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ЕХОКАРДИОГРАФСКИ ИНДЕКС ЗА РАЗГРАНИЧАВАНЕ НА ВИДА БЕЛОДРОБНА ХИПЕРТОНИЯ СЛЕД БЕЛОДРОБЕН ЕМБОЛИЗЪМ – ПИЛОТНО ПРОУЧВАНЕ

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ECHOCARDIOGRAPHIC INDEX FOR PULMONARY HYPERTENSION DISCRIMINATION IN PATIENTS AFTER PULMONARY EMBOLISM - PILOT STUDY

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Резюме.

Цели: Пациенти с резидуални тромботични дефекти и ехокардиографски данни за белодробна хипертония (БХ) се насочват за оценка на наличието на хронична тромбоемболична белодробна хипертония (ХТБХ). Първичната цел на проучването е изследването на ехокардиографски индекс като скринингов маркер за прекапилярна БХ. Вторичната цел е да се тества потенциала му за разграничаване на отделните видове БХ. **Методи и резултати**: Едноцентровото ретроспективно проучване включва 79 пациенти, разделени по пол, възраст, наличието на остатъчни перфузионни дефекти от компютърна томография (КТ) или пулмоангиография, амплитудата на движение на латералния пръстен на трикуспидалната клапа/систолно налягане в белодробната артерия (TAPSE/sPAP), базален диаметър на дясна камера (RV), съотношението (TAPSE/sPAP)/RV x 100, групи БХ – ХТБХ/прекапилярна, комбинирана пре- и посткапилярна БХ (CpcPH), изолирана посткапилярна БХ (IpcPH) и без БХ. От 79 пациенти мъже са 43 (54%), респективно 36 (46%) са жени, на средна възраст 65, резидуални тромботични дефекти при 42(53%). Анализът на хемодинамичните и ехокардиографски данни разделя пациенти като такива без БХ 22(28%), IpcPH – 25 (32%), CpcPH – 16 (20%), и ХТБХ – 16 (20%). Статистически значима разлика се доказва в стойностите на индекса между отделните подгрупи БХ ($p < 0.001$). По-задълбочен анализ доказва статистическата значимост на (TAPSE/sPAP)/RV x 100 за разграничаване на подгрупите БХ. Дефинират се следните граници – стойности над 1.79 за липса на БХ, посткапилярна БХ в диапазона 0.83-1.79, прекапилярна БХ < 0.52 ($p < 0.001$). **Заключение**: Индексът би могъл да служи за метод за скрининг за ХТБХ и дискриминиране на отделните подгрупи БХ.

Ключови думи: белодробна хипертония, белодробен тромбемболизъм, хронична тромбоемболична белодробна хипертония, ехокардиография, TAPSE/sPAP

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Abstract.

Aims: Patients with residual perfusion defects and echocardiographic signs of pulmonary hypertension (PH) are referred for chronic thromboembolic pulmonary hypertension (CTEPH) evaluation. The first aim of this study was to test an echocardiographic index as a screening marker for pre-capillary PH. The secondary aim was to assess its potential for PH type discrimination. **Methods and results**: The single-center's retrospective cohort included 79 patients divided by gender, age, presence of chronic perfusion defects diagnosed by computer tomography (CT) or angiography, tricuspid annular plane systolic excursion/systolic pulmonary artery pressure (TAPSE/sPAP), right ventricle (RV) basal diameter, the ratio (TAPSE/sPAP)/RV x 100, PH groups – CTEPH/pre-capillary, combined pre- and post-capillary (CpcPH) and isolated post-capillary (IpcPH) and no PH. From a total of 79 patients – 43(54%) men and 36(46%) women at a mean age of 65, residual clots were detected in 42(53%). Analysis of invasive haemodynamic and echocardiographic data diagnosed no PH in 22 (28%), IpcPH – 25 (32%), CpcPH – 16 (20%) and CTEPH - 16(20%). There was a statistically significant difference in the mean index values between all PH subtypes groups ($p < 0.001$). Further analysis proved (TAPSE/sPAP)/RV x 100 to be statistically significant discriminator of PH subtypes and defined patients with a value above 1.79 as likely having no PH, leading post-capillary PH in the range of 0.83-1.79, pre-capillary PH < 0.52 ($p < 0.001$). **Conclusion**: The index might serve as a screening method for CTEPH and possible PH type discrimination.

Key words: pulmonary hypertension, pulmonary embolism, chronic thromboembolic pulmonary hypertension, echocardiography, TAPSE/sPAP

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INTRODUCTION

According to the European Society of Cardiology (ESC) guidelines 2022 PAH is defined as mean pulmonary arterial pressure > 20 mmHg during right heart catheterisation (RHC). Pre-capillary PAH, in particular CTEPH or group IV PH, is defined as elevated pulmonary vascular resistance (PVR) > 2 WU and pulmonary capillary wedge pressure (PCWP) < 15 mm Hg, i.e. excludes left heart disease [1, 2]. Combined pre- and post-capillary is differentiated by elevated PCWP and left heart filling pressures.

CTEPH is defined by the presence of fibrotic organisation of unresolved thromboemboli [1, 2]. The major difference from PH type 1 stems from the leading proximal location of pulmonary artery obliteration in comparison to distal arteriopathy in the former. Over-perfusion of the microvasculature of unoccluded zones is a key pathophysiological mechanism for CTEPH development and a major contributor to increased PVR [2, 3]. RV adaptation to abnormal loading conditions is similar in both CTEPH and PAH type 1 and consists of homeometric and heterometric (maladaptive) phases. The initial rise in PVR leads to adaptive hypertrophy, increased contractility and preserved cardiac output (homeometric adaptation). In the long term the RV reaches a point of decompensation when it can no longer bear the extremity of pulmonary artery pressure. In the final state dilation and dysfunction with increased filling pressures of the RV occur (heterometric adaptation) [2, 4, 5].

The diagnosis of CTEPH requires at least three month optimal anticoagulation after a first documented episode of PE and the presence of symptoms such as dyspnoea and reduced functional capacity as well as echocardiographic signs of elevated pulmonary pressure with or without RV involvement before pulmonary angiography verification of residual perfusion defects. [1, 2, 6] The basic echocardiographic parameter for RV - PA coupling is defined by the ratio TAPSE/sPAP, i.e. systolic RV function divided by the systolic pulmonary pressure with a lower limit of normal > 0.55. [1, 7, 8]. The heterometric phase of RV cardiac remodeling consists of change not only in its function, but also in its size. There is evidence of early RV decompensation in patients with PAH and CTEPH due to abnormal loading conditions (elevated PVR), determined by RV systolic dysfunction and dilation. [3, 9, 10]. Grouping the three basic echo parameters (TAPSE/sPAP and RV basal diameter) into a single ratio defined as (TAPSE/sPAP)/RV x 100 may more precisely discriminate between different haemodynamic categories of PH.

The aim of the current study is to test whether (TAPSE/sPAP)/RV x 100 might serve as a screening marker for pre-capillary PH/CTEPH. Furthermore, we attempted to prove reference ranges for different PH types (pre-capillary, post-capillary, combined pre- and post-capillary and no PH).

MATERIAL AND METHODS

The retrospective cohort study encompassed 79 patients for a period of 67 months (January 2018 - July 2024) registered in the National Heart Hospital (NHH) system GlobalHis under ICD I26.0 (pulmonary embolism with mention of acute cor pulmonale) and I26.9 (pulmonary embolism without mention of acute cor pulmonale), who were either diagnosed at the time of hospitalisation or had a history of PE, followed by subsequent anticoagulation for at least three months and CT, conventional pulmonary angiography or SCPECT/CT evidence of residual thrombotic defects. Cases without optimal anticoagulation were excluded. The chosen time period was based on the increased follow-up of patients after PE due to the fact NHH was officially declared a tertiary center for CTEPH during that time.

Patients were divided by gender, age, CT or pulmonary angiography evidence of chronic perfusion defects, PH group - pre-capillary, for the purpose of the study CTEPH, CpcPH and IpcPH and no PH based on invasive haemodynamic data, echocardiographic parameters during follow-up - TAPSE, sPAP, acceleration time, (AT), RV basal diameter, and the newly introduced index as a ratio (TAPSE/sPAP)/RV x 100. NoPH subgroups included 17 healthy controls and 5 patients with an invasively proven normal pulmonary pressure despite previous PE and no residual perfusion defects on follow-up. Patients with no invasive study were discriminated into echocardiographic no PH group or echocardiographic positive for PH based on sPAP > 30 mmHg, AT < 105 ms. sPAP echocardiographic values were derived from the tricuspid regurgitation jet and patients in the echocardiographic noPH subgroup with an unmeasurable jet velocity and normal AT were given sPAP value of 30 mmHg.

The statistical analysis was carried out with Numbers 12.0 and Jamovi 2.3.28.0. [11, 12]. Descriptive statistical methods were used. Relative frequency was defined as a percentage. One-way ANOVA test was used for comparison between index values in PH groups. Shapiro-Wilk and Levene's tests were used respectively to assess the normality and equality of variances. Tukey's post-hoc analysis was carried out. Predictive cut-off values for the (TAPSE/sPAP)/RV x 100 ratio for PH type determination were derived by receiver operating characteristic (ROC) curve analysis and exact cut-off value was determined using Youden's index. Binomial logistic regression models was applied for assessing adjusted associations between CTEPH/, IpcPH and noPH respectively and (TAPSE/sPAP)/RV x

100. Pearson's correlation coefficient was used. For all tests p<0.05 was considered a statistically significant result with a confidence interval (CI) 95%.

RESULTS

Table 1 depicts demographic, echocardiography, and haemodynamic characteristics of all 79 patients in the study, in particular those with PH. Male was the predominant sex – 43 (54%) and female 36(46%). The median age of the cohort was 65 with a range 12-90 years, for men – 63 (IQR: 52-71.5) and women – 67.50 (IQR: 56-71.5) – Figure 1. During follow-up 42 (53%) patients had residual perfusion defects diagnosed by CT, pulmonary angiography or SPECT/CT. A total of 41 (53.16%) had subsequent right and left heart catheterisation. One patient with a highly likely diagnosis of CTEPH did not undergo catheterisation due to comorbidity, however, he was included in the above-mentioned category. All patients with no perfusion defects, but with invasively proven either PH type were assigned under the relevant category.

Table 2 presents haemodynamic data of all positive for PH patients (36). The median sPAP was 74 (IQR: 63-91.25 mm Hg), for each PH subtype – IpcPH 30 (IQR: 39-48 mmHg), CpcPH 72 (IQR: 59.5-88 mmHg) and CTEPH 86 (IQR: 82-98 mmHg). A markedly positive correlation between echocardiographic and invasively derived sPAP was proven with r - 0.9, p < 0.001. Furthermore, (TAPSE/sPAP)/RV x 100 index correlated significantly with haemodynamic measurements from the invasive study (p < 0.001).

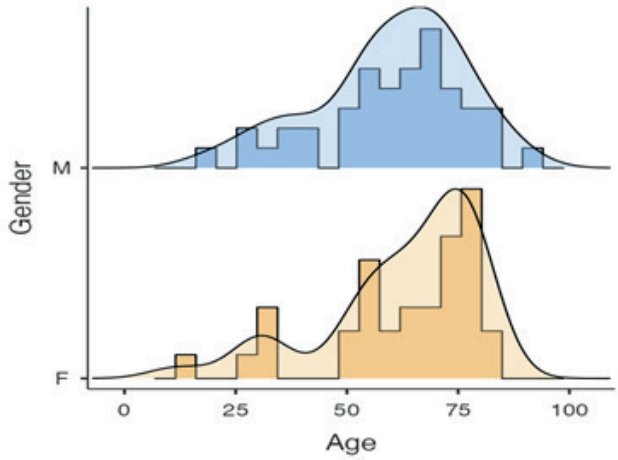

Fig. 1. Distribution by age and gender

The initial distribution of all subjects into PH groups included echocardiographic derived PH groups labeled as echocardiographic positive for PH and negative for PH. Given the results of a post-hoc analysis, however, lack of difference was demonstrated between the mean values of (TAPSE/sPAP)/RV x 100 in IpcPH and echocardiographic positive PH (p 0.998) and respectively

Table 1. Summary of patients' distribution into the PH subgroups and their demographic, echocardiographic data and the presence of perfusion defects

Variable	All patients (n=79)	IpcPH (n=25)	CpcPH (n=16)	CTEPH/PAH (n=16)	P value
Age - median (IQR)	65 (53.5-73.5)	72 (56-76)	71 (63.25–78.25)	68.5 (62-72.25)	0.059
Gender F/M	36/43	16/9	9/7	2/14	0.410
Perfusion defects	37/42	12	12	16	0.180
TAPSE median (IQR) mm	18 (15-20)	19 (18-20)	18 (14-19)	14 (11.75-17)	<0.001
Echo sPAP median (IQR) mmHg	45 (30-66)	40 (30-50)	65 (57.5-76.25)	81 (66.5-88.75)	<0.001
RV basal diameter (IQR) mm	39 (34-45.5)	37 (34-41)	42 (37.5-46)	49.50 (46-55.5)	0.004
TAPSE/sPAP median (IQR) mm/mmHg	0.4 (0.23-0.65)	0.45 (0.38-0.5)	0.25 (0.17-0.35)	0.19 (0.13-0.21)	<0.001
(TAPSE/sPAP)/RV x 100 median (IQR) mm²/mmHg	1.09 (0.49-1.79)	1.17 (0.95-1.47)	0.57 (0.41-0.99)	0.32 (0.26-0.42)	<0.001

Abbreviations: **F** – female, M – male, echo sPAP – echocardiographic systolic pulmonary artery pressure, Rv – right ventricle, IpcPH – isolated post-capillary, CpcPH – combined pre- and post-capillary, **CTEPH** – chronic thromboembolic pulmonary hypertension

Table 2. Haemodynamic data of all positive for PH patients

Variable	All PH patients (n=36)	IpcPH (n=5)	CpcPH (n=16)	CTEPH/PAH (n=15)	P value
sPAP median (IQR) mmHg	74 (63-91.25)	40 (39-48)	72 (59.5-88)	86 (81-98)	<0.001
PCWP or LV EDP median (IQR) WU	18 (13.75-22.25)	21 (18-26)	22 (20.75-25)	13 (12-14.5)	0.097
PVR median (IQR) WU	5.15 (3.3-8.45)	0.9 (0.8-1.6)	4.65 (3.3-5.43)	8.3 (6.05-14.3)	<0.001
(TAPSE/sPAP)/RV x 100 median (IQR) mm²/mmHg	0.47 (0.3-0.9)	1.25 (1.17-1.36)	0.57 (0.41-0.99)	0.31 (0.25-0.44)	<0.001

Abbreviations: **PCWP** – pulmonary capillary wedge pressure, **PVR** – pulmonary vascular resistance

between no PH and echocardiographic negative for PH (p 0.967). For this reason both pairs were merged into no PH and IpcPH respectively.

Thus PH type groups included IpcPH in 25 (32%) patients, CpcPH in 16 (20%) and CTEPH 16 (20%). The reported higher incidence for CTEPH compared to epidemiology data from larger cohort studies (0.4-6%) was supposedly due to deliberate investigation of highly suspected cases [6]. The median values of (TAPSE/sPAP)/RV x 100 for each subcategory were as they follow – IpcPH 1.17 (IQR: 0.95-1.47), CpcPH 0.57 (IQR: 0.41-0.99) and CTEPH 0.32 (IQR: 0.26-0.42). Table 1 shows that neither demographic characteristics nor the presence of perfusion defects could determine the PH type. However, all three parameters sPAP, TAPSE and RV basal diameter were of significance, in particular CTEPH patients had higher sPAP (r 0.53, $p < 0.001$) and RV basal diameters (r 0.62, $p < 0.001$) and lower TAPSE (r -0.5, $p < 0.001$). In comparison, IpcPH patients had the reverse correlation for these parameters – sPAP (r -0.64, $p < 0.001$), RV basal diameters (r -0.52, $p < 0.001$) and TAPSE (r 0.55, $p < 0.001$). Overall, (TAPSE/sPAP)/RV ratio correlated negatively in CTEPH r -0.59 ($p < 0.001$), and positively in IpcPH 0.74 ($p < 0.001$). However, statistically significant correlation was not proven for CpcPH (p 0.088). A larger cohort study is required in order to obtain more precise data and verify the results.

One-way ANOVA analysis further proved a statistically significant difference between the new index values among the PH groups (F 94.42, $p < 0.001$, CI-95%). More detailed post-hoc analysis rendered the results – IpcPH-CpcPH 0.57 ($p < 0.001$), IpcPH-CTEPH 0.85 ($p < 0.001$) and CTEPH-CpcPH 0.28 (p 0.037). (TAPSE/sPAP)/RV x 100 ratio range in each category was disturbed as it follows – IpcPH 1.22 ± 0.36, CpcPH 0.64 ± 0.32, CTEPH 0.37 ± 0.18. Figure 2 presents (TAPSE/sPAP)/RV x 100 distribution among PH subtypes. Figure 3 denotes a graphical analysis of the (TAPSE/sPAP)/RV x 100 value and the probability for each PH positive type.

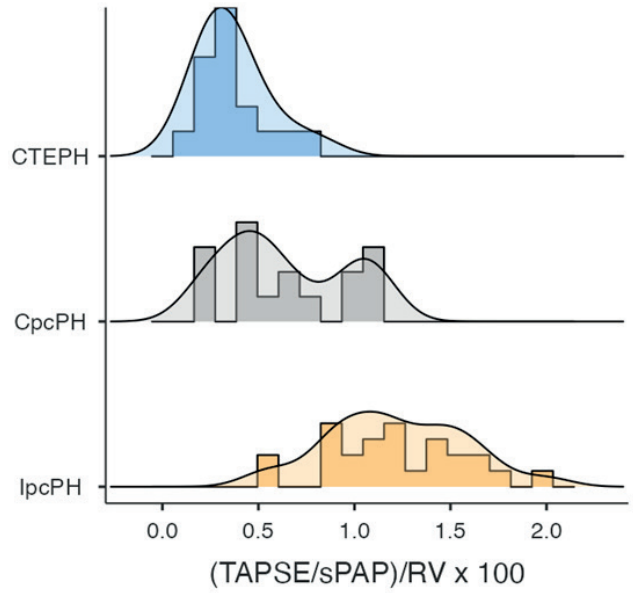

Fig. 2. Descriptive plot for the index (TAPSE/sPAP)/RV x 100 range for each PH subtype (CI 95%)

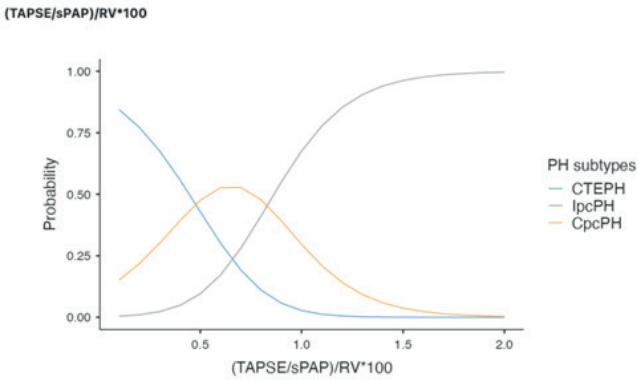

Fig. 3. Graphical presentation of the regression analysis, depicting the probability for a given PH subtype based on the value of (TAPSE/sPAP)/RV x 100

The graphical analysis demonstrates crossing of CTEPH and CpcPH curves at a value for (TAPSE/sPAP)/RV x 100 of 0.5 giving a tendency for lower likelihood for CTEPH with increasing values. The range of the index with a higher probability of CpcPH is between 0.5-0.8 defined by the CTEPH and IpcPH curves respectively, with higher incidence for IpcPH with increasing index values.

Given the results from a binomial analysis of patients with CTEPH versus those without i.e., IpcPH and CpcPH, along with a cut-off index value of 0.52 sensitivity was estimated at 87.5% and specificity of 83% AUC 0.90. In comparison, for this specific study TAPSE/sPAP with the proven cut-off value of 0.32 for pre-capillary PH yielded sensitivity 93.8% and specificity 63.4%, AUC 87.7%. Moreover, the newly proposed index proved to be a more accurate predictor of pre-capillary PH/CTEPH than the standard TAPSE/sPAP 0.83 vs 0.79 and r2McF 0.42 vs 0.36.

A cut-off value of 0.83 derived from a binomial test of patients with IpcPH and those without (CTEPH and CpcPH) rendered sensitivity of 92% and specificity 84.4%. Figure 4 represents ROC curves for CTEPH and IpcPH.

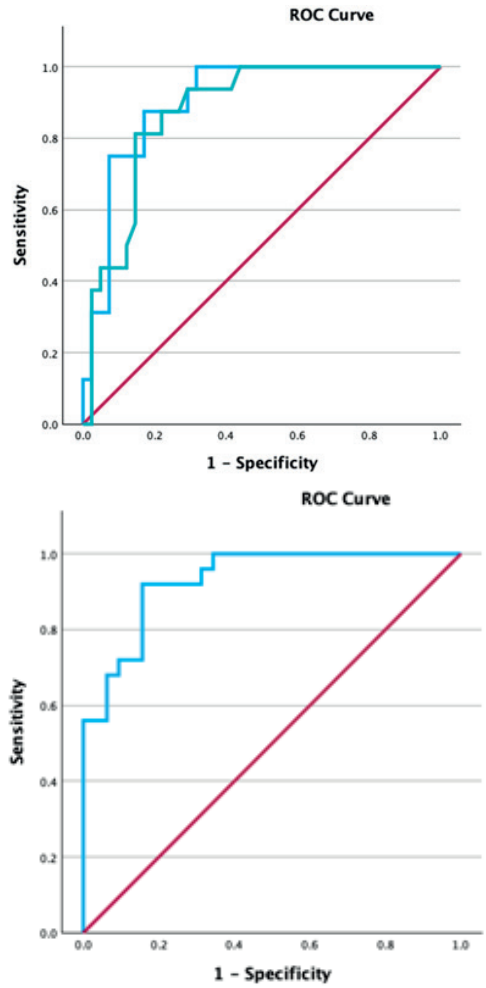

Fig. 4. ROC curves. Left ROC curve for CTEPH, blue line represents (TAPSE/sPAP)/RV x 100, green – TAPSE/sPAP. Right ROC curve for IpcPH.

Statistically significant difference for the (TAPSE/sPAP)/RV x 100 ratio was also demonstrated between patients with and without PH ($p < 0.001$). Based on the presented data the following range could be proposed: no PH values above 1.79, leading post-capillary PH 0.83-1.79, grey zone 0.53-0.82 for CpcPH and those with a higher chance of isolated pre-capillary PH/CTEPH below 0.52. The small sample size is a major limitation and further evaluation among a larger number of patients is desired.

DISCUSSION

The prognosis and haemodynamics in PH are determined by the relationship between RV contractility and RV afterload, defined as ventriculoarterial coupling. The golden standard for evaluation of the RV-PA coupling is an invasive measurement of the ratio between the telesystolic elastance of RV (Ees), marker of RV contractility independent of afterload, and the elastance of pulmonary arterial circulation (Ea). Values of Ees/Ea > 1 (in particular 1.5-2) are proven to best characterise optimal RV-PA coupling, while Ees/Ea < 0.805 signifies RV dysfunction and Ees/Ea < 0.7 – right-sided heart failure and clinical worsening. Corresponding echocardiographic parameters for the critical point of ventriculoarterial coupling ratio of 0.7 are TAPSE 16, FAC < 40% as well as TAPSE/sPAP < 0.55 [7, 8, 9, 13, 14].

The proposed index (TAPSE/sPAP)/RV x 100 represents the major determinants of RV cardiac remodeling in practice. The combination of these basic echocardiographic parameters into a simple ratio might serve as a more precise screening marker for RV-PA coupling and PH type discrimination than conventional methods. The higher afterload in pre-capillary PH and CTEPH results in earlier and more advanced RV-PA decoupling, i.e RV dysfunction and dilation, compared to other PH types. Therefore patients with pre-capillary PH/CTEPH would supposedly have lower index values.

The results of this study of 79 patients, of whom 57 with PH, with a documented PE episode and followed-up on optimal anticoagulation clearly proves the correspondence between (TAPSE/sPAP)/RV x 100 ratio below 0.52 and CTEPH (a statistically significant result with $p < 0.001$). The negative correlation between the new index value and CTEPH may be explained by the worse ventriculoarterial coupling compared to patients with IpcPH.

The data analysis demonstrates good screening sensitivity for CTEPH of 87.6% for values below 0.52 and for IpcPH respectively sensitivity – 92% for values above 0.83. The reliance on such an easily obtainable echocardiographic index might support the follow-up of CTEPH patients and their referral to tertiary centres for invasive study and subsequent treatment. (TAPSE/

sPAP)/RV x 100 could serve as a screening method for idiopathic PH given the observed tendency for a higher incidence of haemodynamic evaluation of patients with heart failure with a preserved ejection fraction (HFpEF).

LIMITATIONS

The major limitations of the current study are its retrospective characteristic, the small cohort and as a result the limited number of patients who underwent invasive haemodynamic evaluation. Despite the good sensitivity and specificity for the evaluated index, verification with a prospective study among a larger cohort is required. Another drawback is the higher proportion of echocardiographic derived data, in particular pulmonary artery pressure. Further evaluation of patients in tertiary centres is of crucial importance in order to obtain more precise data.

CONCLUSION

The study presents the index (TAPSE/sPAP)/RV x 100 as a marker of RV-PA coupling as a potential screening test for CTEPH and PH type discrimination.

No conflict of interest was declared

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