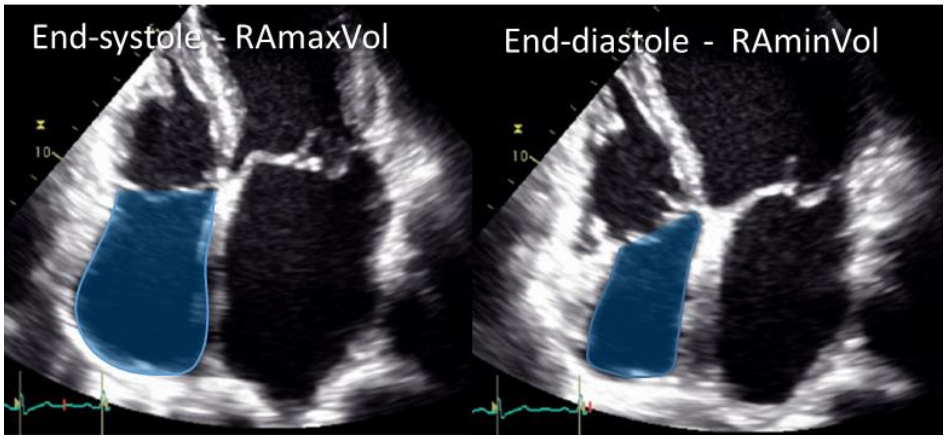


Figure 5. TTE atrial dedicated 4Ch view is used for measuring RAmaxArea and RAminArea. RA max and min volumes are obtained with the monoplane disks-summation method from RA area tracings. Subsequently, RAEI could be easily calculated as RAEI=[(RAmaxVol-RAminVol)/RAminVol]x100.

Knowledge gap driving our studies

The knowledge gap driving the 4th study originated from the TTE IVC assessment limitations for RAP estimation. Therefore, we postulated that RAEI might improve RAP estimation compared to the conventional IVC assessment in patients with various chronic cardiac conditions.

Aims of the thesis

General aim of the thesis

This thesis aimed to assess and validate i)TTE-measured LAEI and CMR-measured LAEI as novel parameters for the non-invasive evaluation of PCWP, and ii) TTE-measured RAEI as a novel parameter for the non-invasive evaluation of RAP.

Specific aims of the studies

In the 1st study, we compared TTE-measured LAEI for PCWP assessment against conventional DD parameters in a cohort of patients with various chronic cardiac diseases. We aimed to i) explore the correlation between LAEI and PCWP; ii) evaluate the independent and added value of LAEI for PCWP prediction over clinical and DD parameters; iii) compare the accuracy of LAEI for high PCWP identification head-to-head with the 2016 DD algorithm; iv) derive and validate a simple equation for predicting PCWP from LAEI.

In the 2nd study, we assessed TTE-measured LAEI diagnostic performance for PCWP evaluation in patients with MV stenosis, prosthesis, and repair. We aimed to evaluate in these challenging cardiac subgroups (i) the correlation between LAEI and PCWP, (ii) the independent and additive predictive role of LAEI for PCWP estimation over clinical and conventional TTE parameters, and (iii) the accuracy of LAEI for identifying elevated PCWP.

In the 3rd study, we evaluate CMR-measured LAEI diagnostic performance for PCWP estimation in a cohort of patients with DCM. We aimed to i) explore the correlation between CMR-measured LAEI and PCWP; ii) evaluate the independent and added value of LAEI for PCWP prediction over clinical and conventional CMR parameters; iii) evaluate the accuracy of LAEI for high PCWP identification; iv) derive and validate a simple equation for predicting PCWP from LAEI.

Finally, in the 4th study, we compared TTE-measured RAEI for RAP estimation against conventional IVC assessment in a cohort of patients with various chronic cardiac diseases. We aimed to i) explore the correlation between RAEI and RAP; ii) evaluate the independent and added value of RAEI for RAP prediction over clinical and echocardiographic parameters, including IVC assessment; iii) compare the accuracy of RAEI for elevated RAP identification against IVC assessment; iv) derive and validate a simple equation for predicting RAP from RAEI.

Material and Methods

Study population

- 1st study: Single-center, retrospective, observational, cross-sectional study. We screened chronic cardiac patients who underwent a clinically indicated RHC, from May 2015 to December 2019, at the Department of Cardiac, Thoracic, Vascular Sciences, and Public Health, University of Padua Hospital. During this period, 742 patients underwent both RHC and a complete TTE exam within 24 hours. All patients were elective hospitalizations and had no change in clinical status or medications between the two exams. We excluded patients without adequate TTE image quality or LA dedicated views (n=44). Moreover, we excluded patients with MV prosthesis (n=23), surgical or transcatheter MV repair (n=18), and MV stenosis (n=8). The final study population included 649 patients, randomly divided into derivation (n=509) and validation (n=140) cohorts. The local ethics committee approved the study, and patients enrolled provided informed consent.

- 2nd study: Single-center, retrospective, observational, cross-sectional study. We screened 784 chronic cardiac patients, electively admitted to the cardiology department of the University of Padua Hospital from February 2019 to February 2022, who underwent both a clinically indicated right heart catheterization (RHC) and a complete transthoracic echocardiographic exam (TTE) within 24 hours. We included patients with rheumatic MV stenosis, mitral annular calcification (MAC) with degenerative MV stenosis with an effective orifice area (EOA) ≤ 3.5 cm^2, MV prosthesis, and MV surgical repair. All the patients were hemodynamically stable and received no therapeutic or volemic changes between the two exams. Of the eligible 197 subjects, we excluded patients with MR above mild (n=17), aortic insufficiency

above mild (n=2), inadequate echocardiographic image quality, or absence of dedicated LA 4Ch and 2Ch views (n=11). The final study population included 167 patients. The patients enrolled provided informed consent, and the local ethics committee approved the study.

- 3rd study: Single-center, retrospective and prospective, observational, cross-sectional study. We screened DCM patients referred for further diagnostic evaluation to our tertiary center (Department of Cardiac, Thoracic, Vascular Sciences, and Public Health, the University of Padua Hospital) from February 2019 to February 2022. We included only the subject who underwent, within 24 hours, clinically indicated RHC and CMR exams. All patients were hemodynamically stable and elective admission and underwent no therapeutic change between the two exams. We excluded patients with Afib (n=5), patients with MV prosthesis (n=2), and patients with insufficient CMR image quality related to frequent ventricular ectopic beats (n=3). The study population comprised 126 DCM patients divided into a derivation (n=92, retrospective) and a validation (n=34, prospective) cohort. The enrolled patients provided informed consent, and the local ethics committee approved the study.

- 4th study: Single-center, retrospective and prospective, observational, cross-sectional study. We screened chronic cardiac patients who underwent a clinically indicated RHC, from December 2019 to May 2022, at the Department of Cardiac, Thoracic, Vascular Sciences, and Public Health, University of Padua Hospital. During this period, 615 patients underwent both RHC and a complete TTE exam within 24 hours. All patients were elective hospitalizations and had no change in clinical status or medications between the two exams. We excluded patients without adequate TTE image quality or RA dedicated views (n=15). Moreover, we excluded patients with

tricuspid valve prosthesis (n=5), surgical tricuspid valve repair (n=7), and tricuspid valve stenosis (n=2). The final study population included 586 chronic cardiac patients divided into a derivation (n=406, retrospective) and a validation (n=180, prospective) cohorts.

Right heart catheterization

RHC was performed in all patients with a Swan-Ganz catheter (SGC), following standard methodology, through a femoral transvenous approach. The external fluid-filled pressure transducer was zeroed before the study with the supine patient's midthoracic line, corresponding to the heart level. The SGC balloon was inflated and advanced until it reached the pulmonary capillary wedge position. The pulmonary capillary wedge position was identified by fluoroscopy and pressure-waveform and confirmed by pulmonary vein oxygen saturation (SatO2 >95%) by a blood sample analysis drawn from the catheter tip. PCWP measurement was performed by analyzing the pressure-time recordings at the end of a normal expiration by averaging at least three cardiac cycles. PCWP was defined as elevated using the cut-offs >12 and >15mmHg[4,5,23].

Subsequently, the SGC balloon was deflated, and the tip was progressively retracted until it reached the RA position, identified by fluoroscopy and pressure-waveform. RAP measurement was performed by analyzing the pressure-time recordings at the end of a normal expiration by averaging at least three cardiac cycles. RAP was defined as elevated when ≥10 mmHg[71].

Transthoracic echocardiographic exam

In studies 1,2, and 4, TTE exams were performed using a Vivid E9 imaging system (GE Vingmed Ultrasound, Horten, Norway) equipped with a standard M5S probe. TTE exams were exported, and standard measurements were performed offline according to ASE/EACVI guidelines [23,24,71,122] by a reader blinded to clinical and RHC data, using a vendor-independent software package (ComPACS; MediMatic Srl, Genoa, Italy). LAEI calculation required LAmaxVol and LAminVol. LAmaxVol was obtained with the biplane disks-summation method from LA area tracings at end-systole (ES) in LA dedicated 4Ch and 2Ch views. LAminVol was calculated similarly, with LA area tracings obtained at end-diastole (ED). LA appendage and pulmonary veins were not included in LA tracings. Finally, LAEI was calculated as LAEI=[(LAmaxVol-LAminVol)/LAminVol]x100. In Afib patients, measurements were averaged from three consecutive cardiac cycles.

Additional TTE measurements in study 1 included peak early (E) and late (A) mitral inflow velocities, E/A ratio, mitral annulus septal and lateral early peak diastolic velocities (septal e', lateral e'), E/e', TRmaxVel, LV volumes, LVEF, and MR severity. Additional TTE measurements in study 2 included MV mean gradient (MG), the MV EOA calculated with the continuity equation, and the PASP. The net atrioventricular compliance (Cn) was calculated as Cn= 1270x(MV EOA/E-wave downslope)[123].

In study 4, RAEI calculation required RAmaxVol and RAminVol obtained with the monoplane disks-summation method from RA area tracings at ES and ED in atrial dedicated 4Ch view. Finally, RAEI was calculated as RAEI=[(RAmaxVol-RAminVol)/RAminVol]x100. In Afib patients, measurements were averaged from three consecutive cardiac cycles. Additional TTE measurements in study 4 included RV end-diastolic area (EDA) and fractional area change (FAC), tricuspid annulus plane systolic excursion (TAPSE), TR severity, IVC max

diameter, and IVC collapsibility index (CI), calculated as IVC collapsibility index=[(IVC max diameter-IVC min diameter during rapid inspiration)/IVC max diameter]x100.

Cardiovascular magnetic resonance

In study 3, all patients were scanned using a 1.5 T CMR scanner (Magnetom Avanto, Siemens Healthineers, Erlangen, Germany) with ECG-triggering and phased array coil system, following standard protocol[124]. Cine images were acquired during expiratory breath-holds using a balanced, steady-state free precession (SSFP) and included multiple short-axis (slice thickness 6 mm, gap 2 mm; repetition time 2.5–3.8 ms; echo time 1.1–1.6 ms, average in-plane resolution 1.5×2.4 mm, flip angle 45° to 60°, temporal resolution 40–45 ms) and 4-ch, 2-ch and 3-ch long axis acquisitions.

CMR measurements were performed by an operator blinded to RHC and clinical data using CVi42 software (Circle Cardiovascular Imaging Inc, Calgary, Canada). LV and RV volumes were measured, excluding papillary muscles, from the endocardial border tracings on short-axis images at ED and ES. LVEF and RVEF were calculated from the corresponding ED and ES volumes with the conventional formula. LV mass was calculated by subtracting endocardial from epicardial LVEDV tracings and multiplying it by 1.05 g/cm3.

LAmaxVol and LAminVol were calculated applying the biplane area-length method from the LA areas contoured respectively at ES and ED in both long-axis 4Ch, and 2Ch views. Pulmonary veins were excluded from LA tracings. Moreover, also LA appendage was excluded from LA tracings due to its inconsistent visualization in the 2-Ch view. LAEI was calculated as LAEI=((LAmaxVol-LAminVol)/LAminVol)x100.

Reproducibility analysis

LAEI and RAEI reproducibility assessment included inter- and intra-reader variability in repeated analysis of randomly selected cases (n=40 in study 1; n=20 in study 2; n=20 in study 3; n=30 in study 4). Repeated measurements were performed on the same images by the same reader at least one month later and by a second independent reader, blinded to all prior measurements.

Statistical analysis

Continuous variables were summarized as mean±standard deviation (SD) and categorical variables as absolute number (AN) with percentage (%). Paired samples T-test, independent samples T-test, Chi-Square analysis, and Pearson and Spearman correlation coefficients were applied as appropriate. lnLAEI and lnRAEI were derived by log-transformed LAEI and RAEI, respectively. Multivariate hierarchical linear regression analyses were used to explore, using the F-test, the independent and added predictive role of lnLAEI and lnRAEI over clinical TTE and CMR parameters for PCWP and RAP estimation, respectively. lnLAEI and lnRAEI diagnostic accuracy for elevated PCWP and RAP identification were assessed using receiving operating characteristic (ROCs) curves, and areas under the curves (AUCs) were compared using the DeLong method. The optimal lnLAEI and lnRAEI cut-offs were identified with the Youden index. Diagnostic accuracy for the identified cut-offs was tested using 2x2 tables for standard diagnostic tests. lnLAEI and lnRAEI linear regression equations for PCWP and RAP estimation were tested using Bland-Altman analysis. Inter- and intra-reader variability was assessed using the coefficient of variation (CoV) and intraclass correlation coefficient (ICC). P-value<0.05 was considered statistically significant. Statistical analysis was performed using SPSS 26.0 (SPSS, Chicago, US) and Medcalc 19.6.1 (MedCalc, Ostend, Belgium).

Results

Study 1: Left atrial expansion index for non-invasive estimation of pulmonary capillary wedge pressure: a cardiac catheterization validation study

Population characteristics

The study population included patients with various chronic cardiac pathologies (Table 1a) randomly divided into derivation (n=509) and validation (n=140) cohorts with comparable clinical, PCWP, and echocardiographic features (Table 2a).

Table 1a**.** Primary cardiac diseases leading to RHC exam

All (n=649) *	
Ischemic heart disease	96(14.8)
Dilative cardiomyopathy	97(14.9)
Pulmonary hypertension	59(9.1)
Aortic stenosis	224(34.5)
Aortic insufficiency	26(4.0)
Mitral regurgitation	79(12.2)
Tricuspid regurgitation	11(1.7)
Hypertrophic cardiomyopathy	15(2.3)
Restrictive cardiomyopathy	3(0.5)
Arrhythmogenic cardiomyopathy	4(0.6)
Constrictive Pericarditis	4(0.6)
Others	31(4.8)

Values are n (%). * Only the primary cardiac disease leading to RHC exam was reported in patients with more than one cardiac pathology.

Table 2a. Clinical, PCWP, and echocardiographic parameters in the study population, derivation, and validation cohorts

	All (n=649)	Derivation group (n=509)	Validation group (n=140)	p
Age, yrs	66±14	66±14	64±16	0.07
Body mass index, Kg/m^2	26±4.6	26±4.5	27±4.8	0.33
Male	381(59)	297(58)	84(60)	0.73
PCWP, mmHg	14±7.6	14±7.7	14±8.0	0.71
Systolic blood pressure, mmHg	126±21	126±21	125±20	0.65
Diastolic blood pressure, mmHg	73±12	73±12	74±11	0.67
Mean blood pressure, mmHg	91±13	91±13	91±12	0.99
Heart Rate, bpm	72±17	72±17	72±16	0.97
Atrial fibrillation	140(22)	111(22)	29(21)	0.78
LVEF, %	50±15	50±15	49±15	0.74
LAmaxVol, ml/m^2	49±23	50±23	48±25	0.64
LAEI, %	69±53	68±51	73±59	0.33
lnLAEI	3.89±0.93	3.90±0.89	3.87±1.05	0.76
E/A	1.3±0.8	1.3±0.8	1.3±0.8	0.93
E/e'	14±7	14±7	14±7	0.90
TRmaxVel, m/s	2.8±0.6	2.8±0.6	2.8±0.6	0.74
MR > moderate	110(17)	89(18)	21(15)	0.49

Values are mean ± SD or n (%). PCWP= pulmonary capillary wedge pressure; LVEF= left ventricular ejection fraction; LAmaxVol= left atrial maximum volume; LAEI= left atrial expansion index; lnLAEI= log-transformed left atrial expansion index; TRmaxVel= tricuspid regurgitation maximum velocity; MR= mitral regurgitation.

Derivation cohort analysis

The derivation cohort was divided into PCWP>12 mmHg (n=251) and PCWP≤12 mmHg (n=258) subgroups. Higher PCWP was associated with male gender, Afib, faster HR, and higher body mass index (BMI). Moreover, PCWP>12 mmHg was associated with lower LAEI, larger left atrium, reduced LVEF, higher E/A, E/e', TRmaxVel, and more severe MR (Table 3a).

Table 3a**.** High and low PCWP subgroups comparison in the derivation cohort.

Derivation group (n=509)			
	PCWP≤12 (n=258)	**PCWP>12 (n=251)**	**p**
Age, yrs	66±16	67±13	0.777
Body mass index, Kg/m^2	25±4	27±5	**<0.001**
Male	131(51)	166(66)	**0.001**
PCWP, mmHg	9±2.6	21±6.3	**<0.001**
Systolic blood pressure, mmHg	128±21	124±21	0.052
Diastolic blood pressure, mmHg	73±12	72±12	0.553
Mean blood pressure, mmHg	92±13	90±13	0.157
Heart Rate, bpm	69±15	75±18	**<0.001**
Atrial fibrillation	23(9)	88(35)	**<0.001**
LVEF, %	55±12	44±17	**<0.001**
LAmaxVol, ml/m^2	42±17	57±25	**<0.001**
LAminVol, ml/m^2	21±14	41±25	**<0.001**
LA reservoir Vol, ml/m^2	20±4	15±4	**<0.001**
LAEI, %	97±50	38±30	**<0.001**
lnLAEI	4.4±0.53	3.3±0.83	**<0.001**
E/A	1.0±0.6	1.7±1.0	**<0.001**
E/e'	12±6.3	16±7.7	**<0.001**
TRmaxVel, m/s	2.8±0.6	2.9±0.6	**0.035**
MR > moderate	33(13)	56(22)	**0.005**

Values are mean ± SD or n (%). Abbreviations as in Table 2a.

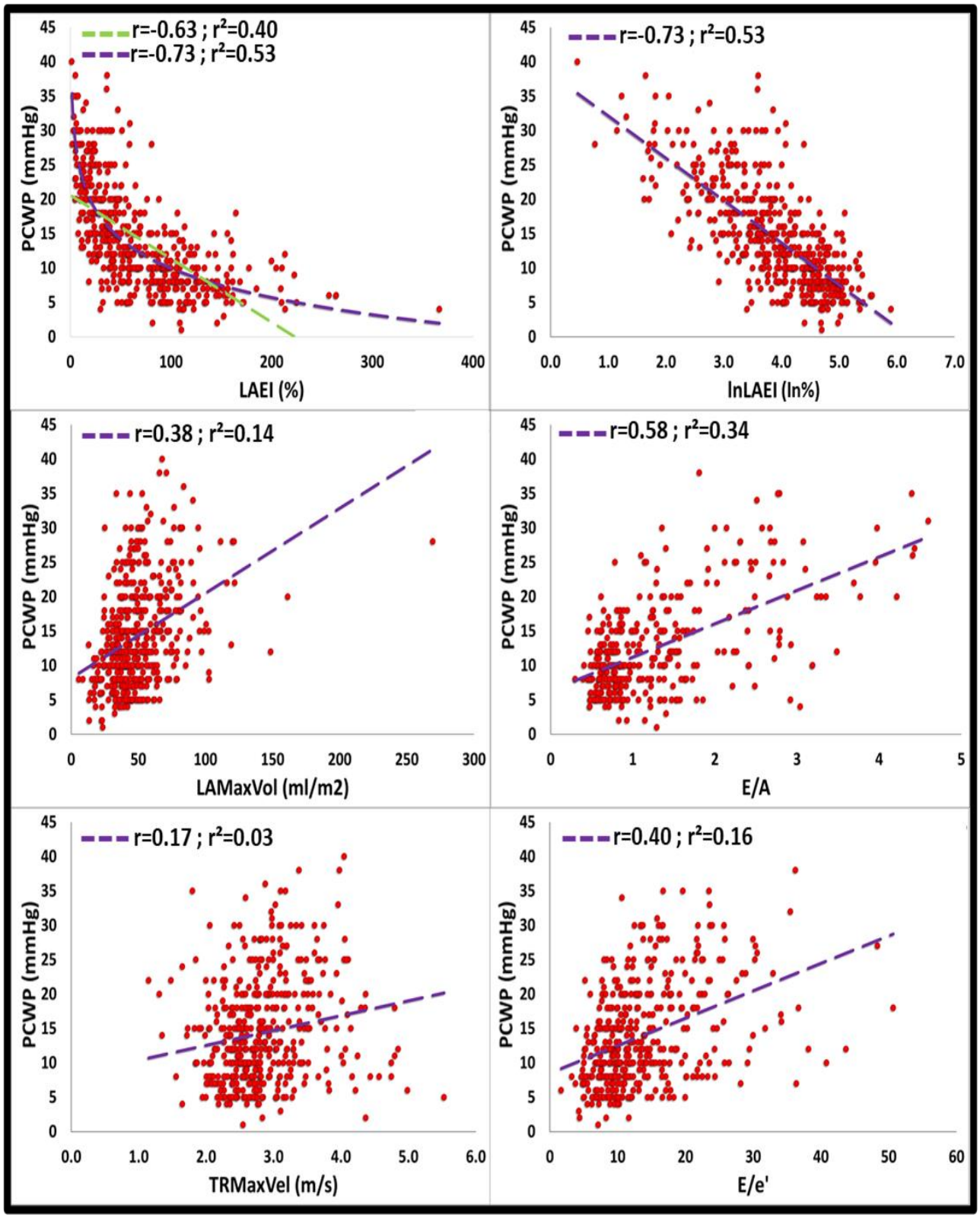
Table 4a summarizes PCWP linear correlation with LAEI and DD parameters. LAEI-PCWP depicted a logarithmic correlation, whereas DD parameters showed a weak linear correlation with PCWP (Figure 1a). Of note, log-transformed LAEI (lnLAEI) showed the strongest linear correlation with PCWP (r=-0.73; p<0.001) among all the other DD parameters.

Table 4a. PCWP correlation analysis in the derivation group.

Derivation group (n=509)		
	PCWP (mmHg)	
	r	**p**
Body mass index, Kg/m^2	0.24	**<0.001**
Heart Rate, bpm	0.20	**<0.001**
LVEF, %	-0.44	**<0.001**
LAmaxVol, ml/m^2	0.38	**<0.001**
LAEI, %	-0.63	**<0.001**
lnLAEI	-0.73	**<0.001**
E/A	0.58	**<0.001**
E/e'	0.40	**<0.001**
TRmaxVel, m/s	0.17	**<0.001**
Mitral regurgitation*	0.32	**<0.001**

* 6-grade scale (no/trivial, mild, mild/moderate, moderate, moderate/severe, and severe). Abbreviations as in Table 2a**.**

Figure 1a. PCWP scatter-plots correlation analysis in the derivation cohort for LAEI (top left), lnLAEI (top right), LAmaxVol (middle left), E/A (middle right), TRmaxVel (bottom left), E/e' (bottom right).



The multivariate hierarchical linear regression for PCWP prediction was composed of three predefined steps. The 1st model included BMI, Gender, HR, Afib, LVEF, and MR severity (R= 0.58; R^2adjusted=0.33). Next, the 2nd model added DD parameters (LAmaxVol, E/A, E/e', and TRmaxVel) to the 1st model, providing a significant predictive power improvement (R= 0.72; R^2adjusted=0.51; p<0.001 from the 1st model). Finally, the 3rd model added lnLAEI to the 2nd model, providing a further significant predictive power improvement (R=0.80; R^2adjusted=0.63; p<0.001 from the 2nd model). In addition, lnLAEI resulted in an independent PCWP predictor even when accounting for DD and clinical parameters (Table 5a).

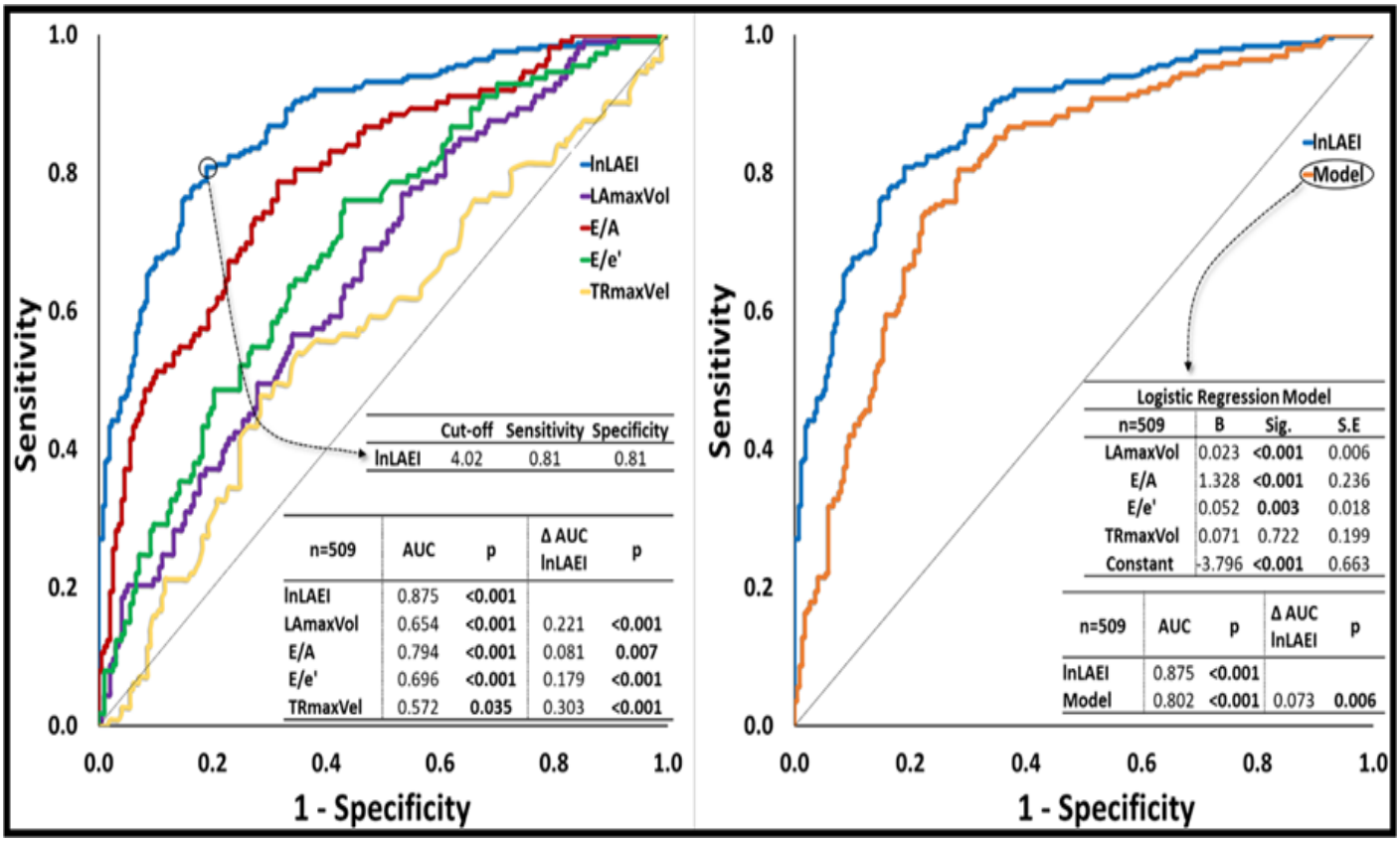
Table 5a. Multivariate regression analysis for PCWP prediction in the derivation cohort.

	Derivation group (n=509)								
	1st Model			**2nd Model**			**3rd model**		
	R^2 adj.=0.33 R=0.58; F=43.4			**R^2 adj.=0.51 R=0.72; F=55.5**		**p<0.001 from 1st Model**	**R^2 adj.=0.63 R=0.80; F=82.3**		**p<0.001 from 2nd Model**
	B	**CI (95%)**	**p**	**B**	**CI (95%)**	**p**	**B**	**CI (95%)**	**p**
K	10.45	[5.39;15.52]	**<0.001**	-6.08	[-11.26;-0.90]	**0.021**	17.61	[11.87;23.35]	**<0.001**
Body mass index, kg/m²	0.29	[0.17;0.41]	**<0.001**	0.33	[0.23;0.43]	**<0.001**	0.23	[0.14;0.32]	**<0.001**
Male	1.10	[-0.03;2.23]	0.056	0.92	[-0.07;1.91]	0.069	0.91	[0.05;1.77]	**0.038**
Heart Rate, bpm	0.01	[-0.02;0.05]	0.413	0.04	[0.01;0.07]	**0.018**	0.03	[0.00;0.05]	0.056
Atrial fibrillation	3.43	[2.06;4.81]	**<0.001**	3.40	[2.11;4.68]	**<0.001**	0.68	[-0.51;1.87]	0.260
LVEF, %	-0.16	[-0.20;-0.12]	**<0.001**	-0.10	[-0.13;-0.07]	**<0.001**	-0.05	[-0.08;-0.02]	**0.003**
MR *	0.91	[0.58;1.24]	**<0.001**	0.14	[-0.18;0.47]	0.387	0.15	[-0.13;0.43]	0.305
LAmaxVol, ml/m²				0.02	[0.00;0.05]	0.067	0.00	[-0.02;0.02]	0.925
E/A				3.43	[2.71;4.14]	**<0.001**	2.13	[1.48;2.78]	**<0.001**
E/e'				0.21	[0.14;0.27]	**<0.001**	0.09	[0.03;0.16]	**0.003**
TRmaxVel, m/s				1.34	[0.57;2.11]	**0.001**	0.74	[0.07;1.42]	**0.031**
lnLAEI							-4.11	[-4.73;-3.49]	**<0.001**

* 6-grade scale (no/trivial, mild, mild/moderate, moderate, moderate/severe, and severe). Abbreviations as in Table 2a.

lnLAEI diagnostic accuracy for PCWP> 12 mmHg identification was significantly higher than each DD parameter (lnLAEI AUC=0.875, p<0.001; ΔAUC lnLAEI-LAmaxVol=0.221, p<0.001; ΔAUC lnLAEI-E/A=0.081, p=0.007; ΔAUC lnLAEI-E/e'=0.179, p<0.001; ΔAUC lnLAEI-TRmaxVel=0.303, p<0.001) with an optimal cut-off of lnLAEI<4.02. Moreover, lnLAEI diagnostic accuracy for PCWP>12 mmHg identification remained superior to a logistic regression model that included LAmaxVol, E/A, E/e' and TRmaxVel (ΔAUC lnLAEI-Model= 0.073, p=0.006) (Figure 2a).

Figure 2a. ROC analysis for PCWP>12mmHg identification in the derivation cohort. Comparison of lnLAEI and each DD parameter (left) and their association (right) AUCs for elevated PCWP identification.



Validation cohort analysis

lnLAEI<4.02 performance for PCWP> 12 mmHg identification was tested in the validation cohort in two different subgroups. Since the 2016 DD algorithm could not be applied to patients with Afib and significant MR, the first validation subgroup (n=98) excluded patients with Afib and/or significant MR and compared lnLAEI<4.02 against the 2016 DD algorithm (Table 6a).

Table 6a. lnLAEI<4.02 and 2016 DD algorithm accuracy comparison for elevated PCWP identification in the validation subgroup without Afib and/or MR>moderate.

Validation Group (Excluded Afib and/or MR>Moderate)									
			PCWP			**Diagnostic Tests**		**Agreement with RHC**	**p**
			High	Low	*Total*	*Prevalence*	*Sensitivity*		
		Positive	28	8	36	0.34	0.85		
	lnLAEI	*Negative*	5	57	62	Specificity	Accuracy	*Cohen's K*	0.71±0.07
ALL		*Total*	33	65	98	0.89	0.88		
(n=98)			**PCWP**			**Diagnostic Tests**		**Agreement with RHC**	**<0.001**
			High	*Low*	*Total*	*Prevalence*	*Sensitivity*		
		Positive	23	15	38	0.35	0.72		
	DD*	*Negative*	9	46	55	Specificity	Accuracy	Cohen's K	0.45±0.09
		Total	32	61	93	0.75	0.74		
			PCWP			**Diagnostic Tests**		**Agreement with RHC**	
			High	*Low*	*Total*	*Prevalence*	*Sensitivity*		
		Positive	13	3	16	0.27	0.76		
	lnLAEI	*Negative*	4	43	47	*Specificity*	*Accuracy*	*Cohen's K*	0.73±0.1
LVEF≥50%		*Total*	17	46	63	0.94	0.89		
(n=63)			**PCWP**			**Diagnostic Tests**		**Agreement with RHC**	**<0.001**
			High	*Low*	*Total*	*Prevalence*	*Sensitivity*		
		Positive	10	12	22	0.27	0.59		
	DD	*Negative*	7	34	41	*Specificity*	*Accuracy*	*Cohen's K*	0.30±0.13
		Total	17	46	63	0.74	0.70		
			PCWP			**Diagnostic Tests**		**Agreement with RHC**	
			High	*Low*	*Total*	*Prevalence*	*Sensitivity*		
		Positive	15	5	20	0.46	0.94		
	lnLAEI	*Negative*	1	14	15	*Specificity*	*Accuracy*	*Cohen's K*	0.66±0.12
LVEF<50%		*Total*	16	19	35	0.74	0.82		
(n=35)			**PCWP**			**Diagnostic Tests**		**Agreement with RHC**	0.93
			High	*Low*	*Total*	*Prevalence*	*Sensitivity*		
		Positive	13	3	16	0.50	0.87		
	DD*	*Negative*	2	12	14	*Specificity*	*Accuracy*	*Cohen's K*	0.67±0.14
		Total	15	15	30	0.80	0.83		

*five indeterminate patients for the 2016 DD algorithm. Abbreviations as in Tables 1a and 2a.

The 2016 DD algorithm was applied following the recommended stepwise evaluation of E/A with E velocity, E/e'; TRmaxVel, and LAmaxVol, for both reduced and preserved LVEF. lnLAEI diagnostic accuracy was higher than 2016 DD algorithm (lnLAEI: sensitivity=85%; specificity=89%; accuracy=88%; 2016 DD algorithm: sensitivity=72%; specificity=75%; accuracy=74%, five patients indeterminate), furthermore, Cohen's K coefficient of agreement with RHC was significantly higher for lnLAEI than 2016 DD algorithm (lnLAEI<4.02: K=0.71±0.07; 2016 DD algorithm: K=0.45±0.09; p<0.001). These results were driven by higher diagnostic accuracy of lnLAEI in the subgroup of patients with preserved LVEF, whereas the diagnostic accuracy of lnLAEI resulted comparable to the 2016 DD algorithm for patients with reduced LVEF. lnLAEI<4.02 was tested in the remaining validation cohort of patients with Afib and significant MR (n=42). Of note, lnLAEI showed good diagnostic accuracy also in this subgroup (sensitivity=94%; specificity=67%; accuracy=88%) (Table 7a).

Table 7a. lnLAEI<4.02 accuracy for elevated PCWP identification in the validation subgroup with Afib and/or MR>Moderate.

Validation Group (Afib and/or MR>Moderate) (n=42) *						
		PCWP			**Diagnostic Tests**	**Agreement with RHC**
		High	*Low*	*Total*	*Prevalence*	*Sensitivity*	*Cohen's K*
	Positive	31	3	34	0.79	0.94	
lnLAEI	*Negative*	2	6	8	*Specificity*	*Accuracy*	0.63±0.15
	Total	33	9	42	0.67	0.88	

*Afib=21 patients; MR>moderate=13 patients; Afib plus MR>Moderate=8 patients. Abbreviations as in Tables 2a and 3a.

Finally, the lnLAEI regression equation obtained in the derivation cohort for PCWP estimation (PCWP=38.3-6.2xlnLAEI) was tested in the validation cohort and was able to predict invasively measured PCWP (PCWP invasively measured-PCWP estimated=-0.4±5.4 mmHg) (Figure 3a and 4a).

Figure 3a. Bland-Altman plot comparing PCWP predicted through lnLAEI equation and PCWP invasively measured during RHC in the validation cohort.

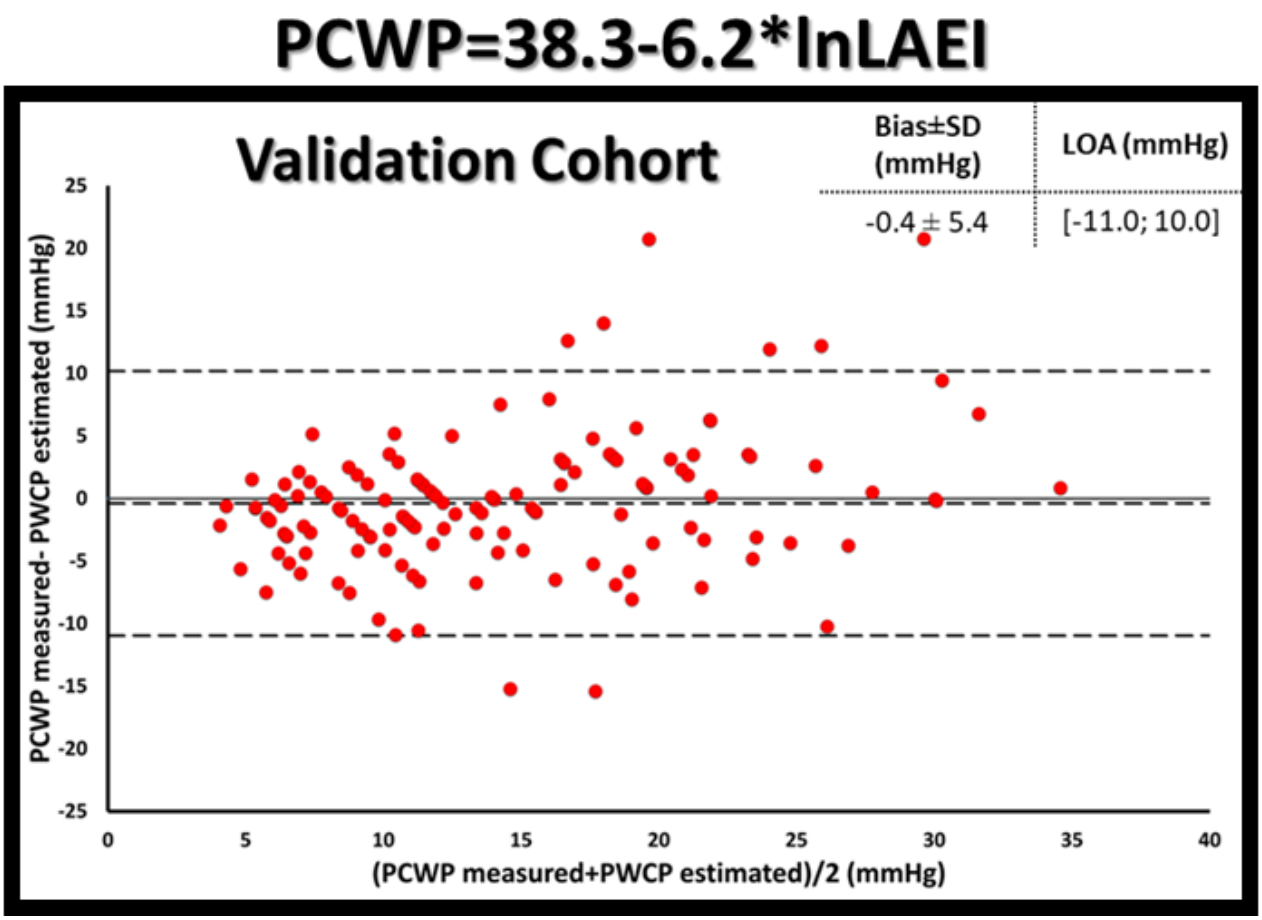
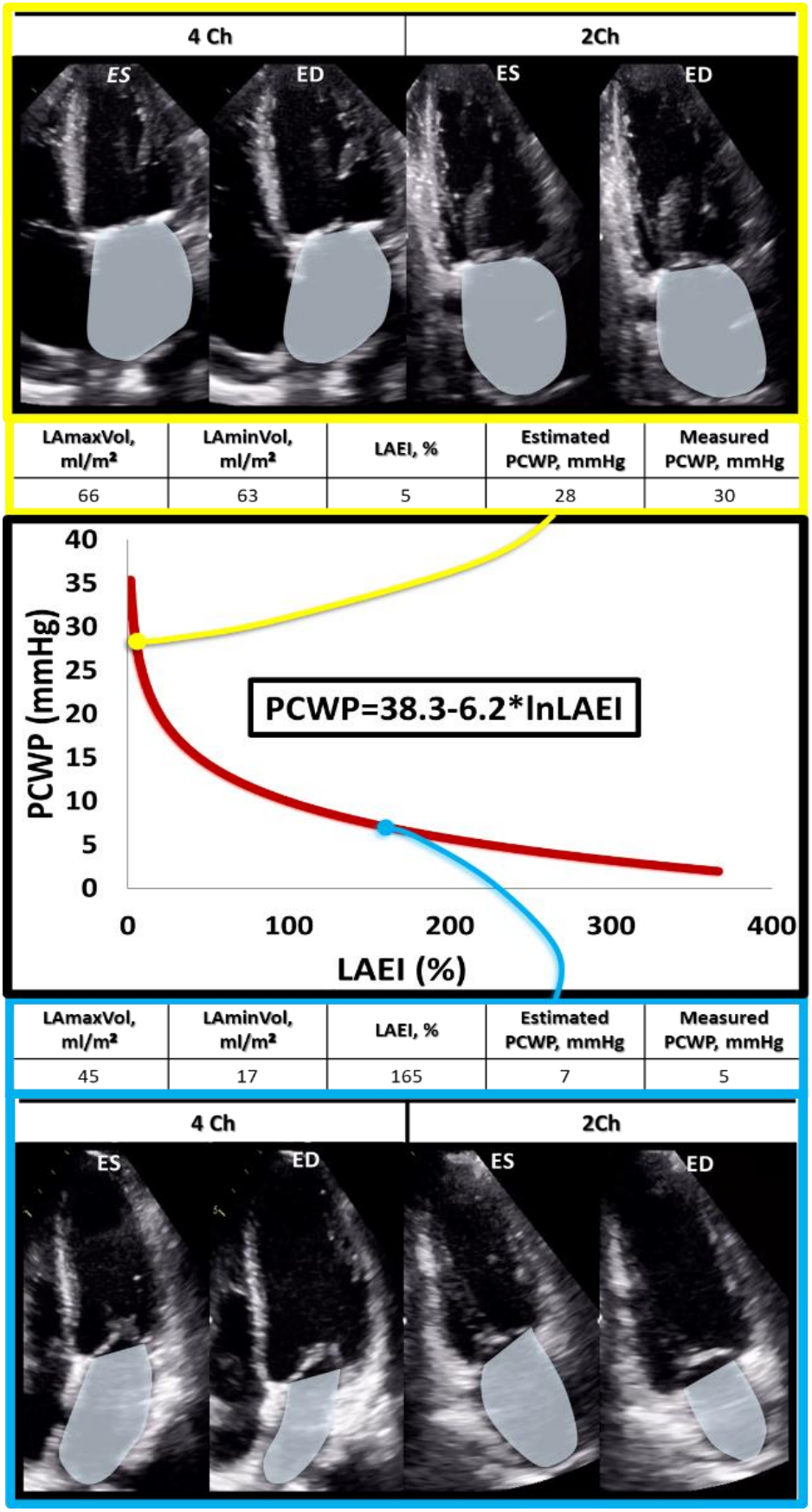


Figure 4a. LAEI calculation example in two patients with low LAEI-high PCWP (top) and high LAEI-low PCWP (bottom), respectively. The location of the two patients on the LAEI-PCWP regression line is depicted in the central graph



Reproducibility analysis

Reproducibility analysis was performed on 40 randomly selected patients. lnLAEI demonstrated a good reproducibility at the intra-reader (CoV[95%CI] and ICC:LAmaxVol= 5.3[4.1;6.5]% and 0.98, LAminVol=6.2[4.8;7.8]% and 0.97, lnLAEI=4.1[3.2;5.0]% and 0.98) inter-reader (CoV[95%CI] and ICC:LAmaxVol=6.1[4.7;7.6]% and 0.97, LAminVol= 7.6[5.9;9.4]% and 0.96, lnLAEI=5.0[3.8;6.1]% and 0.97) variability analysis.

Study 2: Non-invasive evaluation of pulmonary capillary wedge pressure using the left atrial expansion index in mitral valve stenosis, prosthesis, and repair

Population characteristics

The study population included 167 patients composed by 87(52.1%) degenerative MV stenosis, 27(16.2%) rheumatic MV stenosis, 30(18.0%) MV prosthesis (biological n=16; mechanical n=14) and 23(13.8%) MV surgical repair. The population was divided into PCWP>15 (n=95) and ≤15 mmHg (n=72) subgroups. The subgroup with elevated PCWP had a higher proportion of rheumatic MV stenosis, prosthesis, and surgical repair and a lower proportion of degenerative MV stenosis. Patients with higher PCWP were also younger and had a higher proportion of Afib. In addition, the elevated PCWP cohort had lower LVEF, LAEI, Cn, and MV EOA and higher MV MG and PASP than the lower PCWP subgroup (Table 1b).

Table 1b. Clinical and echocardiographic variables for all patients and PCWP>15 and ≤15mmHg subgroups.

		ALL (n=167) Mean ±SD or or N (%)	PCWP≤ 15 mmHg (n=72) Mean ±SD or or N (%)	PCWP> 15 mmHg (n=95) Mean ±SD or or N (%)	P-value
Age (Years)		73±11.5	75±10.5	71±11.9	**0.011**
Gender (Male)		64(38.3)	26(36.1)	38(40.0)	0.609
Body mass index (Kg/m^2)		26.3±4.8	26.2±4.9	26.4±4.8	0.815
Systolic Blood Pressure (mmHg)		127.7±21.6	130.1±19.8	125.8±22.8	0.202
Diastolic Blood Pressure (mmHg)		72.5±11.1	74.2±11.6	71.2±10.6	0.092
Heart Rate (bpm)		72.1±11.6	71.0±11.7	72.8±11.5	0.326
PCWP (mmHg)		18±7.7	11.0±3.2	23.4±5.5	**<0.001**
Atrial Fibrillation		55(32.9)	13(18.1)	42(44.2)	**<0.001**
Subgroups	*Degenerative MV Stenosis**	87(52.1)	50(69.4)	37(38.9)	**<0.001**
	Rheumatic MV stenosis#	27(16.2)	3(4.2)	24(25.3)	
	*MV prosthesis^*	30(18.0)	11(15.3)	19(20.0)	
	MV surgical repair°	23(13.8)	8(11.1)	15(15.8)	
LV End-Diastolic Volume (ml/m^2)		60±27.0	56±19.1	64±31.4	0.053
LV Ejection Fraction (%)		54±13.0	57±10.4	52±14.3	**0.012**
LA Max Volume (ml/m^2)		65±43.1	59±40.1	70±44.8	0.095
LAEI (%)		41±30.7	60±35.4	27±15.5	**<0.001**
lnLAEI		3.40±0.86	3.87±0.72	3.05±0.79	**<0.001**
MV mean gradient (mmHg)		5.5±3.6	3.9±1.8	6.8±4.1	**<0.001**
MV effective orifice area (cm^2)		2.0±0.8	2.2±0.6	1.7±0.8	**<0.001**
Net AV Compliance (ml/mmHg)		5.7±4.1	7.9±5.0	3.9±1.8	**<0.001**
PASP		42±14.8	37±11.4	46±16.1	**<0.001**

*17 (19.5%) with EOA<1.5cm^2 ; # 20 (74%) with EOA <1.5 cm^2; ^ 9 (30%) with EOA <1.5 cm^2 ; ° 6 (26%) with EOA <1.5 cm^2. Abbreviations. PCWP: pulmonary capillary wedge pressure; MV: mitral valve; LV: left ventricular; LAEI: left atrial expansion index; MV: mitral valve; AV: atrioventricular; PASP: pulmonary artery systolic pressure.

Univariate and multivariate regression analysis

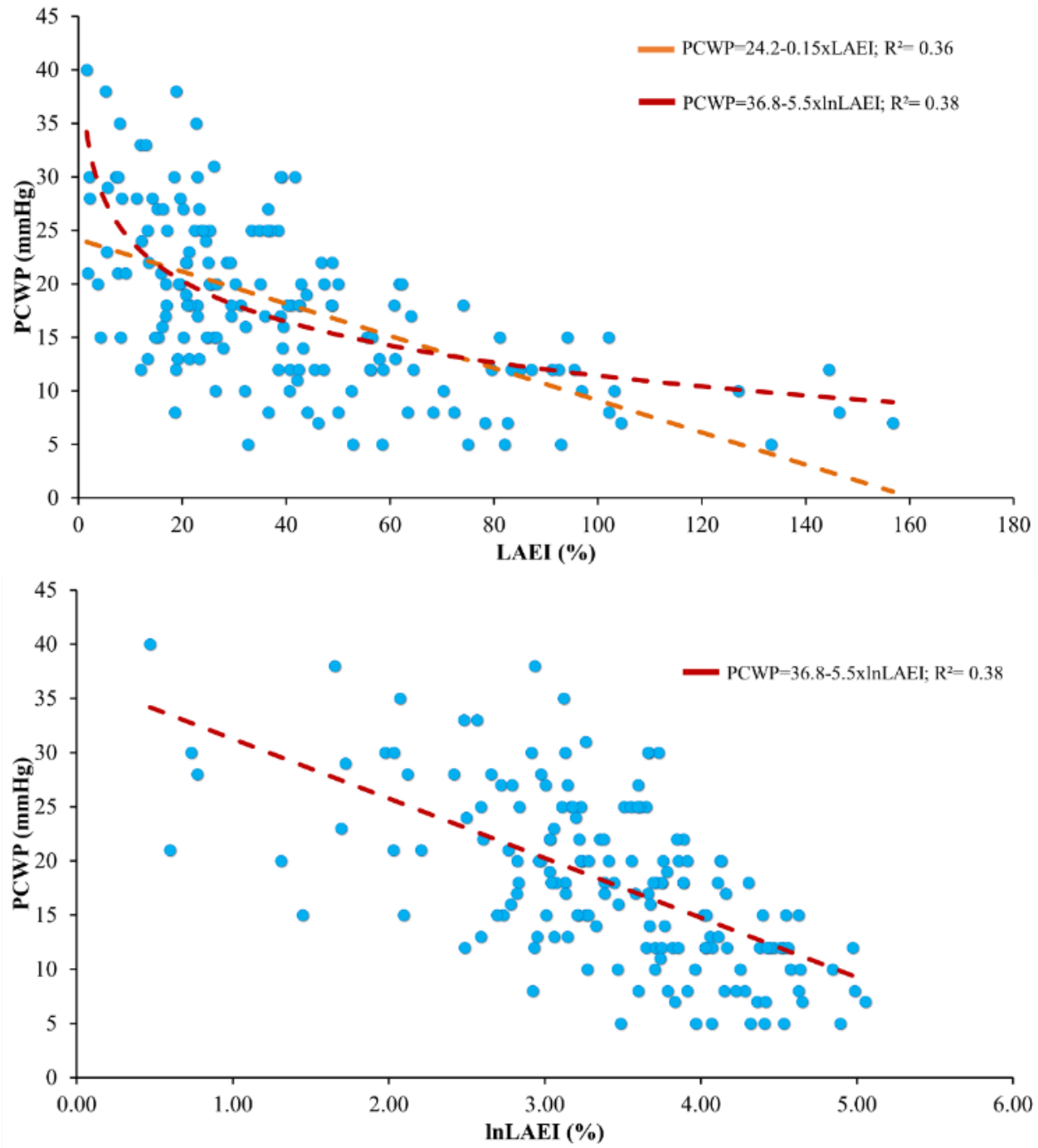
Compared to the other parameters, LAEI showed the highest linear association with PCWP (r=-0.599; p<0.001) (Table 2b). However, the association between LAEI and PCWP was best fitted by a logarithmic correlation (Figure 2b, top), and the log-transformed LAEI (lnLAEI) correlated even higher with PCWP (r=-0.616; p<0.001) (Figure 1b, bottom).

Table 2b. PCWP correlation with clinical and echocardiographic parameters

	PCWP (n=167)	
	Pearson Correlation	**P-value**
Age (Years)	-0.181	**0.019**
Body mass index (Kg/m^2)	0.010	0.901
Systolic Blood Pressure (mmHg)	-0.050	0.519
Diastolic Blood Pressure (mmHg)	-0.072	0.354
Heart Rate (bpm)	0.144	0.064
LV End-Diastolic Volume (ml/m^2)	0.203	**0.009**
LV Ejection Fraction (%)	-0.227	**0.003**
LA Max Volume (ml/m^2)	0.182	**0.019**
LA Expansion Index (%)	-0.599	**<0.001**
lnLAEI	-0.616	**<0.001**
MV mean gradient (mmHg)	0.367	**<0.001**
MV effective orifice area (cm^2)	-0.222	**0.004**
Net AV Compliance (ml/mmHg)	-0.467	**<0.001**
PASP	0.487	**<0.001**

Abbreviations. See Table 1b.

Figure 1b. LAEI (top) and lnLAEI (bottom) correlation with PCWP



Multivariate linear regression analysis for PCWP prediction was composed of two blocks. The first model included clinical (age, Afib, HR, and MV subgroups) and echocardiographic variables (LVEF, MV EOA, MV MG, Cn, and PASP). The second model added lnLAEI to the first model. Of note, lnLAEI significantly increased the model's predictive power (first model Adj R^2=0.443, vs. second model Adj R^2=0.521; p<0.001) and remained an independent PCWP predictor (lnLAEI=-3.290[-4.587 to -1.994]mmHg; p<0.001) with PASP, Cn, MV MG, MV subgroups, and LVEF (Table 3b).

Table 3b. Multivariate linear regression analysis for PCWP prediction

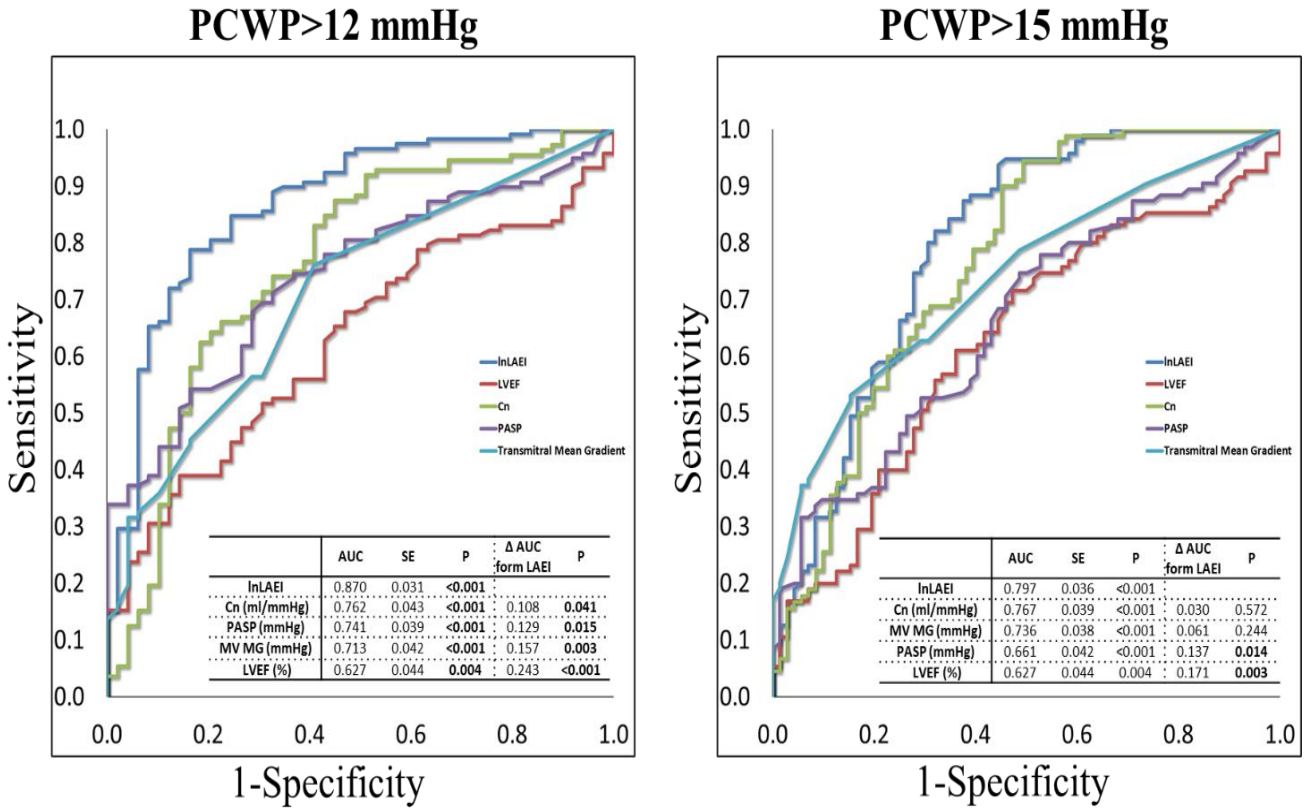
		First Model			**Second Model**		
		R 0.694	**Adj R²** 0.443	**F** 12.561	**R** 0.746	**Adj R²** 0.521	**F** 15.477	**Sig. F Change <0.001**
		B	**95.0% CI**	**P**	**B**	**95.0% CI**	**P**
Constant		20.242	[9.243 to 31.241]	**<0.001**	36.634	[24.559 to 48.710]	**<0.001**
Age (years)		-0.043	[-0.128 to 0.043]	0.325	-0.059	[-0.139 to 0.020]	0.143
Atrial fibrillation		2.558	[0.336 to 4.780]	**0.024**	1.141	[-0.994 to 3.276]	0.293
Heart rate (bpm)		-0.026	[-0.110 to 0.059]	0.551	-0.053	[-0.132 to 0.026]	0.185
MV subgroups*	*Rheumatic MV stenosis*	1.629	[-1.497 to 4.755]	0.305	0.906	[-2.008 to 3.820]	0.540
	MV prosthesis	-3.836	[-7.051 to -0.621]	**0.020**	-3.530	[-6.515 to -0.545]	**0.021**
	MV surgical repair	-2.372	[-5.604 to 0.861]	0.149	-2.803	[-5.807 to 0.201]	0.067
LVEF (%)		-0.135	[-0.224 to -0.047]	**0.003**	-0.087	[-0.171 to -0.002]	**0.044**
MV effective orifice area (cm^2)		1.527	[-0.343 to 3.397]	0.109	0.929	[-0.822 to 2.680]	0.296
MV mean gradient (mmHg)		0.589	[0.198 to 0.980]	**0.003**	0.431	[0.063 to 0.799]	**0.022**
Net Atrioventricular Compliance (ml/mmHg)		-0.576	[-0.872 to -0.281]	**<0.001**	-0.475	[-0.751 to -0.198]	**0.001**
PASP		0.164	[0.096 to 0.233]	**<0.001**	0.103	[0.034 to 0.171]	**0.003**
lnLAEI					-3.290	[-4.587 to -1.994]	**<0.001**

* Degenerative MV stenosis used as the reference. Abbreviations. See Table 1b.

LAEI accuracy for elevated PCWP identification

lnLAEI identified PCWP>12 mmHg (AUC=0.870; p<0.001) better than Cn (ΔAUC from lnLAEI=0.108; p=0.041), PASP (ΔAUC from lnLAEI=0.129; p=0.015), MV MG (ΔAUC from lnLAEI=0.157; p=0.003), LVEF (ΔAUC from lnLAEI=0.243; p<0.001) (Figure 2b, left). Moreover, lnLAEI identified PCWP>15 mmHg (AUC 0.797; p<0.001) better than PASP (ΔAUC from lnLAEI=0.137; p=0.014) and LVEF (ΔAUC from lnLAEI=0.171; p=0.003) whereas, despite still being numerically higher, the difference was not statistically significant with Cn and MV MG (Figure 2b, right).

Figure 2b. ROCs for lnLAEI, Cn, PASP, MV MG, and LVEF for identification of PCWP>12 mmHg (left) and >15 mmHg (right).



The derived optimal cut-off lnLAEI<3.69 discriminated PCWP>12 mmHg with 80.2% accuracy (sensitivity=78.8%, specificity=83.7%) and PCWP>15 mmHg with 76.1% accuracy (sensitivity=82.1%, specificity=68.1%) (Table 4b). The previously derived cut-off

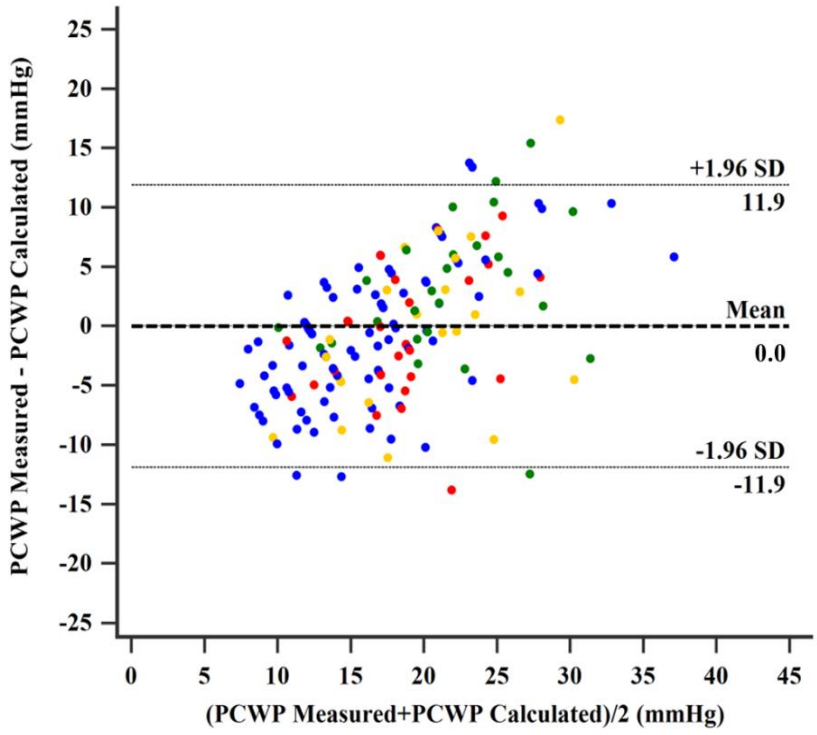
lnLAE<4.02 [1] also showed a comparable accuracy in this population but with higher sensitivity and markedly lower specificity.

Table 4b. lnLAEI<3.69 and lnLAEI<4.02 diagnostic performance for discriminating PCWP>12 mmHg and >15 mmHg

N=167	PCWP > 12 mmHg (n=118; 70.7%)	PCWP > 12 mmHg (n=118; 70.7%)	p	PCWP > 15 mmHg (n=95; 56.9%)	PCWP > 15 mmHg (n=95; 56.9%)	p
	lnLAEI<3.69	***lnLAEI<4.02***		***lnLAEI<3.69***	***lnLAEI<4.02***	
Sensitivity	78.8%	90.7%	**0.003**	82.1%	94.7%	**<0.001**
Specificity	83.7%	61.2%	**<0.001**	68.1%	50.0%	**<0.001**
Accuracy	80.2%	82.1%	0.658	76.1%	75.5%	0.898

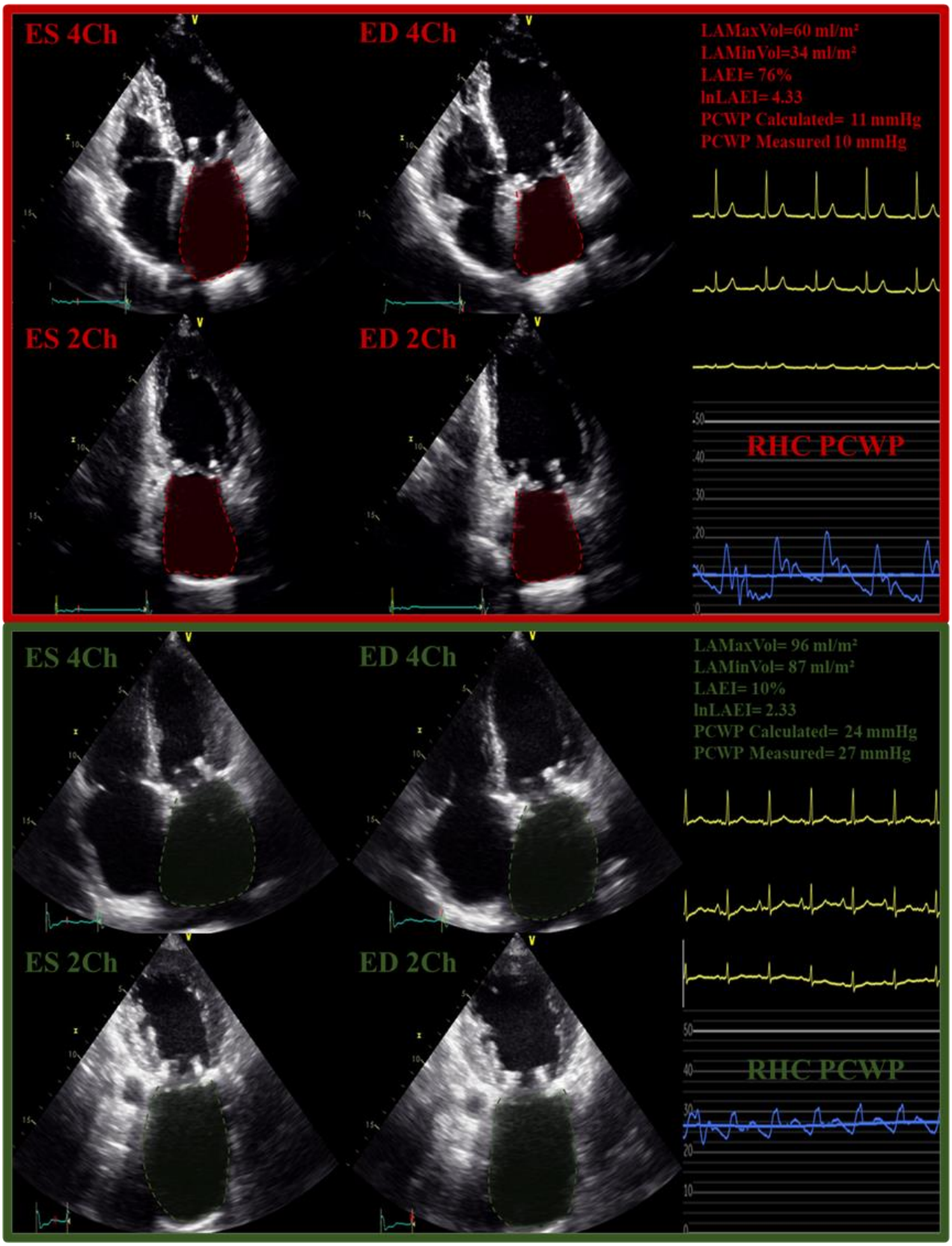
The derived regression equation PCWP=36.8-5.5xlnLAEI estimated invasive PCWP (0.0±6.1mmHg) (Figure 4b). An example of the formula application is shown in Figure 3b.

Figure 4b. Bland-Altman plot comparing invasive measured PCWP with PCWP=36.8-5.5xlnLAEI.



	Bias ±SD (mmHg)	p value	LOA (mmHg)
All (n=167)	0.0±6.1	0.999	[-11.9;11.9]
Degenerative MV stenosis (n=87)	-0.8±5.9	0.210	[-12.4;10.8]
Rheumatic MV stenosis (n=27)	3.1±5.9	**0.011**	[-8.4;14.6]
MV prosthesis (n=30)	0.2±5.6	0.820	[-11.2;10.7]
MV repair (n=23)	0.3±6.9	0.849	[-13.6;13.6]

Figure 1b. MV bioprosthesis patients with normal (top) and elevated (bottom) PCWP. LAEI was calculated as LAEI=[(LAmaxVolume-LAminVolume)/LAminVolume]x100. Invasive PCWP was measured during RHC from the pressure-time recordings. PCWP was effectively estimated non-invasively as PCWP=36.8-5.5xlnLAEI.



Reproducibility analysis

The variability analysis showed excellent intra- and inter-reader reproducibility for LAmaxVol, LAminVol, LAEI, and lnLAEI (Table 5b).

Table 5b. lnLAEI intra inter-reader variability analysis on 20 randomly selected patients.

	Intra-Reader				Inter-Reader			
	CoV (%)	**95%CI**	**ICC**	**95%CI**	**CoV (%)**	**95%CI**	**ICC**	**95%CI**
LAmaxVol	8.8	6.2 to 11.5	0.97	0.92 to 0.98	8.5	5.9 to 11.1	0.97	0.93 to 0.98
LAminVol	9.0	6.3 to 11.8	0.97	0.93 to 0.98	8.3	5.8 to 10.9	0.97	0.94 to 0.98
lnLAEI	6.8	4.8 to 8.9	0.95	0.88 to 0.98	7.5	5.3 to 9.8	0.93	0.84 to 0.97

Abbreviations. CoV: Coefficient of Variation, ICC: Intraclass correlation coefficient

Study 3: Cardiovascular magnetic resonance left atrial expansion index estimates pulmonary capillary wedge pressure in dilated cardiomyopathy

Population characteristics

The study population comprised 126 DCM patients. The population was divided into a derivation (n=92, retrospective enrollment) and a validation (n=34 prospective enrollment) cohort. The clinical and CMR parameters were highly comparable between the two groups (Table 1c).

Table 1c. Study population clinical, PCWP, and CMR parameters compared between the derivation and validation cohorts

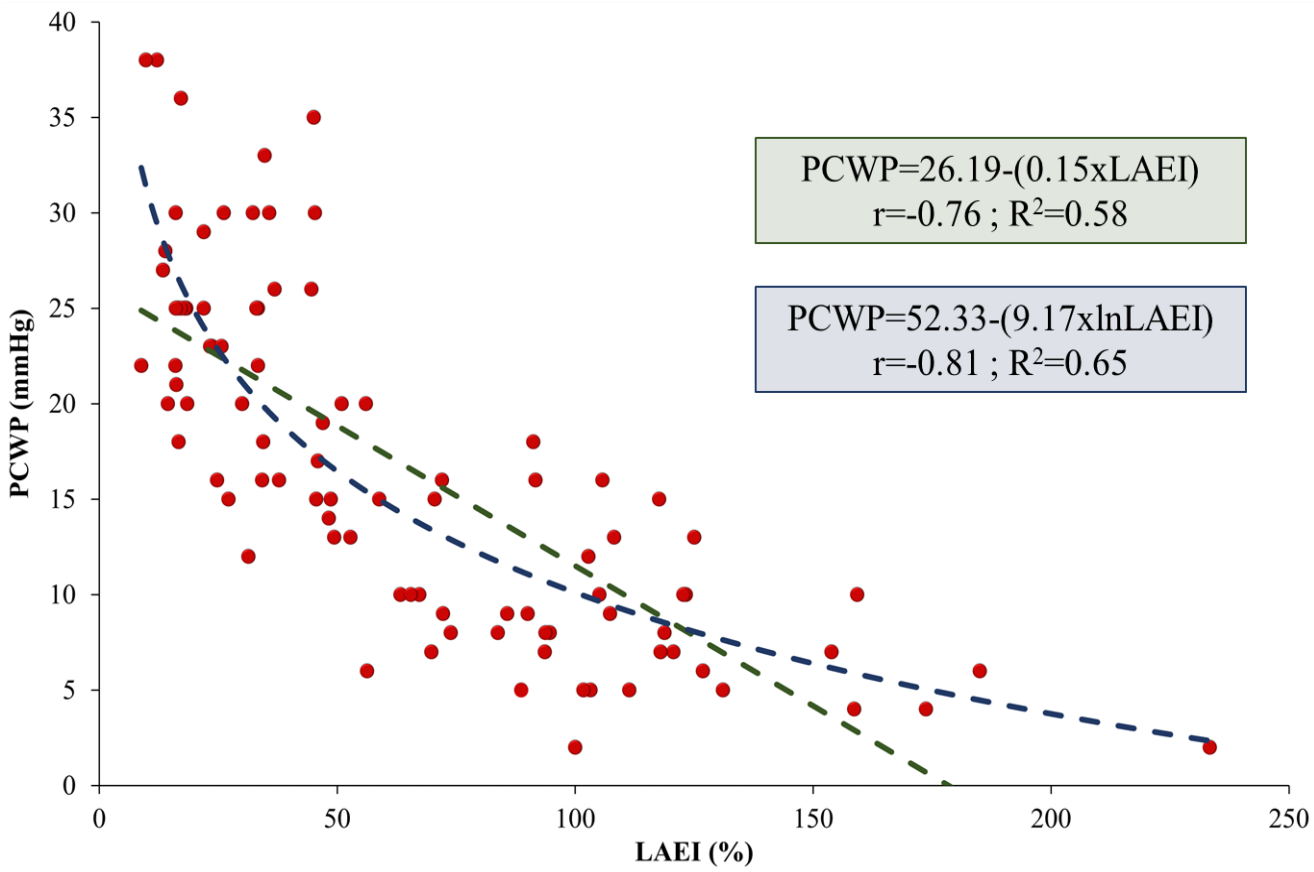
		Study Population (n=126)	Derivation (N=92)	Validation (N=34)	p
Age (years)		47 ±14.2	48 ±14.4	45 ±13.6	0.274
Gender (male)		86 (68%)	60(65%)	26(76%)	0.230
BMI (Kg/m²)		25.5 ±3.9	25.3 ±3.8	25.7 ±4.3	0.618
DCM	*Idiopathic*	75 (60%)	58(63%)	17(50%)	0.370
	Inflammatory	37 (29%)	24(26%)	13(38%)	
	Other	14 (11%)	10(11%)	4(12%)	
Left Bundle Branch Block		27 (21%)	21(23%)	6(18%)	0.530
Systolic blood pressure (mmHg)		115 ±19.4	117 ±19.8	109 ±17.5	0.054
Diastolic blood pressure (mmHg)		72 ±11.8	72 ±11.2	70 ±13.5	0.398
PCWP (mmHg)		16.6 ±9.3	16.6 ±9.1	16.6 ±9.9	0.978
Heart Rate (bpm)		75 ±15.4	75.9 ±15.9	73.5 ±14.1	0.442
LVEDV (ml/m²)		153.8 ±44.8	154.7 ±42.1	151.3 ±52.0	0.706
LVEF (%)		28.1 ±11.0	27.7 ±11.1	29.1 ±11.0	0.529
LV Mass (g/m²)		81.3 ±27.7	83.5 ±28.2	75.4 ±25.6	0.143
RVEDV (ml/m²)		80.8 ±27.8	80.0 ±28.2	83.0 ±27.0	0.600
RVEF (%)		45.7 ±14.2	46.1 ±14.3	44.6 ±13.9	0.621
LAmaxVol (ml/m²)		53.0 ±20.4	50.7 ±17.5	59.4 ±26.0	**0.031**
LAEI (%)		64.6 ±45.3	65.6 ±47.1	61.8 ±40.7	0.681
lnLAEI		3.90 ±0.78	3.901 ±0.80	3.89 ±0.74	0.927
Mitral Regurgitation	*None/trivial*	33 (26%)	23 (25%)	10 (29%)	0.850
	Mild	42 (33%)	32 (35%)	10 (29%)	
	Mild/Moderate	12 (9.5%)	8 (8.7%)	4 (12%)	
	Moderate	21 (17%)	15 (16%)	6 (18%)	
	Moderate/Severe	9 (7.1%)	8 (8.7%)	1 (2.9%)	
	Severe	9 (7.1%)	6 (6.5%)	3 (8.8%)	

Values are mean ± SD or n (%). Abbreviations. BMI: body mass index; DCM: dilated cardiomyopathy; PCWP: pulmonary capillary wedge pressure, LVEDV: left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction; RVEDV: right ventricular end-diastolic volume; LAmaxVol: left atrial maximal volume; LAEI: left atrial expansion index; lnLAEI:log-transformed LAEI.

Derivation cohort analysis

LAEI showed a strong linear correlation with PCWP (r=-0.76; p<0.001). However, a logarithmic curve best fitted the correlation between LAEI and PCWP. Therefore, lnLAEI further improved the linear correlation with PCWP (r=-0.81; p<0.001) (Figure 1c).

Figure 1c. PCWP correlation with LAEI (green) and lnLAEI (blue) in the derivation cohort.



In the derivation cohort, the subgroup with PCWP≥15 mmHg (n=52) had a faster HR, larger LAmaxVol, lower systolic blood pressure, LVEF, RVEF, and lnLAEI than the subgroup with PCWP<15 mmHg (n=40) (Table 2c).

Table 2c. Clinical and CMR parameters comparison between PCWP≥15 and <15 mmHg subgroups of the derivation cohort.

		PCWP<15 (n=40)	PCWP≥15 (n=52)	p
Age (years)		47 ±15.5	49 ±13.6	0.462
Gender (male)		24 (60%)	36 (69%)	0.360
BMI (Kg/m²)		24.7 ±3.5	25.8 ±3.9	0.163
DCM	*Idiopathic*	27 (68%)	31 (60%)	0.500
	Inflammatory	8 (20%)	16 (31%)	
	Other	5 (12%)	5 (9.6%)	
Left Bundle Branch Block		10 (25%)	11 (21%)	0.660
Systolic blood pressure (mmHg)		122 ±18.8	113 ±19.8	**0.028**
Diastolic blood pressure (mmHg)		72 ±10.5	72.0 ±11.8	0.912
PCWP (mmHg)		8.2 ±3.1	23.0 ±6.4	**<0.001**
Heart Rate (bpm)		68 ±13.2	82 ±15.0	**<0.001**
LVEDV (ml/m²)		146.3 ±39.6	161.3 ±43.2	0.090
LVEF (%)		33.8 ±11.0	23.0 ±8.7	**<0.001**
LV Mass (g)		84.4 ±34.1	82.9 ±23.1	0.792
RVEDV (ml/m²)		74.8 ±21.7	84.1 ±32.0	0.115
RVEF (%)		53.6 ±10.1	40.2 ±14.5	**<0.01**
LAmaxVol (ml/m²)		45.7 ±14.4	54.5 ±18.7	**0.016**
LAEI (%)		104.2 ±40.9	35.9 ±24.5	**<0.001**
lnLAEI		4.57 ±0.41	3.39 ±0.62	**<0.001**
Mitral Regurgitation	*None/trivial*	12 (30%)	11 (21%)	0.350
	Mild	17 (42%)	15 (29%)	
	Mild/Moderate	2 (5%)	6 (12%)	
	Moderate	5 (12%)	10 (19%)	
	Moderate/Severe	3 (7.5%)	5 (9.6%)	
	Severe	1 (2.5%)	5 (9.6%)	

Values are mean ± SD or n (%). Abbreviations. As in Table 1c

HR, LVEF, RVEF, LAmaxVol, MR grade, and lnLAEI resulted in PCWP determinants in the univariate analysis. The multivariate analysis for PCWP prediction included a 1st Model comprising MR grade, LAmaxVol, RVEF, LVEF, and HR, in which only HR and LVEF remained independent determinants of PCWP. Notably, adding lnLAEI to the variables included in the 1st Model significantly improved the predictive power (1st Model: Adj-R^2=0.422, F=6.562; 2nd Model: Adj-R^2=0.682; F=17.135; p<0.001 from 1st Model).

Furthermore, in the 2nd Model, lnLAEI remained the only PCWP independent predictor along with HR (Table 3c).

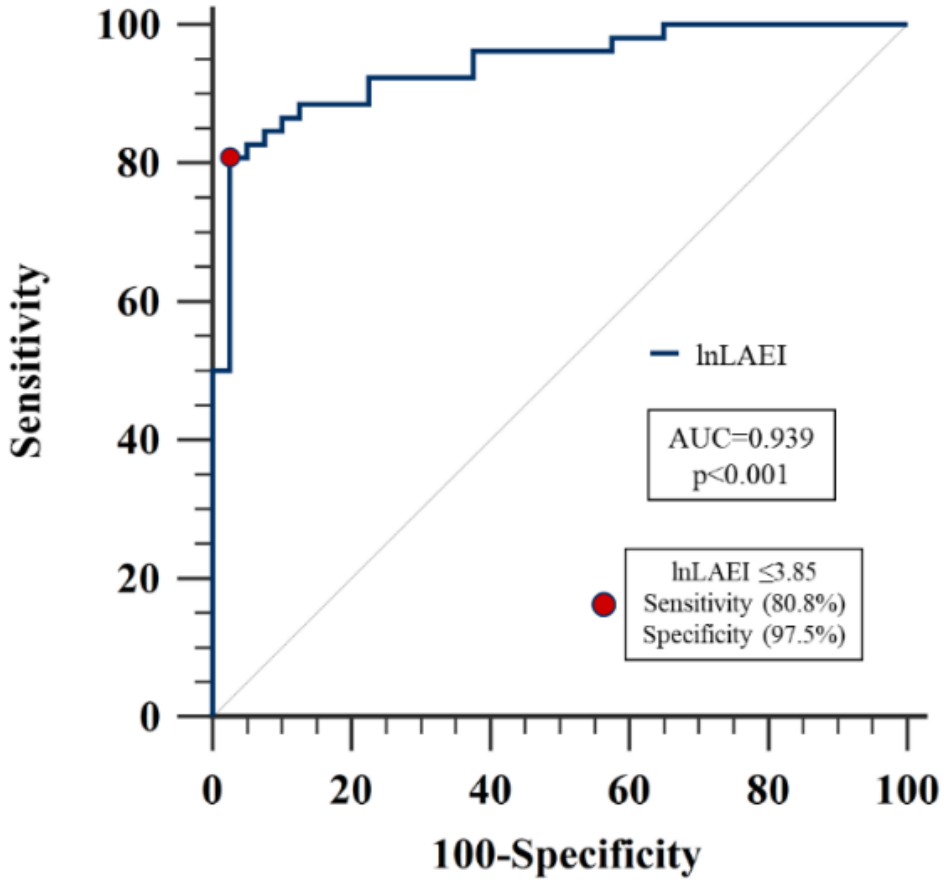
Table 3c. Univariate and multivariate analysis for PCWP prediction in the derivation cohort

		r	Univariate			Multivariate					
						Model 1 (*Adj-R² 0.422 ; F6.562*)			**Model 2** (*Adj-R²=0.682; F=17.135; p<0.001 from Model 1*)		
			Estimate	**SE**	**p**	**Estimate**	**SE**	**p**	**Estimate**	**SE**	**p**
Age (years)		0.11	0.07	0.07	0.296						
Gender (male)*			1.633	1.99	0.413						
BMI (Kg/m²)		0.12	0.297	0.25	0.240						
DCM **	*Inflammatory*		0.042	2.2	0.985						
	Other		-4.100	3.11	0.190						
Left Bundle Branch Block***			0.008	2.26	0.997						
SBP (mmHg)		0.08	-0.036	0.05	0.462						
DBP (mmHg)		0.12	0.101	0.09	0.237						
Heart Rate (bpm)		0.47	0.270	0.05	**< 0.001**	0.201	0.05	**< 0.001**	0.090	0.04	**0.037**
LVEDV (ml/m²)		0.18	0.038	0.02	0.093						
LVEF (%)		0.42	-0.347	0.08	**< 0.001**	-0.066	0.09	0.443	0.050	0.07	0.447
LV Mass (g/m²)		0.11	-0.034	0.03	0.319						
RVEDV (ml/m²)		0.14	0.046	0.03	0.174						
RVEF (%)		0.49	-0.308	0.06	**< 0.001**	-0.158	0.07	**0.026**	0.001	0.06	0.992
LAmaxVol (ml/m²)		0.34	0.176	0.05	**< 0.001**	0.090	0.05	0.074	-0.039	0.04	0.333
LAEI (%)		0.76	-0.147	0.01	**< 0.001**						
lnLAEI		0.81	-9.166	0.71	**< 0.001**				-9.08	1.12	**< 0.001**
Mitral Regurgitation ****	*Mild*		2.174	2.38	0.363	1.417	2.00	0.48	0.898	1.49	0.549
	Mild/Moderate		7.424	3.57	**0.041**	1.476	3.17	0.643	-0.243	2.38	0.919
	Moderate		6.174	2.89	**0.035**	0.962	2.55	0.707	1.281	1.91	0.504
	Moderate/Severe		8.174	3.57	**0.025**	4.827	3.21	0.137	1.340	2.44	0.584
	Severe		9.507	3.99	**0.019**	4.045	3.45	0.244	1.547	2.59	0.552
Intercept						4.363	7.30	0.552	44.909	7.41	**< 0.001**

Abbreviations. As in Table 1. *Female as the reference group; ** Idiopathic as the reference group; *** Narrow QRS as the reference group; ***None/trivial as the reference group.

lnLAEI identified accurately PCWP≥15 mmHg with an AUC=0.939 (p<0.001). The derived optimal cut-off lnLAEI≤3.85 had 80.8% sensitivity and 97.5% specificity for discriminating PCWP ≥15 mmHg in the derivation cohort (Figure 2c).

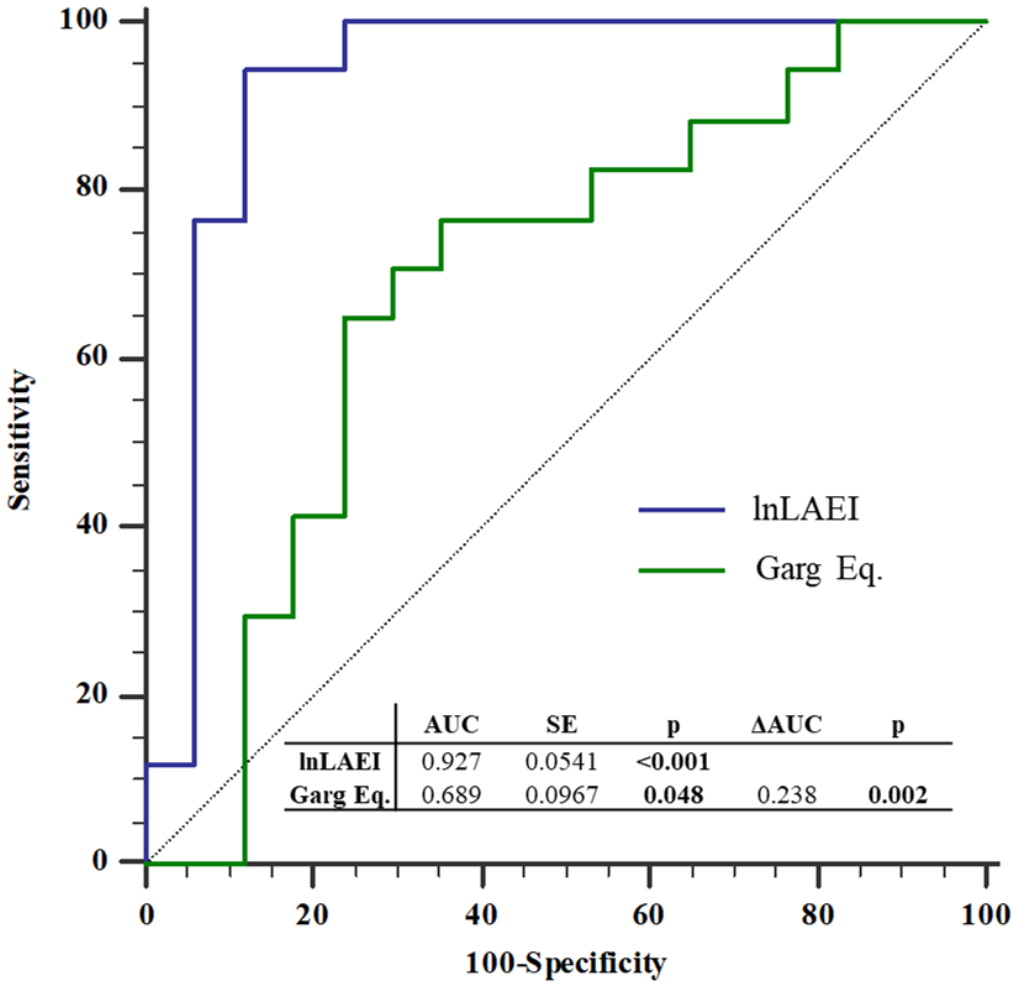
Figure 2c. lnLAEI ROC curve for PCWP≥15mmHg discrimination in the derivation cohort. lnLAEI≤3.85 was identified as the optimal cut-off using the Youden index.



Validation cohort analysis

lnLAEI confirmed an excellent accuracy for PCWP≥15mmHg identification in the validation cohort (AUC=0.927, P<0.001). Furthermore, when lnLAEI AUC was compared with the performance of the recently published Garg equation (PCWP= 6.1352+(0.07204xLAmaxVol)+(0.02256xLVmass)) [125], lnLAEI AUC was significantly higher for PCWP≥15mmHg identification (ΔAUC=0.238, p=0.002) (Figure 3c). Moreover, the validation cohort optimal cut-off for PCWP≥15mmHg identification (lnLAEI≤3.89) was superimposable to lnLAEI≤3.85, providing internal validation for the lnLAEI cut-off previously identified in the derivation cohort.

Figure 3c. lnLAEI and Garg Eq. ROC curves comparison for PCWP≥15mmHg identification in the validation cohort.



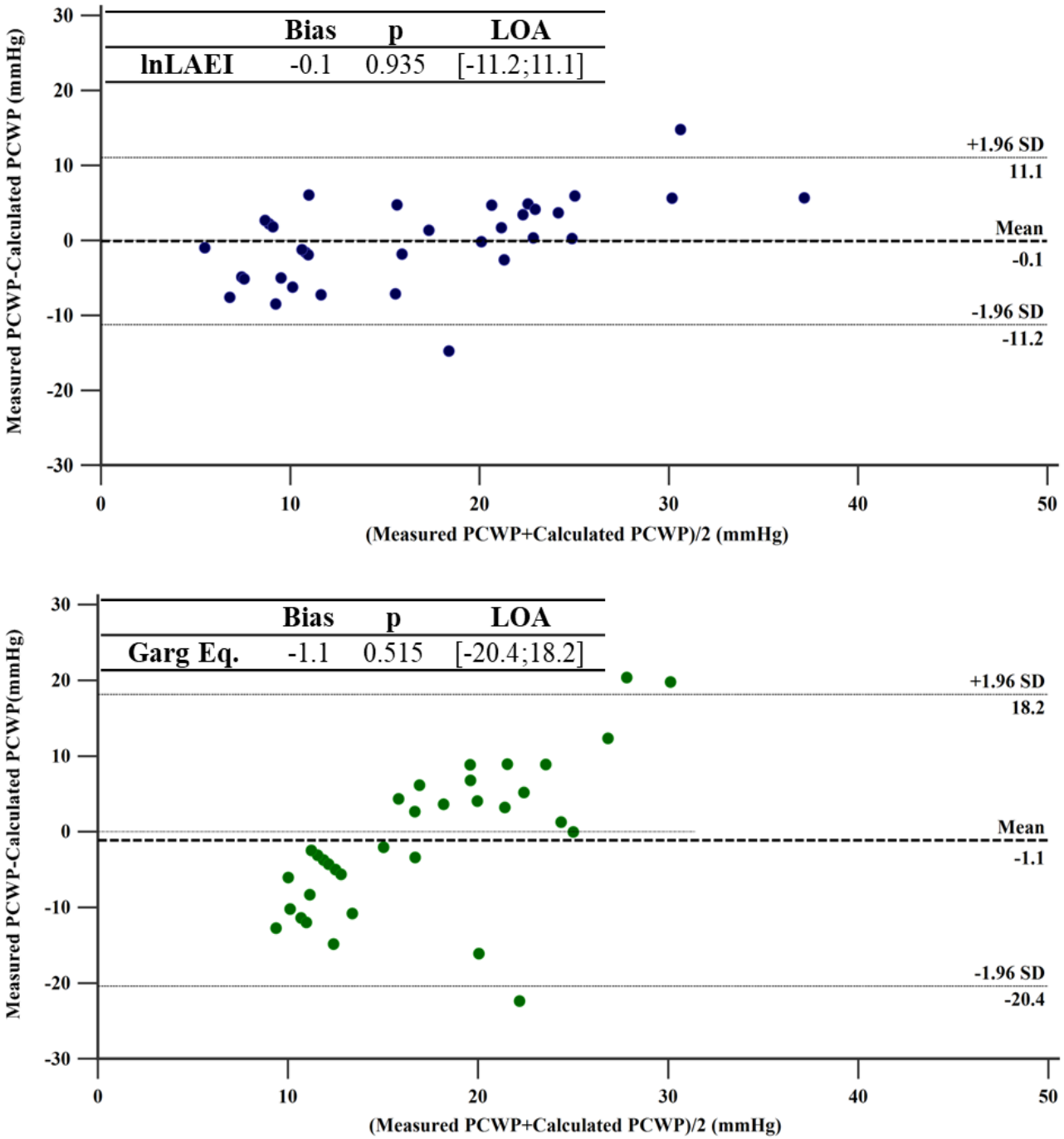
Moreover, in the validation cohort, lnLAEI≤3.85 had a comparable sensitivity (lnLAEI=82.4%, Garg eq.=88.2%; p=0.529) but higher specificity (lnLAEI=88.2%, Garg eq.=35.3%; p<0.001), accuracy (lnLAEI=85.3%, Garg Eq.=61.8%; p=0.041), and positive predictive value (lnLAEI=87.5%, Garg eq.=57.7%; p=0.010) than Garg eq. for PCWP≥15mmHg identification (Table 4c).

Table 4c. lnLAEI and Garg Eq. diagnostic accuracy comparison in the validation cohort

	Validation Cohort (n=34) **PCWP ≥15 mmHg (n=17; 50%)**		**p**
	lnLAEI≤3.85	**Garg. Eq.**	
Sensitivity	82.4 %	88.2 %	0.529
Specificity	88.2 %	35.3 %	**<0.001**
Accuracy	85.3 %	61.8 %	**0.041**
Positive Predictive Value	87.5 %	57.7 %	**0.010**
Negative Predictive Value	83.3 %	75.0 %	0.433

The equation PWCP=52.33-(9.17xlnLAEI) obtained from the derivation cohort was able to predict invasively measured PCWP without systematic bias and with a better agreement (0.1±5.7mmHg) than Garg eq. (-1.1±9.8 mmHg) in the validation cohort (Figure 4c).

Figure 4c. Bland-Altman analysis comparing invasively measured PCWP with PCWP calculated with lnLAEI equation (top) and Garg eq. (bottom) in the validation cohort.



Reproducibility analysis

lnLAEI showed a very good inter and intrareader reproducibility (Table 5c).

Table 5c. Intra-inter reader variability analysis on 20 randomly selected patients

	Intra-Reader				Inter-Reader			
	CoV (%)	**95%CI**	**ICC**	**95%CI**	**CoV (%)**	**95%CI**	**ICC**	**95%CI**
LAmaxVol	8.0	5.4 to 10.3	0.98	0.93 to 0.99	7.7	5.1 to 10.3	0.97	0.94 to 0.99
LAminVol	8.2	6.3 to 11.0	0.98	0.94 to 0.99	7.5	5.0 to 10.1	0.97	0.95 to 0.99
lnLAEI	6.0	4.8 to 8.1	0.96	0.89 to 0.99	6.7	4.5 to 9.0	0.95	0.85 to 0.98

Abbreviations. CoV: coefficient of variation; ICC:intraclass correlation coefficient; CI:confidence interval

Study 4: Right atrial expansion index for echocardiographic estimation of right atrial pressure: a cardiac catheterization validation study

Population characteristics

The study population included 586 patients with various chronic cardiac pathologies (Table 1d) divided into derivation (n=406 retrospective enrollment) and validation (n=180 prospective enrollment) cohorts with comparable clinical, RAP, and echocardiographic features (Table 2d).

Table 1d**.** Primary cardiac diseases leading to RHC exam

	Study Population n=586	
Ischemic Heart Disease	77	(13.1%)
Dilated Cardiomyopathy	85	(14.5%)
Pulmonary Hypertension	55	(9.4%)
Aortic Stenosis	204	(34.8%)
Mitral Regurgitation	81	(13.8%)
Tricuspid Regurgitation	14	(2.4%)
Other CM	19	(3.2%)
Prosthesis dysfunction	19	(3.2%)
Others	31	(5.4%)

Values are n (%). * Only the primary cardiac disease leading to RHC exam was reported in patients with more than one cardiac pathology.

Table 2d. Clinical, PCWP, and echocardiographic parameters in the study population, derivation, and validation cohorts.

	All N=586	Derivation N=406	Validation N =180	p
Age (years)	66.0±14.6	66.6±14.6	64.6±14.6	0.119
Gender (male)	314.0(53.7%)	210.0(51.9%)	104.0(57.8%)	0.185
BMI (Kg/m2)	26.2±4.6	26.3±4.7	26.1±4.4	0.701
Systolic BP (mmHg)	125.5±20.4	125.7±20.6	125.2±19.9	0.769
Diastolic BP (mmHg)	72.6±11.6	72.9±11.9	72.0±10.7	0.376
Mean BP (mmHg)	90.3±12.5	90.5±12.9	89.7±11.6	0.488
HR (bpm)	74.1±19.2	73.9±19.2	74.4±19.4	0.777
AFib	152.0(25.9%)	108.0(26.6%)	44.0(24.4%)	0.583
RHC RAP (mmHg)	7.1±4.3	6.9±4.2	7.6±4.6	0.099
RHC MPAP(mmHg)	24.6±11.2	24.3±11.6	25.3±10.3	0.332
RV EDA (cm2/m2)	12.8±4.3	12.8±4.1	13.0±4.6	0.647
RV FAC (%)	39.0±9.8	39.2±9.9	38.6±9.7	0.483
IVCmaxDiameter (cm)	1.6±0.6	1.6±0.6	1.6±0.6	0.929
IVC CI (%)	58.7±18.2	59.1±17.7	57.9±19.2	0.475
RAmaxVol (ml/m2)	39.6±25.1	39.8±23.8	39.4±28.0	0.856
RAEI (%)	61.7±45.6	61.7±46.7	61.9±43.1	0.951
TAPSE (cm)	2.0±0.5	2.0±0.6	2.0±0.5	0.610
LAmaxVol (ml/m2)	51.5±28.2	51.5±28.9	51.7±26.6	0.936
LVEDV (ml/m2)	74.3±37.7	71.7±35.9	80.1±41.1	0.013
LVEF (%)	50.3±15.2	50.8±14.9	49.0±15.8	0.189
TR None	188.0(32.1%)	133.0(32.8%)	55.0(30.6%)	0.887
TR Mild	210.0(35.8%)	140.0(34.5%)	70.0(38.9%)	0.887
TR Mild- Moderate	63.0(10.8%)	45.0(11.1%)	18.0(10.0%)	0.887
TR Moderate	61.0(10.4%)	45.0(11.1%)	16.0(8.9%)	0.887
TR Moderate-Severe	21.0(3.6%)	14.0(3.4%)	7.0(3.9%)	0.887
TR Severe	43.0(7.3%)	29.0(7.1%)	14.0(7.8%)	0.887

Values are mean ± SD or n (%). Abbreviations. BMI= body mass index; BP=blood pressure; HR= heart rate; Afib= atrial fibrillation; RHC RAP= right heart catheterization right atrial pressure; RHC MPAP= right heart catheterization mean pulmonary arterial pressure; RV EDA= right ventricular end-diastolic area; RV FAC= right ventricular fractional area change; IVC=inferior vena cava; CI=Collassability index; RAmaxVol= right atrial maximum volume; RAEI= right atrial expansion index; TAPSE= tricuspid annulus plane systolic excursion; LAmaxVol= left atrial maximum volume; LVEDV=left ventricular end-diastolic volume; LVEF= left ventricular ejection fraction; TR= tricuspid regurgitation.

Derivation cohort analysis

The derivation cohort was divided into RAP ≥10 mmHg (n=89) and RAP<10 mmHg (n=317) subgroups. Higher RAP was associated with higher BMI, faster HR, Afib, and higher MPAP. Moreover, RAP ≥10 mmHg was associated with lower RAEI, larger right atrium, larger and more dysfunctional right ventricle, reduced LVEF, and more severe TR (Table 3d)

Table 3d**.** High and low RAP subgroups comparison in the derivation cohort.

Derivation Cohort n=405		**RAP<10mmHg (n=317)**	**RAP ≥10mmHg (n=89)**	**p**
Age (years)		66.9±15.2	65.7±12.5	0.490
Gender (male)		158(50%)	52(58%)	0.16
BMI (Kg/m2)		25.9±4.5	27.5±4.9	**0.004**
SBP (mmHg)		126.7±19.8	122.0±22.8	0.055
DBP (mmHg)		73.3±12.1	71.6±11.3	0.249
MBP (mmHg)		91.1±12.6	88.4±13.6	0.084
HR (bpm)		72.0±18.1	80.5±21.4	**<0.001**
AFib		63(20%)	45(51%)	**<0.001**
RHC RAP (mmHg)		5.2±2.0	13.1±4.0	**<0.001**
RHC MPAP (mmHg)		21.8±10.8	33.2±10.0	**<0.001**
RV EDA (cm2/m2)		12.0±3.5	15.5±5.1	**<0.001**
RV FAC (%)		41.0±9.1	32.9±10.1	**<0.001**
IVC max Diameter (cm)		1.5±0.5	2.0±0.7	**<0.001**
IVC CI (%)		61.9±15.0	49.4±22.6	**<0.001**
RAmaxVol (ml/m2)		35.0±18.3	56.8±31.8	**<0.001**
RAEI (%)		72.0±46.8	24.7±19.9	**<0.001**
TAPSE (cm)		2.1±0.5	1.8±0.5	**<0.001**
LAmaxVol (ml/m2)		48.9±22.6	60.5±43.5	**0.001**
LVEDV (ml/m2)		70.6±34.4	75.9±40.7	0.221
LVEF (%)		52.5±14.2	44.9±16.1	**<0.001**
TR	None	120(38%)	13(15%)	**<0.001**
	Mild	116(37%)	24(27%)	
	Mild- Moderate	33(10%)	12(13%)	
	Moderate	28(8.8%)	17(19%)	
	Moderate-Severe	7(2.2%)	7(7.9%)	
	Severe	13(4.1%)	16(18%)	

Values are mean ± SD or n (%). Abbreviations as in Table 2d.

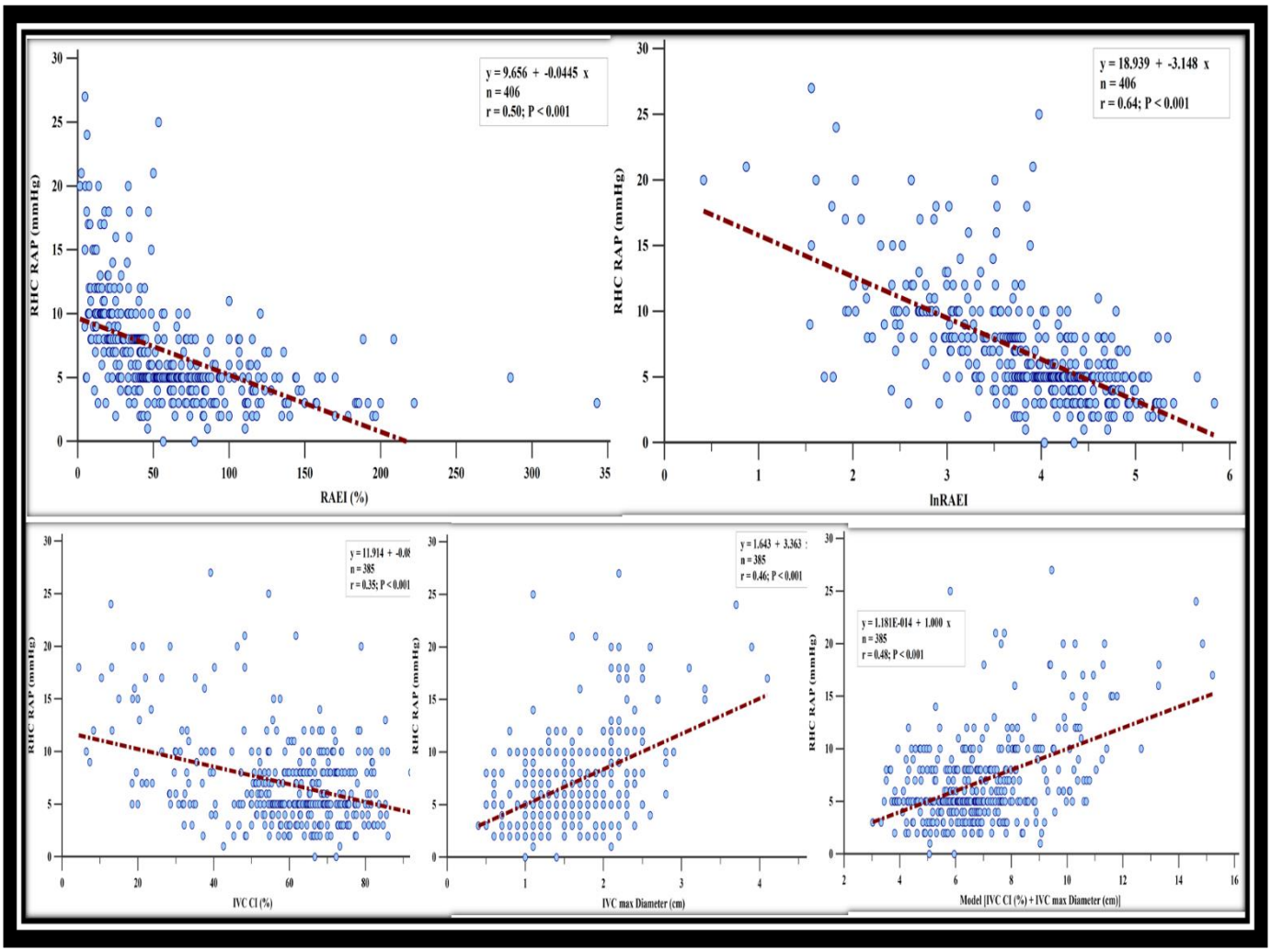
Table 4d summarizes RAP linear correlation with RAEI and other clinical and TTE parameters. RAEI-RAP depicted a strong logarithmic correlation, whereas IVC parameters showed a moderate linear correlation with RAP (Figure 3d). Of note, log-transformed LAEI (lnRAEI) showed the strongest linear correlation with RAP (r=-0.64; p<0.001) among all the other TTE parameters analyzed (Table 4d).

Table 4d. Correlation analysis for RAP

Derivation Cohort n=406	RHC RAP	p
BMI (Kg/m2)	0.19	**<0.001**
HR (bpm)	0.20	**<0.001**
RV EDA (cm2/m2)	0.36	**<0.001**
RV FAC (%)	-0.38	**<0.001**
IVC max Diameter (cm)	0.46	**<0.001**
IVC CI (%)	-0.35	**<0.001**
RAmaxVol (ml/m2)	0.39	**<0.001**
RAEI (%)	-0.50	**<0.001**
lnRAEI	-0.64	**<0.001**
TAPSE (cm)	-0.30	**<0.001**
LAmaxVol (ml/m2)	0.19	**<0.001**
LVEDV (ml/m2)	0.03	0.509
LVEF (%)	-0.22	**<0.001**
TR *	0.27	**<0.001**

Abbreviations as in Table 2d. * 6-grade scale (no/trivial, mild, mild/moderate, moderate, moderate/severe, and severe).

Figure 2d. RAP scatter-plots correlation analysis in the derivation cohort for RAEI (top left), lnRAEI (top right), IVC CI (bottom left), IVC max diameter (bottom middle), IVC CI+IVC max diameter (bottom right)



The multivariate hierarchical linear regression for RAP prediction was composed of three steps. The 1st model included Afib, HR , BMI, RHC MPAP, RV EDA, RV FAC, RAmaxVol, TAPSE, TR severity (R= 0.665; adj.R^2=0.421). The 2nd model added IVC assessment (IVC max diameter, IVC CI) to the 1st model, providing a small but significant predictive power improvement (R= 0.679; adj.R^2=0.437; p<0.001 from the 1st model). Finally, the 3rd model added lnRAEI to the 2nd model, providing a further significant predictive power improvement (R=0.742; adj.R^2=0.529; p<0.001 from the 2nd model). In addition, lnRAEI resulted in an independent PCWP predictor even after accounting for all the other clinical and TTE parameters and IVC assessment (Table 6d).

Table 6d. Multivariate regression analysis for RAP prediction in the derivation cohort

Model	R	R^2	Adjusted R^2	F	p	Comparison Model	ΔR^2	F	df1	df2	p
1	0.665	0.443	0.421	20.467	< .001						
2	0.679	0.462	0.437	19.037	< .001	From 1 Model	0.019	5.87	2	333	0.003
3	0.742	0.550	0.529	25.392	< .001	From 2 Model	0.089	65.456	1	332	< .001

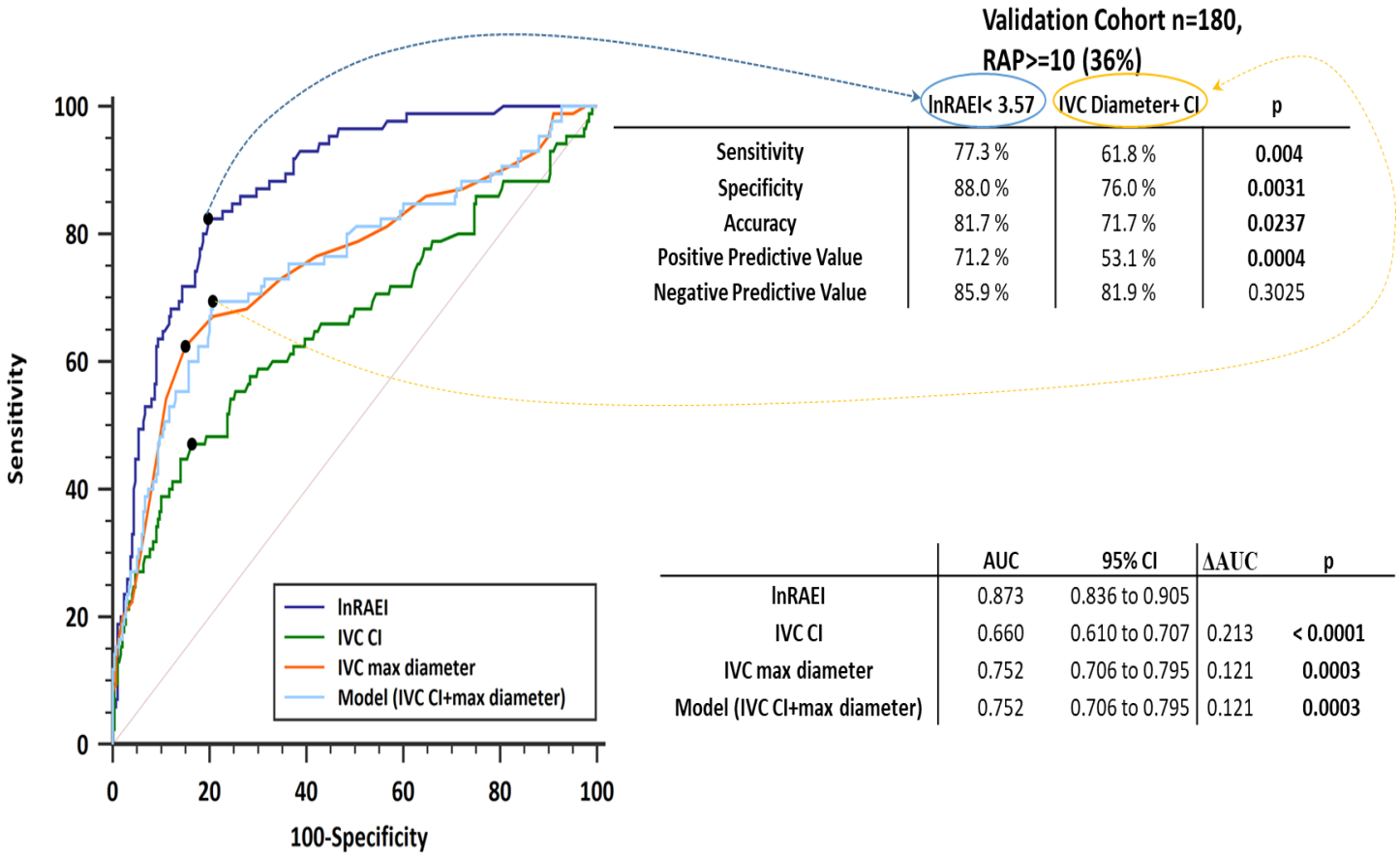
Predictor		Model 1 Estimate	SE	p	Model 2 Estimate	SE	p	Model 3 Estimate	SE	p
Intercept		-1.737	2.013	0.389	-1.576	2.257	0.485	7.259	2.337	**0.002**
Afib		1.825	0.485	**<0.001**	1.506	0.488	0.002	0.6	0.46	0.193
HR (bpm)		0.009	0.01	0.328	0.007	0.01	0.477	0.001	0.009	0.867
BMI (Kg/m2)		0.197	0.04	**<0.001**	0.187	0.039	**<0.001**	0.139	0.036	**<0.001**
RHC MPAP (mmHg)		0.088	0.017	**<0.001**	0.086	0.017	**<0.001**	0.063	0.016	**<0.001**
RV EDA (cm2/m2)		0.182	0.058	**0.002**	0.129	0.06	**0.031**	0.132	0.055	**0.016**
RV FAC (%)		-0.044	0.023	0.059	-0.042	0.023	0.069	-0.028	0.021	0.189
RAmaxVol (ml/m2)		0.004	0.01	0.726	-0.002	0.01	0.866	-0.007	0.009	0.436
TAPSE (cm)		-0.402	0.383	0.295	-0.213	0.386	0.582	0.105	0.356	0.767
TR*	**Mild**	-0.083	0.445	0.853	-0.053	0.439	0.904	0.059	0.402	0.883
	Mild- Moderate	0.006	0.645	0.992	0.127	0.638	0.842	0.195	0.584	0.738
	Moderate	-0.265	0.643	0.681	-0.174	0.635	0.784	-0.608	0.584	0.298
	Moderate-Severe	1.31	1.026	0.202	1.148	1.016	0.259	1.147	0.93	0.218
	Severe	3.508	0.861	**<0.001**	3.078	0.858	**<0.001**	2.181	0.793	**0.006**
IVC max Diameter (cm)					1.067	0.399	**0.008**	0.871	0.366	**0.018**
IVC CI (%)					-0.014	0.012	0.258	-0.006	0.011	0.592
lnRAEI								-1.956	0.242	**<0.001**

* None/trivial TR used as the reference. Abbreviations as in table 2d.

Validation cohort analysis

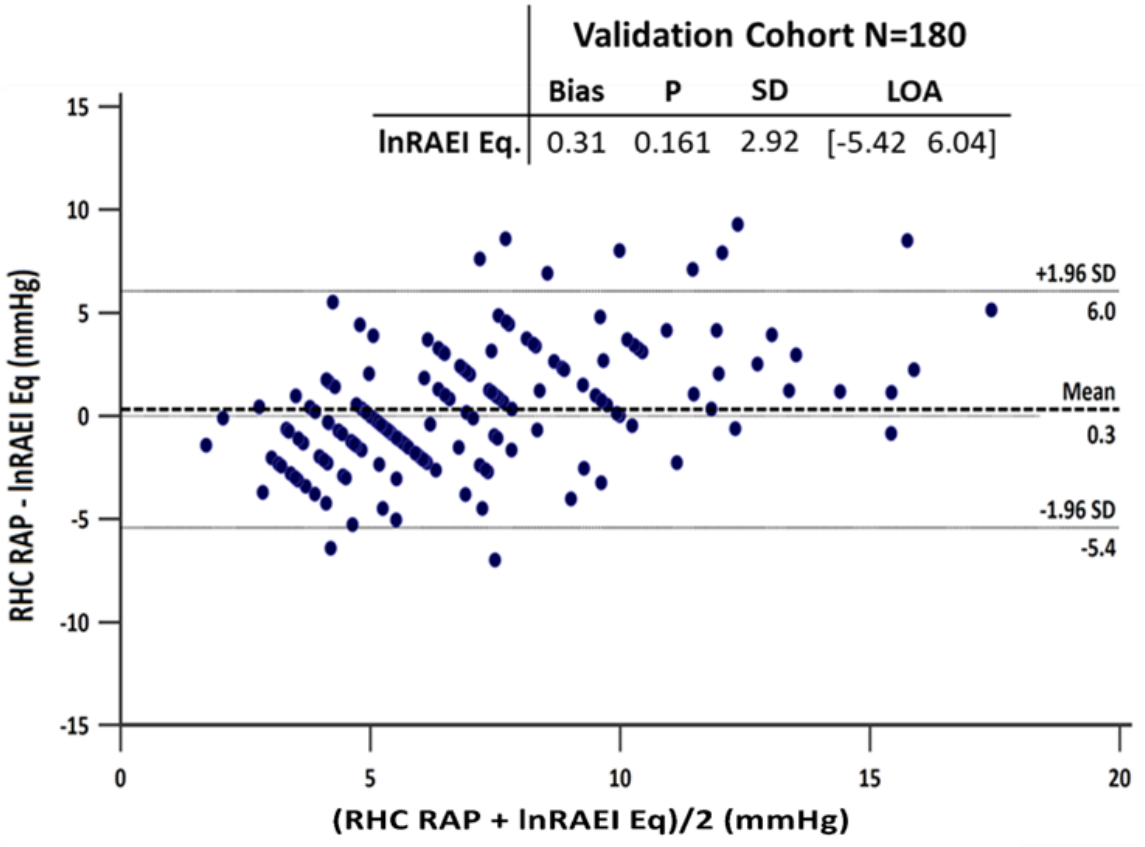
In the derivation cohort, lnRAEI diagnostic accuracy for RAP≥10mmHg identification was significantly higher than IVC diameter and CI and their association (lnRAEI AUC=0.873, p<0.001; ΔAUC lnRAEI-IVC CI=0.213, p<0.0001; ΔAUC lnRAEI-IVC max diameter=0.121, p=0.0003; ΔAUC lnRAEI-Model IVC (CI+max diameter)=0.121, p=0.0003) with an optimal cut-off of lnRAEI< 3.57 (Figure 3d). In the validation cohort, lnRAEI<3.57 cut-off performance for RAP≥10mmHg identification was more accurate than IVC assessment (max diameter+CI) (lnRAEI: sensitivity=77.3%; specificity=88%; accuracy=81.7%; IVC assessment: sensitivity=61.8%; specificity=76%; accuracy=71.4%). In 12 patients (7% of the validation cohort), the IVC assessment was not feasible for inadequate subcostal view.

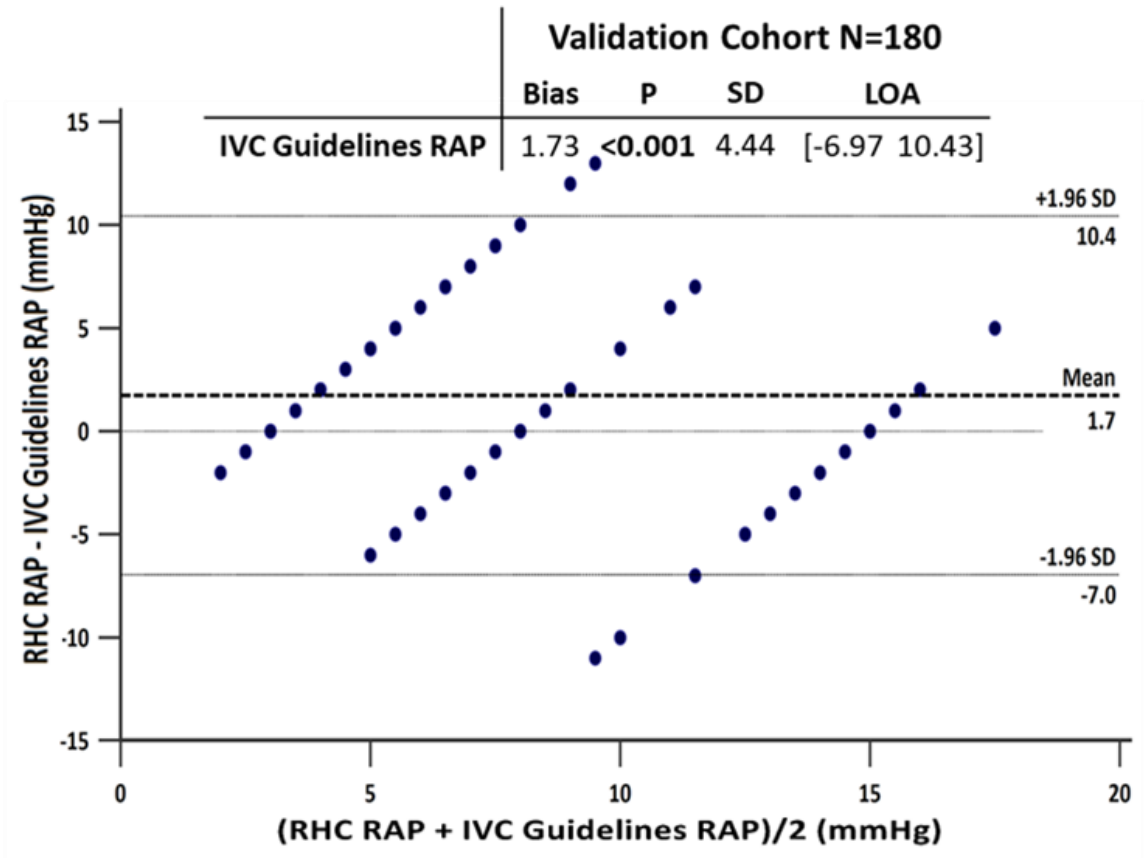
Figure 3d. ROC analysis for identification of RAP≥10mmHg comparing AUC for lnRAEI, IVC max diameter, IVC CI, and a model of IVC assessment that accounted for both IVC max diameter and IVC CI (derivation cohort). lnRAEI<35.7 cut-off diagnostic performance was compared against the IVC assessment for identifying RAP≥10mmHg in the validation cohort.



Finally, lnRAEI regression equation for RAP estimation obtained in the derivation cohort (RAP=18.9-3.15xlnRAEI) predicted invasively measured RAP in the validation cohort (RHC RAP-lnRAEI RAP estimated=0.3±2.9 mmHg) (Figure 4d). Of note, lnRAEI equation was more accurate than the guidelines recommended IVC assessment for RAP estimation (RHC RAP-IVC RAP estimated=1.7±4.4 mmHg).

Figure 4d. Bland-Altman plot comparing RAP predicted through lnRAEI equation (top) and IVC assessment (bottom) against RAP invasively measured during RHC in the validation cohort.





Reproducibility analysis

lnRAEI showed good inter and intrareader reproducibility (Table 5d).

Table 5d. Intra-inter reader variability analysis on 30 randomly selected patients

	Intra-Reader				Inter-Reader			
	CoV (%)	**95%CI**	**ICC**	**95%CI**	**CoV (%)**	**95%CI**	**ICC**	**95%CI**
RAmaxVol	6.1	4.9 to 7.8	0.97	0.93 to 0.99	7.2	5.7 to 9.0	0.95	0.90 to 0.98
RAminVol	6.7	5.8 to 8.1	0.97	0.93 to 0.99	7.5	6.0 to 9.8	0.94	0.89 to 0.97
lnRAEI	5.7	4.3 to 7.6	0.96	0.90 to 0.99	7.0	4.9 to 8.5	0.95	0.88 to 0.98

Abbreviations. CoV: coefficient of variation; ICC:intraclass correlation coefficient; CI:confidence interval

Discussion

In summary, we demonstrated that: i) TTE-measured LAEI estimated PCWP more accurately than the 2016 DD algorithm in patients with various chronic cardiac diseases and could be used for PCWP estimation also in patients with significant MR and Afib, ii) TTE-measured LAEI estimated PCWP in patients with MV stenosis, prosthesis and surgical repair, iii) CMR-measured LAEI allowed PCWP evaluation in patients with DCM and, finally iv) TTE-measured RAEI estimated RAP more accurately than IVC assessment.

In study 1, we found that 1) lnLAEI had a strong linear association with PCWP; 2) lnLAEI showed an independent and added predictive value for PCWP estimation over clinical and DD parameters; 3) lnLAEI<4.02 identified PCWP>12 mmHg with higher accuracy than 2016 DD algorithm; 4) PCWP=38.3-6.2xlnLAEI equation predicted invasively measured PCWP (0.4±5.4 mmHg) in the validation cohort. Previous single-center studies have identified the value of LAEI in predicting high LV FP. Accordingly, S.H. Hsiao and coauthors first described the logarithmic correlation between LAEI and LVEDP in patients with acute and chronic MR and demonstrated LAEI superiority over E/e' for LVEDP>15 mmHg identification in patients referred for coronary angiography exams [89,126]. The same authors demonstrated the superiority of LAEI over E/e' for LVEDP estimation in subjects with acute coronary syndromes [88] and stable angina [87]; moreover, they showed the ability of LAEI to predict future Afib episodes and in-hospital mortality in patients who underwent coronary artery bypass [90] and a potential prognostic role of LAEI in HF [91] and acute coronary syndromes [88]. Finally, S.H. Hsiao and coauthors showed how an echocardiographic-based approach that included LAEI could improve, compared to a symptom-based approach, medication up-titration in patients with heart failure with reduced LVEF increasing long-term prognosis [93]. Furthermore, another research group demonstrated the predictive role for high LVEDP

identification of LAEI obtained with three-dimensional TTE[127]. We provided in the 1st study several additional critical novelties. We were the first to provide internal validation to our results in an independent validation cohort; indeed, validating our results in an independent cohort of subjects provided robustness for the generalizability of our findings. Second, LAEI was never compared head-to-head with the 2016 DD algorithm, which is currently the guidelines recommended approach to non-invasive PCWP evaluation. Indeed, LAEI accuracy for LVFP estimation had never been compared with the four DD parameters accounted together. Furthermore, we used the PCWP values instead of LVEDP values as an invasive FP parameter. Although PCWP and LVEDP have been used interchangeably, they are different measures [128]. PCWP comprehensively describes the hemodynamic burden of LV pathologies on pulmonary circulation (i.e., DD, MR, Afib). Accordingly, PCWP was recently found superior to LVEDP in outcome prediction for HF with preserved EF [10]. Our population had a wide range of PCWP values (PCWP 14±7.6 mmHg) with a balanced proportion of patients with low and elevated PCWP. Indeed, 48.8% of patients had elevated PCWP (49.3% in the derivation cohort and 47.1% in the validation cohort). Therefore our population allowed us to assess lnLAEI over a wide range of PCWP values. The proportion of patients with high and low PCWP in our study was comparable to other recent studies [32,33,59]. Accordingly from previous studies, we confirmed that DD parameters showed only a weak to moderate correlation with PCWP (r: E/A=0.58; E/e'=0.40; TRmaxVel=0.17; LAmaxVol=0.38; all $p<0.001$) [32,33]. We demonstrated that lnLAEI accuracy for PCWP>12 mmHg identification was higher than a predictive model that included all four DD parameters. Moreover, we showed that lnLAEI provided added predictive value and was an independent parameter for PCWP estimation over all four DD parameters currently used for LVFP evaluation combined and other critical variables related to PCWP (i.e., LVEF, MR, and Afib). We showed the superior accuracy of lnLAEI for high PCWP estimation head to head with the 2016 DD algorithm, the currently recognized gold-standard for FP evaluation.

Notably, since the 2016 DD algorithm cannot be applied with Afib and significant MR, lnLAEI accuracy for high PCWP identification was compared with the 2016 DD algorithm only in the validation subgroup without the abovementioned conditions. lnLAEI provided higher accuracy than the 2016 DD algorithm, which was driven by the higher accuracy of lnLAEI in the subgroup of patients with preserved LVEF. A lower accuracy of the 2016 DD algorithm in patients with preserved LVEF was demonstrated [32,33]. Our results support lnLAEI as a diagnostic parameter in patients with preserved LVEF, as already described with other LA reservoir parameters [34,129-132], although controversy exists on the topic [57]. In our study, the DD algorithm resulted in indeterminate assessments in 5.1% of the patients, still, a smaller percentage than previously described [33,36]. Notably, lnLAEI accurately identified high PCWP also in the validation subgroup with Afib and significant MR. Finally, non-invasive PCWP evaluation has been historically dichotomized (high versus low), although a quantitative approach might be more appropriate since PCWP is a continuous variable, and even slight differences might have prognostic implications [63,64]. Indeed, the principal limit of a dichotomized approach relies on grouping under the same category patients with significantly different PCWP values (i.e., PCWP=15 mmHg and PWCP =35 mmHg grouped into elevated LVFP despite relevant absolute PCWP difference). Thus, we derived and validated a simple lnLAEI equation for PCWP prediction. However, although we validated the equation in an independent cohort of subjects, the SD limits were too large to recommend its clinical use as a unique parameter, which might be considered supportive data in the context of a comprehensive evaluation.

The main findings in study 2 were that in patients with MV stenosis, prosthesis, and surgical repair: (i) LAEI remained logarithmically associated with PCWP; (ii) lnLAEI was an independent determinant of PCWP that provided added predictive value over conventional clinical and TTE parameters; (iii) lnLAEI discriminated elevated PCWP better than the other echocardiographic parameters (iv) PCWP=36.8-5.5xlnLAEI approximately estimated

invasive PCWP. In this study, we provided for the first time a simple and fast TTE parameter for evaluating PCWP in these challenging subgroups of patients. Of note, non-invasive PCWP estimation is currently overlooked in these cardiac conditions for lacking simple validated parameters for FP estimation. Our findings suggest that LAEI could provide PCWP insight through LA compliance evaluation, regardless of the conditions primarily responsible for the LA pressure increase. We found that LAEI, as in other cardiac conditions [1,87-89], maintained a logarithmic correlation with PCWP also in patients with MV stenosis, prosthesis, and repair. Furthermore, lnLAEI remained an independent determinant and improved the prediction of PCWP after accounting for clinical (age, Afib, HR, MV subgroups) and echocardiographic (MV MG, MV EOA, PASP, Cn, LVEF) parameters routinely used for the assessment of these conditions. This finding underscores the potential added value of implementing this novel and simple parameter into routine clinical practice. Moreover, lnLAEI discriminated PCWP >12 or > 15 mmHg overall better than Cn, PASP, MV MG, and LVEF. Finally, PCWP=36.8-5.5xlnLAEI estimated invasive PCWP (0.0±6.1mmHg) with a similar accuracy among the different MV subgroups (degenerative MV stenosis: -0.8±5.9mmHg; rheumatic MV stenosis: 3.1±5.9mmHg; MV prosthesis: 0.2±5.6mmHg and MV surgical repair: 0.3±6.9mmHg). However, the lack of a validation cohort limits this specific equation's generalizability. In addition, the wide limit of agreements underscored how, for individual patients, the equation should not be used as the sole parameter for PCWP estimation to avoid potentially misleading results. In contrast, it might serve as an additional supportive parameter for quantitative estimation after the dichotomized approach with lnLAEI<3.69 cut-off has been performed in these cardiac conditions.

In study 3, we demonstrated that CMR-measured LAEI could effectively estimate PCWP in patients with DCM. For the first time, we proved that CMR-measured LAEI could be used as a simple parameter for PCWP estimation. CMR-measured LAEI was logarithmically associated with PCWP, as previously seen with Echo-measured LAEI[1,87]. From our findings,

the CMR-measured LAEI could accurately dichotomize normal versus elevated PCWP in DCM patients referred for CMR (lnLAEI ≤3.85 cut-off: 85.3 % accuracy for PCWP≥15 mmHg identification in the validation cohort). Notably, lnLAEI explained 65% of the PCWP variance, and the coefficient of determination of the 2nd multivariate model was only marginally higher (R^2=0.68) than lnLAEI alone (R^2=0.65), underscoring how the variables in the 2nd model improved only slightly PCWP prediction compared to lnLAEI alone. Therefore, because the model was composed of multiple parameters without significantly improving PCWP variance explanation than lnLAEI alone, we decided to derive and validate a simple and user-friendly regression equation for PCWP estimation from lnLAEI alone. Recently, Garg. et al. estimated PCWP using an equation that included CMR-measured LAmaxVol and LV mass[125]. However, the diagnostic performance for identifying elevated PCWP (sensitivity 39%, specificity 92%) and agreement with the invasive PCWP measurements (limits of agreement: ±10 mmHg) were modest. From our findings, despite the lnLAEI equation being superior to Garg eq., the moderate agreement of the lnLAEI equation with PCWP values suggests that the lnLAEI equation might not still be accurate enough in the single patient if used as the sole method for PCWP evaluation and should instead be intended as an integrative parameter for PCWP quantitative insight. On the other side, the high accuracy lnLAEI ≤3.85 for identifying elevated PCWP would be the parameter that could reliably guide the initial dichotomized evaluation of elevated vs. normal PCWP in these patients.

In study 4, we found that i) RAEI was logarithmically and strongly correlated to RAP; ii) lnRAEI provided independent and added predictive value for RAP assessment over other clinical and echocardiographic parameters, including IVC assessment; iii) lnRAEI was more accurate than IVC assessment for identification of RAP≥10 mmHg, and finally iv) RAP=18.9-3.2xlnRAEI predicted RAP (0.31±2.9 mmHg), more accurately than guidelines recommended IVC algorithm in the validation cohort. In this study, we validated RAEI as a simple and novel TTE parameter for RAP estimation. Confirming our results in the validation

cohort increased the robustness and generalizability of our findings. Furthermore, we demonstrated the diagnostic superiority of RAEI against the currently recommended guidelines IVC assessment for RAP estimation. Our population had a wide range of RAP, allowing us to evaluate RAEI performance over a wide range of values (RHC RAP ranged from 0 to 27 mmHg). In addition, we found that lnRAEI demonstrated good accuracy for identifying RAP≥10 mmHg (81.7% accuracy in the validation cohort). Finally, the lnRAEI equation predicted RHC RAP (0.31±2.9 mmHg) with higher accuracy than the IVC assessment. These findings support RAEI as a non-invasive TTE parameter for quantitative estimation of RAP that might overcome the RAP assessment by ranges (0-5 mmHg, 5-10 mmHg, 10-20 mmHg) currently adopted with IVC evaluation.

Clinical implications and future directions

Our findings introduced LAEI and RAEI as simple and straightforward parameters for the non-invasive assessment of PCWP and RAP in the clinical arena. The strength of these parameters relies on the fact that they could allow a fast and intuitive evaluation of the atria reservoir function and compliance, allowing to provide PCWP and RAP insight independently on the cardiac conditions primarily responsible for their increase, which might overcome several limitations of the current approaches required for non-invasive assessment of LAP and RAP.

LAEI and RAEI have other valuable qualities that might allow widespread use in clinical practice. First, they are simple parameters that do not require specialized training for their application. Second, they could be calculated on every echocardiographic machine since they do not need dedicated statistical software for postprocessing. Third, they are straightforward and fast to calculate since they only need the additional measurement of the corresponding atrial minimal volume over the conventional TTE protocols, which already include the LA and RAmaxVol measures.

Moreover, LAEI could also be implemented in every routine CMR exam without additional dedicated acquisitions, post-processing, or software packages. This would allow CMR exams to provide PCWP estimates with an even more comprehensive evaluation of cardiac physiology for the patients undergoing this diagnostic technique.

The findings of this thesis will pave the path for further studies aiming to evaluate: i) CMR-measured LAEI for PCWP estimation in other cardiac subgroups other than DCM; ii) CMR-measured RAEI for RAP estimation; iii) LAEI and RAEI feasibility for monitoring PCWP and RAP acute changes in critically ill patients and iv) LAEI and RAEI diagnostic accuracy for

evaluation of PCWP and RAP in comparison to other indexes of atrial reservoir function as LA strain and RA strain.

Limitations

The studies performed had limitations that could be summarized as follows:

i) Selection bias. These were single-center studies and included patients referred to our tertiary center for further assessment of cardiac diseases. Therefore some cardiac conditions were more represented than others (i.e., in studies 1 and 4, there was a higher prevalence of aortic stenosis over the other subgroups, whereas, in study 2, there was a higher prevalence of degenerative MV stenosis over the other subgroups). However, since our study populations had a wide range of PCWP and RAP values, we could assess LAEI and RAEI performance over a wide range of LAP and RAP values, increasing the robustness of our findings.

ii) Fully or partial retrospective design. Studies 1 and 2 were fully retrospective, whereas studies 3 and 4 had the derivation cohort retrospectively enrolled. However, since we performed cross-sectional correlation studies and TTE and CMR measurements were blinded to clinical and RHC measurements, the retrospective design would not impact the validity of our results.

iii) Time-lapse between RHC and TTE (in studies 1-2-4) or CMR (in study 3). RHC and TTE/CMR were not simultaneous. However, the exams were performed within 24 hours. All patients had chronic cardiac conditions, were elective admission for further clinically indicated assessment of cardiac diseases, were hemodynamically stable, and did not undergo any intervening changes in clinical status or medications between the exams.

iv) In study 2, MV EOA was calculated with the continuity equation for consistency among the different MV subgroups. Although continuity equation is the recommended method for MV EOA assessment in patients with degenerative MV stenosis,

prosthesis, and surgical repair, in patients with rheumatic MV stenosis is a secondary method with MV area planimetry or pressure half-time methods usually preferred.

v) Caution for clinical use of the equations derived in the studies as the sole parameter for PCWP and RAP assessment. First of all, the limited population subgroup size did not allow for validating the lnLAEI equation in study 2. However, the lnLAEI equation in studies 1 and 3 and lnRAEI in study 4 had been internally validated in independent validation cohorts. Of note, despite the lnLAEI and lnRAEI equation outperforming the conventional TTE or CMR parameters routinely used (i.e., DD algorithm or IVC assessment) respectively for PCWP and RAP assessment, the derived equations LOA values still underlined a moderate agreement with the invasive measures that might still suggest caution for the use of the equations as the sole approach for pressure estimation, whether the dichotomized approach, despite being less informative, resulted more robust and should be the one that initially guides PCWP and RAP assessment.

vi) Study findings were limited to chronic cardiac patients. We did not explore the validity of these parameters in patients with acute cardiac diseases; therefore, the potential usefulness of LAEI and RAEI for PCWP and RAP monitoring in acute settings must be assessed in future studies.

vii) Finally, prospective studies are needed for external validation of our findings and to compare lnLAEI and lnRAEI performance with other LA and RA reservoir function parameters as reservoir strain.

Conclusions

In conclusion, we found that TTE-measured LAEI outperformed DD parameters and the 2016 DD algorithm for PCWP estimation in a large cohort of patients with various cardiac diseases and also allowed non-invasive PCWP assessment in patients with MV stenosis, prosthesis, and surgical repair. Furthermore, CMR-measured LAEI resulted in an accurate and straightforward parameter for PCWP assessment in DCM patients. Finally, TTE-measured RAEI resulted in a novel and fast parameter more accurate than IVC assessment for RAP estimation.

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