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Prediction of pulmonary hypertension in older adults based on vital capacity and systolic pulmonary artery pressure

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Abstract

Objective: Right heart catheterization (RHC) is associated with a higher procedural risk in older adults, but non-invasive estimation of pulmonary hypertension (PH) is a challenge. We aimed to elaborate a non-invasive prediction model to estimate PH.

Methods and design: We retrospectively analysed 134 older adults (70.0 years ±12.3; 44.9% males) who reported to our clinic with unclear dyspnea between 01/2015 and 01/2020 and had received RHC as a part of their diagnostic workup. Lung function testing, analysis of blood gas samples, 6 min walk distance and echocardiography were performed within 24 hours of RHC.

Main outcome measures: In a stepwise statistical approach by using an in/exclusion algorithm (using the AIC criterion) we analysed non-invasive parameters to test their value in predicting PH (defined as mean pulmonary artery pressure, PA_{mean}, >25mmHg). Discrimination capability of the final model was measured by the AUC (area under curve) from an ROC (receiver operating characteristics) analysis.

Results: We yielded a sensitivity of 87.2% and a specificity of 62.5% in a combinatorial logistical model with systolic pulmonary artery pressure (sPAP) and forced vital capacity (VC_{max}), the discrimination index was 86.7%. The odds ratios for an increase of 10 mmHg of sPAP were 2.99 (2.08–4.65) and 1.86 (1.11–3.21) for a 1l decrease in VC_{max}. On their own, VC_{max} proved to be specific (83.3%), while sPAP was a sensitive (79.1%) predictor for PH.

Conclusions: We provide a combinatorial model to predict PH from sPAP and VC_{max} in older adults, which may help to avoid invasive procedures.

Keywords

Risk assessment, pulmonary circulation, echocardiography, vital capacity, avoiding invasive procedures

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Introduction

Elucidating the etiology of dyspnea in multimorbid patients can be challenging and often requires cardiological, pneumological, rheumatological, infectious or endocrinological investigations. A crucial factor for diagnosis is pulmonary hypertension, PH, given its high correlation with both morbidity and mortality.[1] The current ESC guidelines differentiate between isolated pre-and post-capillary PH as well as combined pre- and post-capillary PH, CpcPH.[2] Non invasive parameters of mortality risk stratification in pulmonary arterial hypertension (PAH) and PH have been established and have been validated in other cohorts.[3,4] Recently, hypochloremia has been suggested as a non-invasive marker to predict one, three- and five-year-survival in PH.[5]

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However, definitive diagnosis demands right heart catheterization (RHC), which is an invasive method with associated risks. Especially in older adults invasive investigations are often complicated and sometimes not feasible. Echocardiography studies have provided an array of parameters and indices to non-invasively predict P(A)H and outcome.[6–10] FEV_1 (forced exspiratory volume in one second), exercise induced desaturation and 6 MWD (6 minute walk distance), carbon monoxide transfer coefficient (KCO) and carbon monoxide diffusing capacity of the lung (DLCO) have been associated with echocardiographic systolic pulmonary artery pressure (sPAP) in univariate analysis.[11,12] Additionally, cardiopulmonary exercise testing (CPET) seems to contribute to the prognostic values of 6 MWD in predicting survival in PH.[13]

In summary, a considerable number of single non-invasive variables have been suggested as surrogates for predicting or estimating PH, but none are sufficiently robust for clinical use on their own. This may be due to high interdependence between the variables due to the complex pathophysiology of PH.

Developing an easily applicable prediction model for PH is of utmost clinical importance, since diagnosis of PH is often prolonged, with deleterious consequences, including mortality, in patients with chronic heart failure. To fill this gap we developed a stepwise statistical approach to elucidate a model consisting of non-invasive variables to estimate PH probability with minimal interdependence of variables. Our aim is to provide a non-invasive tool for clinicians to quickly estimate PH probability in older adults in daily practice.

Methods

We retrospectively analyzed 134 older adults admitted to our clinic between 01/2015 and 01/2020 for clinical evaluation and differential diagnosis of dyspnea, all of whom received right heart catheterization as a part of their differential diagnostic workup during hospital stay. The indication for RHC was stated when the reason for dyspnea was not discovered with non-invasive measures. Older adults were defined as being 70 years of age or older or at least 55 years with clinically significant cardiopulmonary limitations (at least NYHA II). Prior to RHC, presence of, or progression of previously diagnosed coronary artery disease had to be excluded invasively or non-invasively. In case of clinical and echocardiographic congestion at hospital admission, patients were treated with intravenous-diuretics and RHC was performed at a clinically recompensated state. Patients had provided written consent to anonymous data usage at hospital admission. In the presence of unclear dyspnea with the need for further medical check-up, there were no exclusion criteria to the study. We collected baseline characteristics (Tables 1 and 2) of our patients, including available blood chemistry, LFT, echocardiography, 6 MWD, and blood gas analysis.

Table 1. Baseline characteristics.

Age	70.0years ± 12.3
Weight	83.48 kg ± 17.5
BMI	28.9 kg/m^2±5.6
Males	44.9%
Hypertension	80.5%
Diabetes	21.6%, 9.7% on insulin
Smokers	24.6%
Coronary artery disease	31.3%
Cardiomyopathy	28.4%
Atrial fibrillation	41.8%
Oral anticoagulation	54.5%
Chronic obstructive pulmonary disease	27.8%
Restrictive pulmonary disease	11.0%
History of myocardial infarction	9.7%
History of CABG	8.3%
History of stroke	7.5%
Hemoglobin	13.8 g/dl ± 1.9
GFR	67.4 ml/min ± 23.0
LDL cholesterol	103.1 mg/dl ± 42.3
LTOT	22.9%
CPAP	12.3%
NIV	9.1%
ACE / ARBs	71.4%
CCB	30.8%
Beta-blockers	72.2%
Diuretics	81.1%

Baseline characteristics, mean values and standard deviations are listed where appropriate (n = 134.). Chronic obstructive pulmonary disease was defined as a Tiffeneau index < 70%. Relevant restrictive lung disease was defined as a VC_{max}<85%. CABG: coronary artery bypass grafting; GFR: glomerular filtration rate calculated by MDRD-formula; LTOT: long-term oxygen treatment; CPAP: continuous positive airway pressure ventilation; NIV: non-invasive, bilevel, ventilation; ACE/ARBs: angiotension converting enyzme/angiotensin receptor blockers; CCB: calcium channel blockers.

We established a clinically oriented priority list of non-invasive independent variables for further univariate analysis with the dependent variable mean pulmonary artery pressure (PA_{mean}): Sex, age, hypertension, coronary artery disease, valvular dysfunction (defined as at least grade II stenosis or insufficiency on transthoracic echocardiography), left ventricular ejection fraction (LVEF: separation via eyeballing into normal, >50%, moderately reduced, 40–50%, and highly reduced, <40%), right ventricular ejection fraction, RVEF [normal: TAPSE (tricuspid annular plane systolic excursion) >15mm, and considerably reduced <10mm], systolic pulmonary artery pressure (sPAP) and oxygen content in capillary blood at rest, c_aO_2

Table 2. Characteristics of echocardiography and lung function testing.

Preserved LVEF (EF > 50%)	75.9%
Midrange reduced LVEF (40–50%)	3.0%
Considerably reduced LVEF (<40%)	21.1%
Preserved RVEF (TAPSE >15mm)	76.0%
Considerable reduction of RVEF (TAPSE <10 mm)	16.5%
Relevant valvular dysfunction (≥grade II)	38.5%
VCmax	2.6l ± 1.0
FEV1	1.9l ± 0.8
RV	3.0l ± 1.4
RV/TLC	122.9%±36.3
KCO	69.4%±27.6

Echocardiografic findings and lung function testing. Mean values and standard deviations are shown where appropriate. LVEF: left ventricular ejection fraction, defined with eyeballing by an experienced echocardiographer; RVEF: right ventricular ejection fraction, defined by TAPSE; TAPSE: tricuspid annular plane systolic excursion; VC_{max}: vital capacity; FEV_1: forced expiratory ventilation in 1 s; RV: residual volume; RV/TLC: residual volume/total lung capacity; KCO: transfer coefficient of the lung for carbon monoxide, CO (n = 134).

[calculated according to the formula: S_aO_2 (%) x Hb (g/dl) x 1,34 (ml/g) + p_aO_2 (mmHg) x 0,0031 (1/mmHg·ml/dl)], 6 MWD, vital capacity (VC_{max}) and FEV_1. Echocardiography was performed by experienced cardiologists. All non-invasive tests had to be done within 24 hours before right heart catherization (RHC) and patients or legal guardians had to give their written consent to anonymous data usage and RHC exams (for information on the RHC procedure see supplement 1).

We aimed to calculate a prediction model consisting of non-invasive parameters to estimate the probability of pulmonary hypertension in older adults. This should help to reduce the number of invasive procedures in older adults to the necessary minimum without missing adequate treatment options. Pulmonary hypertension was defined as an invasively measured PA_{mean} >25 mmHg. Hemodynamic definitions were applied according to the ESC guidelines 2015.[2]

Statistical approach

Descriptive and exploratory analyses of study data were performed with SPSS (IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp.) Normality was tested with the Kolmogorov-Smirnov (including Lilliefors significance correction). Differences between subgroups were analyzed by Mann-Whitney U-test statistics and Kruskal-Wallis H-test to evaluate the relevance of explanatory variables. Spearman's Rho correlation coefficients were used as a measure of association. Multivariable regression modeling was performed with functions from the R-Program.[14,15]

By considering sex and age as potential confounders, we used an in/exclusion algorithm (using the AIC criterion) to elucidate the most relevant variables for the prediction model. We dichotomized PA_{mean} (≤25 mmHg vs. >25 mmHG) and analyzed logistic multivariable regression models. A stepwise forward/backward modelling was calculated. Discrimination capability of the final model was measured by the AUC (area under curve) from an ROC (receiver operating characteristics) analysis. For an estimate of sensitivity and specifity (incl. 95%-CI) a cut-off value was set at 0.5. Odds Ratios (OR) were deduced from the regression coefficients and estimated probabilities of PA_{mean} >25 mmHg were displayed. Internal consistency for the estimation of the model parameters was performed with bootstrapping (B = 500). The predictive capabilities of the final model were visualized in a nomogram.

Results

Our patients showed a plethora of cardiovascular risk factors with 80.5% hypertensives, 21.6% diabetics and 24.6% smokers. Cardiomyopathies and coronary artery disease were present in 50%. Almost half of our patients suffered from atrial fibrillation and one third showed relevant valve disorders (38.5%), which, together with the high amount of hypertensives, the mainly preserved LVEF (75.9%) and RVEF (76.0%) would suggest more cases of post-capillary PH of all PH patients (64.9% overall). However, the majority showed a combination of pre- and post-capillary PH (CpcPH, 40.2%; 36.8% isolated pre-capillary, 23.0% isolated post-capillary), mainly with preserved cardiac output (mean cardiac index 2.3l/min/m^2). Heart failure medication had been established in most cases. Additionally, lung disease, either obstructive or restrictive, had been diagnosed in one third of patients, 22.9% had an established long-term oxygen supply (cumulative data from RHC are provided in Table 3).

Univariate analysis

Univariate analysis of the independent variables and PA_{mean} revealed that 6 MWD (r = –0.33), FEV_1 (r = –0.34), VC_{max} (r = –0.32), valvular dysfunction (p < .001), TAPSE (p < .001), sPAP (r = 0.58) and oxygen content (r = –0.25) should be more closely analyzed in a prediction model. Arterial hypertension (p = 0.751), coronary artery disease (p = 0.397) and LVEF (p = 0.863) did not show any differences and were not included in the following regression analysis.

Table 3. Data from right heart catheterisation.

RA_{mean}	8.7mmHg ± 5.4
RV_{sys}	49.8 mmHg ± 21.3
RV_{dia}	3.6 mmHg ± 5.4
PA_{sys}	49.2 mmHg ± 21.8
PA_{dia}	21.7 mmHg ± 10.3
PA_{mean}	31.8 mmHg ± 13.4
$PCWP_{mean}$	14.4 mmHg ± 7.2
Pulse pressure (PA_{sys}-PA_{dia})	27.5 mmHg ± 15.0
Cardiac Output	4.4l/min ± 1.2
Cardiac Index	2.3l/min/m2 ± 0.6
PVR	348.3 dyn·s·cm^{-5} ± 300.3
SVR	1823.5 dyn·s·cm^{-5} ± 710.7

Data of right heart catheterisation. RA_{mean}: mean right atrial pressure; RV_{sys}: systolic right ventricular pressure; RV_{dia}: diastolic right ventricular pressure; PA_{sys}: systolic pulmonary artery pressure; PA_{dia}: diastolic pulmonary artery pressure; PA_{mean}: mean pulmonary artery pressure; $PCWP_{mean}$: mean capillary wedge pressure; PVR: pulmonary vascular resistance; SVR: systemic vascular resistance. Mean values with standard deviations (n = 134).

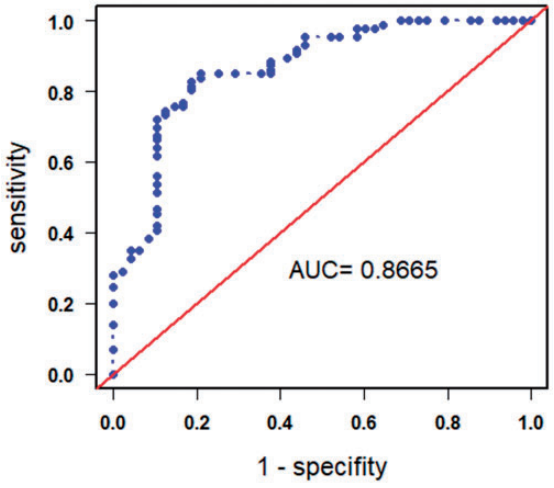

Figure 1. Area under the curve (AUC) after validation of the model (bootstrapping, n = 134).

Sex (p = 0.596) and age (r = 0.40) as potential confounders were considered (Table 1a and b of supplement 2).

Logistic multivariable regression model

Initially, non-parametric correlations were calculated and displayed considerable correlations between PA_{mean}, sPAP (r = 0.58; p < .001), oxygen content (r = –0.25; p < .001), 6 MWD (r = –0.33; p < .001), VC_{max} (r = –0.31; p < .001) and FEV_1 (r = –0.33; p < .001, see Figure 1 in supplement 3). This, however, signifies that inclusion of all parameters in the model is not warranted due to interdependence of the parameters. The variables alone differed significantly between PA_{mean} above and below 25 mmHg, but would produce a systematic error in a regression model.

For a full and plausible logistic regression model a clinical decision on restriction of variables had to be made. We chose to include sPAP; VC_{max}, FEV_1, 6 MWD, RVEF-TAPSE, valve dysfunction, oxygen content, sex and age. Significance was yielded for sPAP (< .001) and VC_{max} (p = .021), but not for 6 MWD (p = .276), FEV_1 (p = .222), RVEF-TAPSE (p = .399), valve dysfunction (p = .230), oxygen content (p = 810), age (p = .128) and sex (p = .127; for full regression data see Table 2a in supplement 2). After stepwise forward/backward modeling (AIC analysis), VC_{max} and sPAP remained for further analysis. Thus, a reduced model was calculated with sPAP and VC_{max}. as well as sex and age, the latter two did not play a significant role and were omitted in the final model (for regression data see Table 2b in supplement 2).

Regression coefficients were converted to Odds Ratio (OR): the OR for a 10 mmHg increase in sPAP was 2.99 (95% CI: 2.08–4.65) and 1.86 for a 1 l decrease in VC_{max} (95% CI: 1.11–3.21).

Separate univariate ROC analysis yielded an estimated specificity for sPAP of 81.3% (70.8% to 91.7%) and sensitivity was 79.1% (69.8% to 87.2%). The estimated specificity for VC_{max} was 83.3% (72.9% to 93.8%) and sensitivity was 46.5% (36.1% to 57.0%). In the final multivariable logistic regression model sPAP and VC_{max} discriminated well in terms of the presence of PH (discrimination index 86.7%, AUC 0.8665, Figure 1). Sensitivity was 87.2% and specificity 62.5% at a cut-off value of 0.5.

Discussion

We assessed non-invasive risk predictors for pulmonary hypertension in a population of older patients reporting for differential diagnosis of unclear dyspnea. With a mean age of 70.5 years our patients represent a multi-morbid population.

We systematically analyzed both pneumological and cardiological factors in terms of their value for a prediction model for PH. The complexity of PH was demonstrated through multiple interactions between the potential independent variables, which forced us to set clinical priorities for the model (Table 2 of supplement 2). For instance, FEV_1, oxygen content, TAPSE and 6 MWD differed significantly between patients with and without PH and may provide clues to suspect PH in patients with dyspnea (Figures see supplement 3), but inclusion in the model was not useful due to their interaction potential. The problem of multiple variables has

already been addressed in the literature and careful selection of parameters has been suggested.[16]

We used a stepwise approach to filter the most suitable factors, which left sPAP and VC_{max} as the most predictive factors. Recently, Lurz et al. analyzed the role of PH in severe tricuspid regurgitation and its implications for transcatheter tricuspid valve repair (TVVR) with the MitralClip™ technique in 243 patients.[17] They found that the diagnostic accuracy of echocardiography to detect an invasive systolic PA pressure >50 mmHg was only 55% in their population,[17] which suggests that sPAP alone has insufficient diagnostic value for PH detection. Using our model by adding VC_{max} may achieve a higher diagnostic yield. In the logistic model especially sPAP displayed a sinusoid relationship in terms of probability for PA_{mean} >25 mmHG, while VC_{max} had a curvilinear course (Figure 2). The figure illustrates that an sPAP increase boosts the probability of PH between 30 to 50 mmHg-the corridor in which clinical decision-making is often problematic. The interpretation of the significance of an sPAP in this range, in terms of the presence of PH, can be difficult.

In our combined (sPAP and VC_{max}) logistic model we yielded a sensitivity of 87.2% and specificity of 62.5%. This produced a benefit in sensitivity compared to a separate analysis of the factors (sPAP: 79.1% and VC_{max} 46.5%), but at the expense of specificity (sPAP 81.3%; VC_{max} 83.3%). A discrimination index of 86.7% of the combined model (see Figure 2) is relevant for clinical purposes. Moroever, the complementary nature of the two variables (VC_{max} as a specific factor and sPAP as a sensitive marker) can be integrated into clinical practice. Patients with low sPAP in echo

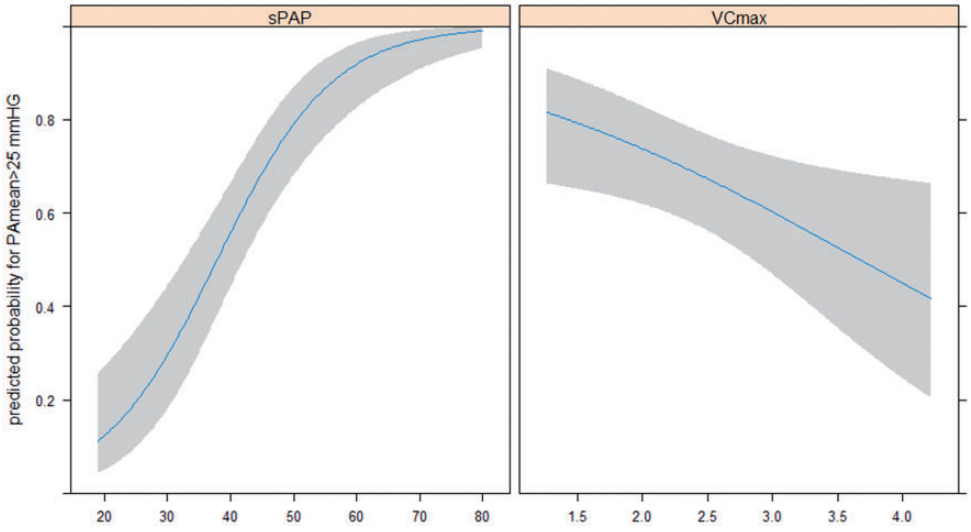

Figure 2. Estimated probability (x-axis) for PA_{mean} (mean pulmonary artery pressure) >25mmHg from the logistic model für sPAP (systolic pulmonary artery pressure) and VC_{max} (maximal vital capacity). The y-axis shows sPAP [mmHg] on the left and VC_{max} [l] on the right (n = 134).

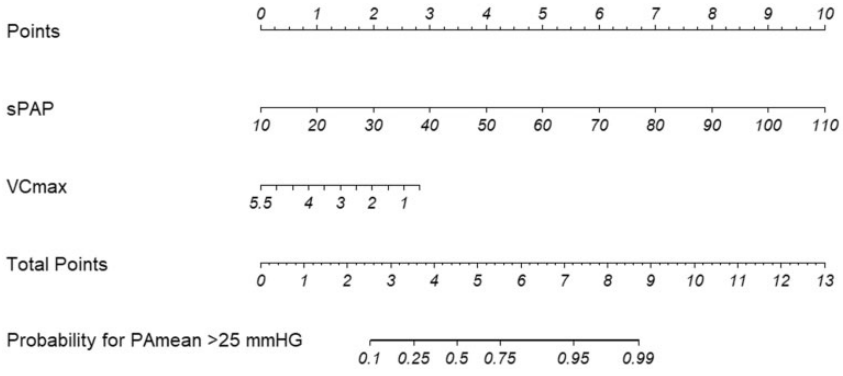

Figure 3. Nomogram with evaluation of the independent variables on a linear scale (total points given). The points reflect the probability of PA_{mean} (mean pulmonary artery pressure) >25mmHg.

but clinical symptoms compatible with PH need to be further investigated. VC_{max} can provide additional, valuable information on risk stratification (see nomogram, Figure 3). We are aware that VC_{max} is dependent on age and fluid status (congestion may reduce VC_{max} temporarily). However, in our study fluid status has not been a confounder since we only perform RHC (apart from the intensive care unit) after recompensation with diuretics. A single measurement of VC_{max} may not be sufficient to give the diagnosis PH. However, over time, relative changes of VC_{max} in a patient could provide clinicians with valuable information on increasing risk of PH and may guide clinical decision making on escalating medical therapy.

In the nomogram an sPAP of 40 mmHg (three points) and a VC_{max} of 41 (one point) cumulates in a PH probability of around 37% (a total of four points), while a VC_{max} of 11 (2.5 points) with the same sPAP leads to a probability of 75% (5.5 points)! Thus, VC_{max} is an important discriminator of PH likelihood in the sPAP grey zone of 30–50 mmHg. VC_{max} is suitable for a prediction model, because it also integrates the dimensions age and body surface.

Correale et al., 2019 have implemented a scoring system to predict PH entirely through echocardiographic factors in a small population of cardiological patients ($n = 64$) and yielded similar sensitivity and specificity (93 and 67%, AUC 0.786) compared to our model.[18] They suggested right atrial and ventricular diastolic area, maximal velocity of tricuspid regurgitation and left ventricular ejection fraction as variables. However, the right ventricle is often difficult to visualize and measure, especially in concomitant pulmonary disease with dynamic hyperinflation. In our study right ventricular function, expressed by TAPSE, was not a suitable prediction factor of PH. We are aware that TAPSE only measures annular plane excursion and has limited validity in regional wall motion abnormalities, but nevertheless seems to be a predictor of major cardiovascular events in patients with stable coronary artery disease.[19] TAPSE is often easily measurable and does not take much time in clinical routine. The value of RV dysfunction as a factor to predict mortality is well-established.[20] Therefore integration of geometric and dynamic parameters of RV function, such as right ventricular and atrial strain, may also add information to a PH prediction model. RV- peak systolic strain rate, for instance, was recently shown to predict peak oxygen consumption in patients with group I PH ($AUC = 0.88$) and may also be used as a variable in future models for others than PH group I.[21]

The ratio of TAPSE/sPAP as a marker of RV/PC coupling (right ventricular-pulmonary circulation), which has shown predictive quality in hospitalization frequency in heart failure patients,[22,23] could also be used in a future prediction model of PH. Guazzi et al., 2015 used EOV (exercise oscillatory ventilation) during CPET and TAPSE/sPAP to predict major cardiac events.[23] However, CPET is not always applicable in daily clinical routine, contrary to LFT (and VC_{max}).

Additionally, LVEF did not prove to be a predictor of PH, which emphasizes that there may be other parameters, such as the unspecific BNP or the more subtle parameter left ventricular strain, to express (left) cardiac stress. Evidence exists that enhanced BNP is a marker of the presence of CpcPH in patients with severe aortic stenosis.[24]

LFT parameters and PH prediction have also been reported in the literature. An interesting study of 105 patients with idiopathic pulmonary fibrosis (IPF) revealed that the ratios FVC/DLCO (forced vital capacity/diffusion capacity) and diameters of pulmonary artery/aorta were useful adjuncts to sPAP to predict PH in a linear regression model ($R^2 = 0.39$).[25] Another small study ($n = 61$) with IPF patients regressed FVC/DLCO and resting pulse oximetry with PA_{mean} as a continuous variable ($R^2 = 0.55$).[26] Whether these models are reliable in cardiological patients without lung disease is unclear.

Our study population adds valuable information to the literature because it consisted of typical multimorbid, older patients of internal medicine with a high coincidence of cardiological and pulmonary diseases, a group often excluded in clinical trials. In these patients PH diagnosis is usually difficult, because symptom progression can be subtle and early risk assessment is of paramount importance.[27–29] In such a population integration of parameters of LFT and echo seems reasonable. Integration of a greater number of variables into a prediction model of PH does not facilitate prediction due to the high interdependence of the factors. Our approach systematically reduced the number of factors necessary to elaborate a powerful model with complementary factors, which can be incorporated into clinical practice.

Thus, our study provides an important tool for personalized stratification to detect PH in older adults without invasive procedures. We provide a clinically applicable model for physicians treating older adults to estimate PH probability and reduce the number of invasive procedures, such as RHC, which have a higher peri-procedural risk and put older patients under a lot of stress. This would apply to situations, in which a low risk score for PH is calculated. However, in case of a high probability for PH invasive diagnostics will still be necessary (despite higher procedural risks) to discriminate the etiologies of PH and choose the appropriate treatment options.

Limitations

There are limitations to our study. Methodological limitations due to the retrospective nature of the study and the limited sample size have to be acknowledged. Although, we provided internal validation of our model, the scoring system has to be validated in larger cohorts. Our population consisted of multimorbid but still mobile (mean 6 MWD 321 m) patients with a high percentage of pulmonary co-morbidities, bearing the risk of selection bias. The common denominator of our patients was dyspnea, 64.9% of which had PH as a diagnosis. Additionally, our model does not allow a statement on the etiology of PH. Larger populations with different clinical profiles and pre-test probabilities for PH would be necessary to validate our clinically appealing approach. Additionally, NTproBNP values were not completely available and had no predictive power in our model.

Conclusion

In summary, we elaborated an easily applicable model of non-invasive parameters as predictors of pulmonary hypertension in older adults. VC_{max} and sPAP provided a valuable complementary model particularly useful in the group with lower sPAP in echo. Our model helps to stratify the probability of PH in elderly, multimorbid patients. This easily applicable model could be used as a standard in cardiopulmonary practice to predict PH in older adults and help to further reduce unnecessary invasive procedures in older patients without missing treatment options.

Data availability

Supplementary analyses and data will be made available by the corresponding author on reasonable request.

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Declaration of conflicting interests

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Ethical approval

The study complies with the Declaration of Helsinki. Written informed consent has been obtained from the participants or their legal representatives. After consultation of the local ethics committee (University Münster, Germany) a direct vote of the committee was not necessary due to the retrospective nature of the study and analysis of our own institutional data.

Guarantor

The corresponding author is responsible for the validity and discretion of data analysis.

Contributorship

Both authors contributed to the design and compilation of the study. SW wrote the manuscript, JH did the statistics.

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Supplemental Material

Supplementary material for this article is available online.

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