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Research article

A pulmonary hypertension targeted algorithm to improve referral to right heart catheterization: A machine learning approach

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ABSTRACT

Background: Pulmonary hypertension (PH) is a pathophysiological problem that may involve several clinical symptoms and be linked to various respiratory and cardiovascular illnesses. Its diagnosis is made invasively by Right Cardiac Catheterization (RHC), which is difficult to perform routinely. Aim of the current study was to develop a Machine Learning (ML) algorithm based on the analysis of anamnestic data to predict the presence of an invasively measured PH.

Methods: 226 patients with clinical indication of RHC for suspected PH were enrolled between October 2017 and October 2020. All patients underwent a protocol of diagnostic techniques for PH according to the recommended guidelines. Machine learning (ML) approaches were considered to develop classifiers aiming to automatically detect patients affected by PH, based on the patient's characteristics, anamnestic data, and non-invasive parameters, transthoracic echocardiography (TTE) results and spirometry outcomes.

Results: Out of 51 variables of patients undergoing RHC collected, 12 resulted significantly different between patients who resulted positive and those who resulted negative at RHC. Among them 8 were selected and utilized to both train and validate an Elastic-Net Regularized Generalized Linear Model, from which a risk score was developed. The AUC of the identification model is of 83 % with an overall accuracy of 74 % [95 % CI (61 %, 84 %)], indicating very good discrimination between patients with and without the pathology.

Conclusions: The PH-targeted ML models could streamline routine screening for PH, facilitating earlier identification and better RHC referrals.

1. Background

Pulmonary hypertension (PH) is a type of high blood pressure that affects the arteries in the lungs and the right side of the heart. During the 6th World Symposium on Pulmonary Hypertension the definition of Pulmonary Hypertension has been amended [1], with a subsequent

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confirmation in 2022 ESC/ERS guidelines [2]. According to this new guideline pulmonary hypertension is defined by a mean pulmonary arterial pressure (mPAP) equal to or greater than 20 mmHg, typically determined through invasive measurement via right heart catheterization (RHC) [2]. So, this new guideline lowered the threshold for diagnosing of PH, from a mean pulmonary arterial pressure (mPAP) of 25 mm Hg to above 20 mm Hg. This was based on several independent groups findings which showed that even a little increase in mPAP over 20 mmHg is linked to a higher risk of death and the advancement of the illness [3,4]. However, according to current guidelines the new definition do not allow any specific therapy.

Right heart catheterization (RHC) is currently the gold standard diagnostic tool for pulmonary hypertension (PH) due to its accuracy in measuring pulmonary arterial pressure and cardiac output, which are critical for confirming a PH diagnosis and differentiating PH subtypes. However, RHC is an invasive tool, requires specialized facilities and trained personnel, which can be challenging in low-resource settings or for patients with comorbidities that increase the risks of invasive procedures. Therefore, it is of primary interest to improve a correct diagnosis using non-invasive tools. Transthoracic echocardiography (TTE) is the primary non-invasive imaging tool for raising diagnostic suspicion of PH. In clinical practice it is used to screen for PH and assess the severity and progression in patients already diagnosed with the condition. Indeed, TTE can estimate systolic pulmonary artery pressure (sPAP) by measuring the tricuspid regurgitant velocity (TRV), a surrogate for pulmonary pressures. However, ultrasound estimation of pulmonary artery systolic pressure is not always feasible and may be inaccurate in patients with suboptimal acoustic windows.

Consequently, no other procedure can accurately identify which patients should undergo RHC to ensure a reliable diagnosis of PH. As a result, PH often remains undiagnosed, contributing to disease progression and an increased risk of mortality.

In recent years, there has been a growing interest in machine learning algorithms for their performance in clinical decision-making in cardiovascular diseases [5]. In this scenario, machine learning has shown great promise in aiding the non-invasive detection of PH as an alternative or adjuncts to RHC for diagnosing and monitoring these conditions. In fact, with the application of machine learning algorithms on data that includes medical records, imaging studies, and other relevant clinical information, non-invasive diagnostic models can be developed. In some observational studies, this model demonstrated to accurately predict the likelihood of PH, facilitating early detection and intervention without necessitating catheterization [6–9].

Alternative clinical scores to identify patients deserving of RHC are even more pressing considering recent pharmacological breakthroughs that have slowed disease progression and improved survival [10–12]. Therefore, a machine learning approach holds great potential for early diagnosis of pulmonary hypertension by improving the interpretation of complex datasets, automating pattern recognition, and personalizing predictive models. This can lead to earlier intervention, ultimately improving patient outcomes.

Accordingly, we aimed to develop and validate a machine learning—based AI algorithm for improving TRV capability to diagnose PH using anamnestic data and non-invasive parameters such as smoking habit, TTE results and spirometry outcomes.

2. Materials and methods

2.1. Study design and population

This single-center observational study was designed to identify patients with PH within cohorts belonging to categories at high risk of developing the disease, such as connective tissue disease, congenital heart disease, HIV infection and portal hypertension. The study population consisted of 226 patients from high-risk groups for PH, recruited at the Pulmonary Hypertension Center of Monaldi Hospital, Naples, Italy, between October 2017 and October 2020. These patients underwent diagnostic protocols according to the 2015 ESC/ERS guidelines [13] in force at the time, including clinical assessment, resting echocardiography, and RHC. Exclusion criteria involved individuals with FVC $<$ 40 % predicted, severe left heart disease, pregnancy, or confirmed PH diagnosis/treatment. Echocardiography was performed blindly to RHC results, and RHC was conducted for confirmation in all patients to minimize bias. Patients diagnosed with PH were followed up for three years.

2.2. Clinical assessment

Inclusion criteria for enrolment included demographic data, comorbidities, hospitalization data, vital signs, echocardiography, hemodynamics measured by RHC, spirometry, blood gas analysis, lung function, WHO FC and six minutes walking distance (6MWD) and laboratory tests.

2.3. Transthoracic Doppler echocardiography at rest

An echocardiographic examination was performed on all patients. Two-dimensional and color-flow-guided continuous-wave Doppler echocardiographic recordings at rest were obtained by experienced cardiac sonographers (EG and CN) using 3.6–4 MHz Duplex probes and conventional equipment (Vivid 7, GE Healthcare, Milwaukee, WI, USA) [14,15].

Tricuspid annular plane systolic excursion (TAPSE) was calculated in the apical 4-chamber view, using optimal longitudinal alignment. The determination of pulmonary artery systolic pressure (PASP) was based on calculating the RV-RA gradient using the modified Bernoulli equation and diameter and degree of collapse of the IVC according to the formula RAP + RV-RA gradient, where RV-RA gradient is 4 (peak tricuspid regurgitant jet velocity) [16].

For all calculations, the mean value of at least three TRV measurements was used. The TAPSE/PASP ratio was calculated for each patient as an index of ventricular arterial coupling. The ejection fraction (EF) was then measured using the biplane method of disks (modified Simpson's rule) [16]. The presence of pericardial effusion, the degree of tricuspid valve regurgitation, and the thickness of the interventricular septum were also assessed.

2.4. Right heart catheterization

RHC was performed in the supine position using trans jugular access with an 8 F introducer set (MXI100, MEDEX, Smiths Group PLC, UK) (MXI100, MEDEX, Smiths Group PLC, UK) and triple-lumen 7F-Swan-Ganz thermodilution catheters from Edwards Lifesciences (REF:131F7, Edwards Lifesciences LLC, Irvine, CA, USA). Pressures were continuously recorded and averaged over several respiratory cycles during spontaneous breathing. Cardiac output (CO) was measured by thermodilution by averaging three measurements with no less than 10 % variation between measured values. The zero-reference point for pressure recordings was set at 1/3 of the thoracic diameter below the anterior thoracic surface according to the 2015 ESC/ERS guidelines [17]. PVR was calculated using the formula PVR= (mPAP-PWP)/CO. Pulmonary artery compliance was calculated as the ratio of stroke volume to pulse pressure (SV/PP): SV/PP (ML/mmHg) = (stroke volume) / (pulmonary systolic pressure - diastolic pressure).

2.5. Statistical analysis

Continuous variables were expressed as mean and standard deviation (SD). Data distribution was tested for normality through the Shapiro–Wilk test. Unpaired Student's t-test or Wilcoxon rank-sum test, as required, was used for comparison between 2 groups. Categorical variables were expressed as a percentage and were compared using the chi-

square test or the Fisher's exact test. A P-value (P) of $< .05$ was considered significant. Bonferroni's correction was used for multiple hypothesis correction, if necessary. Statistical analyses were carried out to compare patients affected by PH and non. Statistical analysis was performed using R Core Team (version 4.2.1, Austria).

2.6. Machine learning classification

Machine learning (ML) approaches were considered to develop classifiers aiming to automatically detect patients affected by PH, based on the patient's characteristics, anamnestic data, and non-invasive parameters, TTE results and spirometry outcomes (Fig. 1). The dataset was split into 60 % for training and cross-validation and 40 % for testing. The rationale behind this division was that, to minimize bias and overfitting issues, a classifier should be tested on a separate set of data. We performed "stratified sampling", where the split of training and testing was made by preserving the percentage of samples for each class (positive and negative to PH). Repeated (N = 100) 3-fold cross validation was employed. Since the dataset was unbalanced, we employed a synthetic minority over-sampling technique (SMOTE) to down samples the majority class and synthesizes new minority instances by interpolating between existing ones by using a ratios **1:2** (where the minority class is half the size of the majority class. Binary classification performance measures were adopted according to standard formulae [18].

2.7. Feature selection

Because of the large number of features available, it was essential to carefully select features to construct a robust model. It was important to ensure that the number of features utilized in the final classifier and their overall quantity were restricted to the number of subjects experiencing the event being detected. This limitation was crucial to mitigate the risk of overfitting in the machine learning model. Additionally, having a concise set of clinical features played a significant role in simplifying the clinical interpretation of the results, focusing attention on the most informative and relevant clinical features [19]. Therefore, the feature selection process involved two main steps: relevance analysis, as outlined in reference [20], and Elastic Net-based Feature Ranking, as described in reference [21].

According to Foster et al. [19], in the second stage of our feature selection process, we adopted a feature removal strategy. This approach was used to further reduce the number of features, in line with the rule of thumb that suggests having at least 10 times as many data points as there are features in the model. For example, in linear models, the number of parameters corresponds to the number of input features, with each feature being assigned a parameter, as described by Foster et al. [19].

The relevance analysis performed by Wilcoxon Signed-Rank Test and aimed to identify the features changing more significantly among PH and non-PH. All the features changing significantly between PH and non-PH (p-value less than 0.05) were selected at this stage.

The second stage focused on Elastic Net-based Feature Ranking, which is a regularization technique that introduces a linear L2 penalty to address the shortcomings of the Least Absolute Shrinkage and Selection Operator (LASSO). The Elastic Net method calculates feature weights while simultaneously conducting feature selection by assigning a weight of zero to most irrelevant or redundant features. To determine the penalty parameters, a K-fold cross-validation was performed on the training dataset. Features were then ranked in descending order based on their importance scores.

2.8. Risk score model

The chosen features were utilized to both train and validate an Elastic-Net Regularized Generalized Linear Model, from which a risk score was developed.

For the implementation of the Elastic Net (EN) model, we employed the "glmnet" method available in the "caret" package [22,23] within the R programming environment (version 3.6.0, http://www.r-project.org/

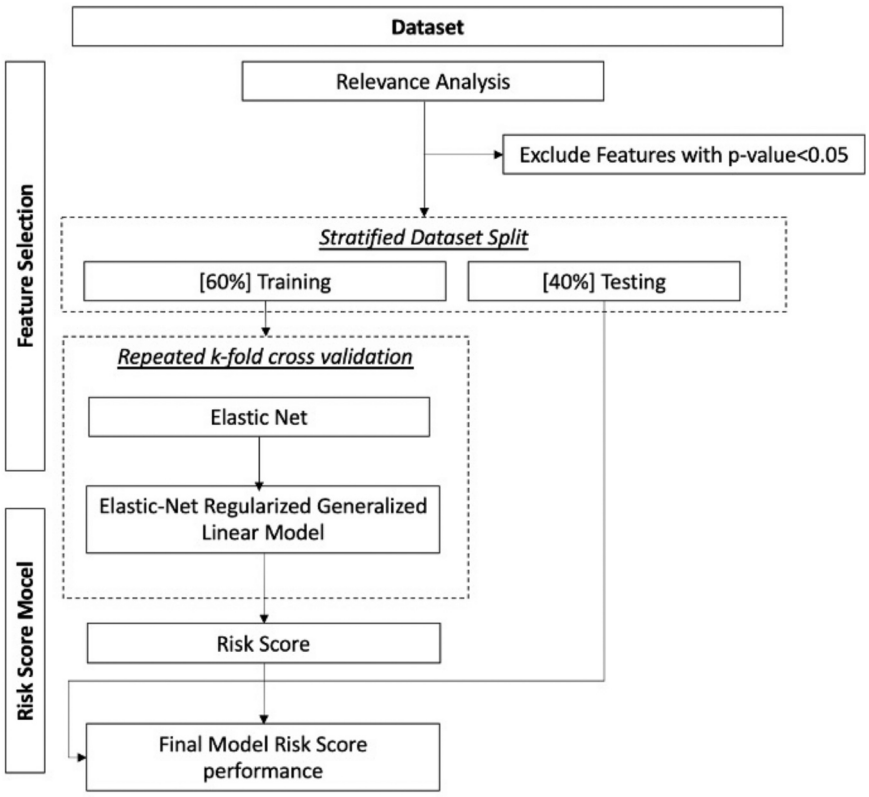

Fig. 1. : Framework of machine learning.

). During each training of the EN model, we conducted a grid-search to fine-tune both α and λ parameters.

To elucidate, feature selection and training of the machine learning model, which encompassed tuning classifier parameters, were performed on a subset consisting of 60 % of the total patient population. This training data was further employed to validate the classifier's performance through k-fold cross-validation. Specifically, we adopted a repeated 3-fold person-independent cross-validation approach to validate the model's effectiveness. Subsequently, the model underwent testing on an independent dataset, comprising approximately 40 % of the total patient population. This test aimed to assess the model's capacity to automatically identify PH patients.

The "risk score" of the model was obtained through regression analysis and serves as a threshold value that signifies the risk of PH. The determination of the cut-off points for risk probability scores was guided by test characteristics. Specifically, the cut-off was established as the median value derived from the distribution of probability plots in the test set.

2.9. Ethics

The study was conducted in accordance with the Declaration of Helsinki and its amendments, followed the International Conference on Harmonization Guideline for Good Clinical Practice, and was approved by local institutional review boards/ethics committees. All patients gave informed consent to the study which complied with the Declaration of Helsinki and was approved by the Institutional Review Board of Monaldi Hospital (protocol n. 4/18) and founded by an institutional grant from the Italian Ministry of Healthcare (GR-2016–02364727).

3. Results

3.1. Patient characteristics

From October 2017 until October 2020, a total of 226 patients were enrolled into the study at Ospedale dei Colli. Out of 226 PAH patients recruited, 168 were female (74,3 %) and 58 (25,7 %) were male (Table 1 and Table S1). For each recruited patient anamnestic data were collected, 6MWD, Spirometry and TTE. All recruited patients underwent RHC for definitive diagnosis of PH. Out of 226 recruited 143 had PH at RHC and 107 of them were female (74.8 %). Baseline characteristics of the cohort are displayed in Table 1. As shown in Table 1, smoking habit, LUPUS, TRV, systemic sclerosis, pulmonary thromboembolism, dilated left and right atrium and dilated right ventricle showed to be statically different between no PH and PH patients (p-value<0.05). On the other hand, Supplementary Table 2 (Table S2) shows all baseline characteristics that were not statistically different between the two groups. Moreover, one of the most widely used parameters by TTE in the evaluation of patients with suspected PH is Tricuspid regurgitation velocity (TRV) [24]. ESC/ERS guidelines recommend grading the probability of PH based on tricuspid regurgitation velocity (TRV) at rest as low (≤2.8 m/s) [25] but as demonstrated by Marra and co-workers in 2018 the cut-off for the risk evaluation of PH should be lowered to 2.55 m/s [26]. Therefore, based on TTE data we have derived TRV and established a TRV threshold at 2.55, which resulted in a statistically significant difference between the two groups of patients.

Most of the continuous variables were non-normally distributed; therefore, non-parametric test was employed (Wilcoxon sign rank test). As shown in Table 2, weight, RV1 and area of left atrium showed to be statistically different (p-value<0.01) between the two groups of patients and have lower values in no PH patients compared to PH patients. Whereas EF showed a statistically significant decrease in PH patients (p-value<0.05).

Table 1
Baseline cohort characteristics statistically different between PH and no PH patients.

Variables	*no PH*	*PH*	*p-values*
Smoking Habit, n (%)			**0.04**
No	73 (88)	109 (76)	
Yes	10 (12)	34 (24)	
Hepatic cirrhosis, n (%)			0.09
No	83 (100)	137 (96)	
Yes	0 (0)	6 (4)	
TRV Threshold			**0.01**
<2.55 (m/s)	6 (7)	29 (20)	
> 2.55 (m/s)	77 (93)	114 (80)	
LUPUS, n (%)			**0.03**
No	83 (100)	134 (94)	
Yes	0 (0)	8 (6)	
Systemic Sclerosis, n (%)			**0.009**
No	52 (63)	113 (79)	
Yes	31 (37)	30 (21)	
Deep Venous Thrombosis, n (%)			0.09
No	81 (98)	131 (92)	
Yes	2 (2)	12 (8)	
Pulmonary thromboembolism, n (%)			**0.04**
No	76 (92)	116 (81)	
Yes	7 (8)	27 (19)	
Dilated right atrium, n (%)			**<0.001**
No	44 (75)	39 (41)	
Yes	15 (25)	57 (59)	
Dilated right ventricle, n (%)			**<0.001**
No	67 (82)	54 (39)	
Yes	15 (18)	85 (61)	
Dilated left atrium, n (%)			**0.1**
No	45 (54)	53 (38)	
Yes	38 (46)	87 (62)	

TRV: Tricuspid Regurgitation Velocity; In bold, P-values less than.05

3.2. Machine learning classification

The data were stratified split into 60 % training (N = 138, 42 noPH vs 96 PH) and 40 % testing (N = 88, 41 noPH vs 47 PH). By using the whole dataset, we started our feature significance analysis utilizing relevance analysis (83 noPH vs 143 PH). From the relevance analysis, 12 features showed a p-value less than 0.05.

In the subsequent phase, we utilized Elastic Net-based Feature Ranking to further reduce the number of features. This process involved applying Elastic Net-based Feature Ranking to the training set, and we also employed a repeated 3-fold cross-validation approach. As per the results obtained from Elastic Net-based Feature Ranking, we identified 10 radiomic features that were potentially predictive. However, in alignment with the guidance provided by Foster et al. [19], considering the limited number of patients in our study, we adhered to the principle of using no more than one feature for every ten "observations/subjects" associated with the outcome of interest. Therefore, we selected the initial 8 features (Smoker, Pulmonary Embolism, TRV, dilated right ventricle, dilated left atrium, Systemic Sclerosis, area of left atrium Weight) for model development. The hyperparameters of Elastic-Net Regularized Generalized Linear Model were tuned during the training and validation. The optimized parameters were alfa= 0 and lambda= 0.77.

The final model was then tested on a dependent set of data considering the selected 8 features and performance are reported in Fig. 2. bThe model achieved an AUC of 83 % [95 % CI(63 %−84 %)] with 95 % CI sensitivity (65 %−94 %), 95 % CI specificity (53 %−83 %) and an overall accuracy of 74 % [95 % CI (61 %, 84 %)], compared with an overall accuracy of 73 %, sensitivity of 63 % and specificity of 84 % and ACC of 73 % for training ste.

The model risk score is presented in Eq. (1).

Table 2
Comparison of continuous variables between no PH and PH patients.

Variables	No PH		PH		
	N	Mean ± SD	N	Mean ± SD	P-value
Age (years)	83	65.2 ± 14.8	143	65.2 ± 13.6	0.8
Weight (Kg)	**79**	71.2 ± 18.7	**143**	75.5 ± 16.1	**0.04**
Height (cm)	79	163.1 ± 8.2	143	164.6 ± 9.1	0.3
6MWD (m)	70	320.5 ± 136.8	126	314.5 ± 153.3	0.7
TAPSE (mm)	83	22.1 ± 5.6	143	21.1 ± 6.1	0.2
PASPs eco (mmHg)	83	55.2 ± 20.7	143	54.7 ± 22.6	0.9
TAPSE_PASPs (mm/mmHg)	83	0.5 ± 0.2	143	0.5 ± 0.3	0.6
EF(%)	**83**	56.9 ± 7.7	**143**	55.1 ± 8.7	**0.03**
SIV (mm)	82	9.8 ± 1.5	143	10.1 ± 1.8	0.1
IVC (mm)	83	17.6 ± 5.2	143	17.7 ± 5.4	0.7
RV1	**29**	38.8 ± 7.8	**94**	44.4 ± 8.0	**0.001**
RV2	18	38.9 ± 10.3	86	38.9 ± 8.4	1
RV3	18	67.5 ± 8.8	85	72.1 ± 10.4	0.08
RA (mm)	11	35.2 ± 32.1	43	25.1 ± 6.9	0.5
LA (mm)	**72**	40.4 ± 5.7	**125**	42.6 ± 6.6	**0.009**
VSTD (mm)	51	47.2 ± 5.3	77	48.8 ± 8.3	0.1
VSTS (mm)	33	30.2 ± 5.1	51	30.8 ± 5.9	0.7
PW (mm)	50	9.3 ± 1.4	76	9.7 ± 1.5	0.3
AoR (mm)	48	30.8 ± 3.4	70	31.3 ± 3.6	0.5
E/e'	40	9.3 ± 3.9	54	8.6 ± 3.5	0.3
PAAT (msec)	34	111.3 ± 19.9	41	103.5 ± 26.6	**0.05**
TRV (m/s)	83	3.3 ± 0.7	142	3.2 ± 0.9	0.9

6MWD: six minutes walking distance; TAPSE: tricuspid annular plane systolic excursion; PASPs: pulmonary arterial systolic pressure; SIV: interventricular septum; IVC: Inferior vena cava; RV1: right ventricular basal-diameter; RV2: RV mid-diameter; RV3: RV longitudinal diameter; RA: right atrial; LA: left atrial; VSTD:Diastolic LV internal dimension; VST: Systolic LV internal dimension; PW: Posterior Wall; AoR: Aortic root; PAAT: Pulmonary artery acceleration time; TRV: Tricuspid Regurgitation Velocity; SD, standard deviation. In bold, P-values less than.05.

$$y \sim 1{\cdot}14 + 0{\cdot}29 * \text{Smoker} + 0{\cdot}59 * \text{Pulmonary Embolism} - 1{\cdot}61 * \text{TRVthresh} + 2{\cdot}61 * \text{dilated right ventricle} + 0{\cdot}53 * \text{dilated left atrium} - 1{\cdot}08 * \text{Systemic Sclerosis} + 0{\cdot}02 * \text{area of left atrium} + 0{\cdot}01 * \text{Weight} \quad (1)$$

The cut-off was chosen as the median of the distribution. The cut-off to automatically detect PH patients was 2.155 [95 % CI 1.99–2.77].

TRV

The same model was also trained and tested with one input variable: TRV. TRV measured through echocardiography has become a valuable, non-invasive diagnostic tool for assessing the likelihood of pulmonary hypertension (PH). Increased TRV can be an indicator of elevated pulmonary artery pressures, which is a hallmark of PH. Therefore, to show that the presented model risk score has better discrimination power compared to the use of the exclusive TRV measurement, we have performed an additive model risk score using only TRV and have presented the results in Fig. 3. As shown in Fig. 3 (A), AUC is much lower at 56 % [95 % CI (53 %−58 %)] with 95 % CI sensitivity (49 %−56 %), 95 % CI specificity (45 %−52 %) than the AUC reported for the model risk score (Fig. 2 (A)). In fact, by employing only TRV, we can automatically discriminate PH patients with only 50 % accuracy vs 74 % accuracy if we consider a linear combination of different variables (Eq. 1). In other words, the model in Fig. 3 is performing no better than random chance. An accuracy of 50 % suggests that the model is not able to distinguish between classes or make meaningful predictions on the task at hand.

4. Discussion

To our knowledge, this study was the first to evaluate the implementation of a machine learning-based model for PH risk assessment in a primary care setting. This ground-breaking approach has the potential to significantly enhance patient outcomes and mitigate healthcare costs associated with the management of PH. The key finding of the current study were i) a machine learning-derived algorithm exhibits superior diagnostic accuracy when compared to the conventional TRV peak-derived sPAP method for diagnosing PH and ii) the diagnosis of PH can also be obtained with a good percentage of confidence from the analysis of non-invasive tests.

PH diagnosis is challenging, as it typically requires invasive measurement by RHC. RHC is a highly specialized procedure that requires sophisticated equipment, trained personnel, and a hospital setting. This makes it expensive, with costs including not only the procedure itself but also pre-procedure assessments, post-procedure monitoring, and potential hospital stays. In many healthcare systems, especially those with limited resources, the high-cost limits widespread access to RHC its use [2,27]. Moreover, unlike non-invasive diagnostics such as echocardiography, RHC is an invasive procedure that involves threading a catheter through the veins into the right side of the heart and pulmonary arteries. This introduces risks such as infection, bleeding, arrhythmias, and, in rare cases, more severe complications like cardiac perforation. For patients with comorbidities or advanced disease, these risks may outweigh the benefits, leading clinicians to avoid or delay the procedure [2,27]. Another aspect not to be neglected is the accessibility. RHC is typically available only at specialized centers, often in urban or academic settings. In rural or underdeveloped regions, patients may lack access to the facilities or specialists needed to perform the procedure. This limits its availability for early diagnosis and regular monitoring of PH patients. Moreover, even if recommended by a physician, the idea of undergoing an invasive heart procedure may cause significant anxiety,

A

Performance	Values
Sensitivity	68%
Specificity	80%
Pos Pred Value	81%
Neg Pred Value	66%
Accuracy	74%
AUC	83%

B

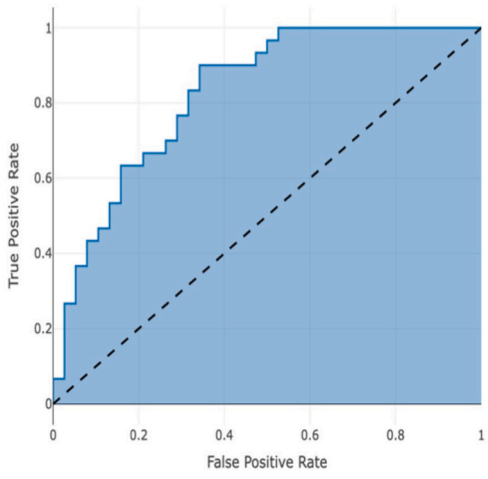

Fig. 2. Model performance, performance of the binary naïve model on the testing set employing 8 features. A) Binary performance; B) ROC curve.

A

Performance	Values
Sensitivity	52%
Specificity	49%
Pos Pred Value	62%
Neg Pred Value	39%
Accuracy	50%
AUC	46%

B

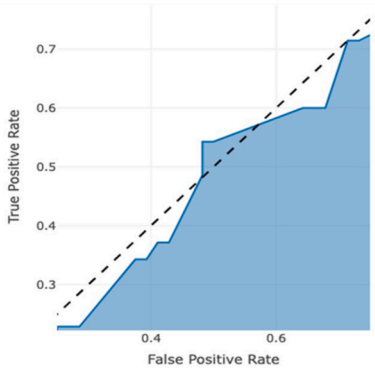

Fig. 3. : Model performance with TRV, Performance of the binary naïve model on the testing set for TRV feature. A) Binary performance; B) ROC curve.

leading some patients to refuse or delay it. And last but not least this may lead to unacceptable delays in diagnosis, which is associated with poorer outcomes [28]. Due to its peculiarity, only RHC as gold standard for diagnosis, there will probably be a delay from symptoms to the effective diagnosis, which will have a major negative impact on prognosis benefit [28].

Routinely screening of PH relies mainly on TTE results and particularly on measurement of the TRV parameter [29], which largely depends on the operator's skill and experience [29]. TRV is the key parameter to screen population at risk of having PH, according to ESC/ERS guidelines [6]. The accuracy of TRV measurement depends on the presence of a measurable tricuspid regurgitation jet. In some patients, particularly those with mild or absent regurgitation, it can be challenging or impossible to obtain reliable TRV values. This limits the utility of TRV in diagnosing PH in patients without significant TR, requiring other markers or invasive measures like RHC for confirmation. TRV is not the only possible measurable parameter that can be obtained from TTE but when comparing TTE estimated systolic Pulmonary arterial pressure (sPAP) with other echo-derived parameters such as pulmonary insufficiency (PI) gradients and right ventricular outflow tract acceleration time (RVOT-AT), several aspects come into play must be considered, particularly specifically in terms of accuracy, feasibility, and limitations, especially in patients with suboptimal acoustic windows [30]. Indeed, TTE-derived sPAP may face challenges in patients with suboptimal acoustic windows, such as those with chronic obstructive pulmonary disease (COPD), obesity, or prior chest surgeries. These conditions can limit visualization of cardiac structures and affect Doppler signal acquisition. In such cases RVOT-AT offers an advantage because it can often be measured even when tricuspid regurgitation is poorly visualized, making it a more reliable marker of pulmonary pressures in patients with suboptimal windows [31]. Moreover, PI gradients can also be a useful secondary measure if pulmonary regurgitation is present, though it depends on clear Doppler signals, which may be hindered by poor acoustic windows.

This study assessed the utility of a machine learning-based approach in patients belonging to high-risk categories in developing PH. Patients at high risk of developing pulmonary hypertension (PH) often have certain predisposing conditions or genetic factors that increase their likelihood of pulmonary vascular disease. Systemic sclerosis, in particular, has a well-documented association with PH, likely due to vascular changes in the lungs that arise from the autoimmune and inflammatory processes in these diseases [29]. Patients in these high-risk groups often benefit from routine monitoring and early screening for PH, as early detection and management can significantly improve outcomes and quality of life. However, diagnosis of PH in high-risk groups presents unique challenges due to overlapping symptoms, complexities of underlying conditions, and the limitations of non-invasive diagnostic tools. Overall, a combination of overlapping symptoms, complex disease presentations, and limitations in non-invasive diagnostics complicates early and accurate PH diagnosis in high-risk groups. Improved screening strategies and multidisciplinary approaches are needed to identify PH earlier in these populations. Indeed, the diagnosis of PH made in our study group using only the canonical noninvasive tools, in particular relying solely on TTE, would provide precise results in just half of the cases. However, the utilization of an integrated model, such as ours, enhances accuracy to 80 % of cases.

Several models have already been presented with the ability of discriminating PH patients [32–34] but they either are focused on a specific subgroup of PH such as PAH [35], [39] or have been applied to a single test [7,32] such as the DETECT study, which is a large, multicenter, real-world, cross-sectional study. This was the first PAH detection study aimed at the development of an evidence-based algorithm using simple clinical data and non-invasive tests for earlier identification of PAH in a mildly symptomatic population. The DETECT algorithm was highly sensitive in the recognition of PAH patients in a cohort of SSc patients. However, the DETECT algorithm was not developed to identify other forms of PH. Indeed, the application of the DETECT algorithm to the total PH population missed 19 % of WHO group 2 PH patients and 37 % of WHO group 3 PH patients, both of which are common in SSc [35].

Another example is that of Kogan et al.'s study who presented a ML approach able to predict PH based on information in Optum's US-based de-identified dataset (2007–2019) [34]. Indeed, this study showed that by working on patient records alone it was possible to make a good approximation of the diagnosis in subgroups of patients with PH, providing the potential to improve patient outcomes by reducing the diagnostic delay in PH [34]. This study underscores the value of integrating ML with large, longitudinal health records to create predictive models that assist in early diagnosis and risk stratification for complex diseases like PH.

The uniqueness of our model our model is that it was able to correctly distinguish between patients with PH and those without PH at diagnosis in cohort of patients who had all clinical indications to undergo RHC. This result was even more evident when comparing our model risk score with the one obtained from the model risk score obtained using the only TRV peak-derived sPAP method, which is the canonic non invasive method used to screen patients who will undergo RHC. Our model is clearly more specific and more sensitive when compared to the canonical non invasive screening method and a possible explanation for that finding is that PH can stem from various underlying conditions. Therefore, its complexity requires an evaluation that cannot be satisfied only by a single technique or measurement of a single parameter. Therefore, our analysis offers meaningful clinical implications for managing pulmonary hypertension (PH) and optimizing healthcare resources. Certainly, speed up diagnosis time may lead to better prognostic stratification and consequent better use of resources to identify subgroups of

patients who need more aggressive therapies and approaches. This approach could be a great support particularly in two specific forms of PH, pulmonary arterial hypertension (PAH) and the thromboembolic form (CTEPH). Detecting PAH and CTEPH in their early stages can be very challenging due to nonspecific symptoms and subtle initial presentations. An advanced version of our prototype might make a significant impact on patient care, enabling an early, targeted and efficient response to complex pulmonary vascular conditions since there are specific, targeted therapies for these PH subtypes.

5. Limitations

This is an observational retrospective, nonrandomized, single-center study representative of a cohort of adult patients belonging to classes at high risk of developing PH who came to the "Ospedale dei Colli" to assess the eventual progression of the disease. Consequently, the recruited patients did not undergo specific interventions for our protocol but followed the standard diagnostic procedure already provided by international guidelines. Indeed, all recruited patients underwent RHC as normally expected. Our ML model was applied using all data available to the clinician prior to RHC and therefore non-invasive. One of the major limitations of our study is the limited and unbalanced number of patients recruited for each class. Moreover, our model is based on the measurement of TRV, and considering the aforementioned caveats this limits the performance of our model. However, our work strived to propose a prototype that might be remodelled on a much larger and heterogeneous court and other parameters such as right ventricular outflow tract acceleration time (RVOT-AT) and/or pulmonary insufficiency gradients may be used as an alternative to TRV.

In our study group of 226 subjects, we had TRV measurements for 225 patients, with 108 of these showing TRV values between 2.7 and 3.4 m/s. Given the pilot nature of this study and the limited sample size, calculating standalone performance metrics (sensitivity and specificity) for TRV at the specific thresholds of 2.55 m/s (rule-out) and 3.4 m/s (rule-in) would be challenging at this stage, as it could result in less reliable metrics due to small subgroup numbers. Therefore, we intend to conduct a more comprehensive analysis in a future study with a larger cohort. This will allow us to better assess the standalone performance of TRV thresholds independently and to make a more robust comparison with our model.

Recognizing that findings from a limited sample size cannot be generalized, upcoming research will confirm the findings from this initial study on a larger data pool. Nonetheless, we have implemented various methodological approaches to address this concern. In fact, we utilized conventional machine learning techniques, which have lower computational complexity compared to more advanced ML algorithms, resulting in fewer parameters to train and minimizing overfitting. Moreover, to counter the limited number of patients in the study, we employed no more than 1 feature for every 10 patients to develop the models. Finally, we balanced the dataset using synthetic samples and we conducted repeated cross-validation to ensure the reliability of the results and reduce overfitting.

6. Future directions

This study represents a pilot analysis, and we recognize the importance of validating our model on larger datasets to enhance its robustness and reproducibility. As a future direction, we plan to conduct a more extensive assessment of the model's performance across specific subgroups within PH and PAH, including gender, ejection fraction (EF), body mass index (BMI), and TRV risk categories. We believe that examining potential performance differences among these subgroups could yield insights with important clinical implications.

By explicitly exploring subgroup variations, we aim to further the model's clinical relevance and applicability, ensuring that it can serve as a reliable tool across diverse patient populations. We have revised the manuscript to outline this future direction.

7. Conclusion

In conclusion, current AI research is still in the early stages, but accumulating evidence suggests that AI-guided research allows researchers to explore novel risk factors contributing to the pathogenesis and pathophysiology of several pathologies especially in what regards cardiovascular pathologies and could represent the missing link in obtaining early diagnosis for events that in other cases could be fatal [36]. Furthermore, the use of artificial intelligence for the management of large amounts of data could be helpful with risk stratification and follow-up of specific patients more accurately. Currently, our machine learning-based approach was effective in evaluating patients belonging to high-risk categories for PH. Indeed, with a good approximation, it was able to recognize patients with the disease compared to patients with normal pressures in the pulmonary circulation.

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Author statement

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Antonio Cittadini: Supervision. **Paola Argiento:** Supervision, Project administration, Investigation. **Davide Lepre:** Visualization. **Erica Maffei:** Data curation. **Alessandra Schiavo:** Visualization, Supervision. **Valeria Valente:** Writing – review & editing. **Lavinia Saldamarco:** Supervision. **Ekkehard Grünig:** Resources, Investigation. **Matteo Mazzola:** Methodology, Data curation. **Alberto Maria Marra:** Supervision, Project administration, Investigation. **Monica Franzese:** Writing – review & editing, Data curation, Conceptualization. **Luna Gargani:** Visualization, Supervision. **Rossana Castaldo:** Writing – original draft, Formal analysis. **Eduardo Bossone:** Visualization, Supervision. **Anna D'Agostino:** Writing – review & editing, Writing – original draft, Project administration, Data curation, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.csbj.2024.11.031.

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