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Predicting 6-minute walking test outcomes in patients with chronic obstructive pulmonary disease without physical performance measures

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ABSTRACT

Background and Objective: Chronic obstructive pulmonary disease (COPD) requires a multifactorial assessment, evaluating the airflow limitation and symptoms of the patients. The 6-min walk test (6MWT) is commonly used to evaluate the functional exercise capacity in these patients. This study aims to propose a novel predictive model of the major 6MWT outcomes for COPD assessment, without physical performance measurements.

Methods: Cardiopulmonary and clinical parameters were obtained from fifty COPD patients. These parameters were used as inputs of a Bayesian network (BN), which integrated three multivariate models including the 6-min walking distance (6MWD), the maximum HR (HR_{max}) after the walking, and the HR decay 3 min after (HRR_3). The use of BN allows the assessment of the patients' status by predicting the 6MWT outcomes, but also inferring disease severity parameters based on actual patient's 6MWT outcomes.

Results: Firstly, the correlation obtained between the estimated and actual 6MWT measures was strong ($R = 0.84$, MAPE = 8.10% for HR_{max}) and moderate ($R = 0.58$, MAPE = 15.43% for 6MWD and $R = 0.58$, MAPE = 32.49% for HRR_3), improving the classical methods to estimate 6MWD. Secondly, the classification of disease severity showed an accuracy of 78.3% using three severity groups, which increased up to 84.4% for two defined severity groups.

Conclusions: We propose a powerful two-way assessment tool for COPD patients, capable of predicting 6MWT outcomes without the need for an actual walking exercise. This model-based tool opens the way to implement a continuous monitoring system for COPD patients at home and to provide more personalized care.

1. Introduction

Chronic respiratory diseases are among the most common diseases associated with high morbidity and premature mortality in the adult population. In particular, chronic obstructive pulmonary disease (COPD) represents the fourth leading cause of death worldwide [1] COPD is characterized by progressive airflow limitation, resulting in shortness of breath and the patients often experience a sudden worsening of symptoms, also known as an exacerbation. The clinical condition of COPD patients is rather complex and requires a multidimensional assessment. This usually includes lung function test, as well as several questionnaires to evaluate the symptoms, the impact of the disease on the patients' quality of life, and the risk of future events [2].

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The 6-minute walk test (6MWT) is a simple and standardized tool that is commonly used to assess the functional exercise capacity of patients with chronic respiratory diseases [3]. The outcomes of the 6MWT include the total distance walked by the patient (6MWD), as well as other relevant cardiopulmonary parameters such as the heart rate (HR), and the oxygen saturation level (SpO_2 measured before and after the test). The 6MWD is considered the main clinical outcome from the test, which correlates with physical activity measures from other tests such as the incremental shuttle walk test [4,5] and has been associated with increased risk for hospitalization and mortality in COPD patients [6,7]. The most common models used to estimate the distance involve patients' physical characteristics such as age, height, and weight [8,9]. However, these models may not properly estimate the 6MWD in COPD patients and additional potential modulators are needed. The accurate prediction of the 6MWD can provide a more precise estimation of the medical condition and functional exercise performance of the patients.

Although the guidelines for the 6MWT state the measurement of HR and SpO_2 as optional [10], these outcomes are commonly recorded and have proven to be relevant markers about the patients' condition [7,11–13]. In particular, the heart rate recovery (i.e., the rate of decrease in HR after the walk cessation) has been suggested as a valuable predictor of worsening and mortality in patients with respiratory diseases [11–13]. In addition, the heart rate values measured at different stages of the test can potentially contribute to describe the 6MWD [14]. More recent studies also included parameters regarding the influence of the test intensity represented as the variation of HR [15–17]. Therefore, it can be concluded that not only the 6MWD provides clinically valuable information, but also other relevant outcomes should be considered to allow a more comprehensive assessment of the patients' functional status and progression.

Recently, the use of Bayesian Networks (BNs) for medical applications represents a field of great interest [18], because of the interpretability of the resulting models, avoiding the limitations of black box models. BNs can effectively deal with decision-support models for complex clinical problems, in which multiple factors are interacting. Among its advantages, BNs offer a powerful framework to combine evidence from different sources. For instance, clinical knowledge and published evidence obtained from meta-analyses can help to design the network structure [19], while the parameters can be learned from data using even small datasets. In particular, Bayesian approaches have been used in COPD patients to predict disease severity from clinical parameters [20,21] as well as its association with mortality and patient's quality of life [22]. Based on these premises, we used the power of BNs to integrate different multivariate models that can predict the main 6MWT outcomes under uncertainty and unobserved variables. The network should combine symptoms and clinical parameters, measures of respiratory functional capacity, and cardiovascular function obtained in COPD patients.

In general, parameters obtained from a 6MWT provide valuable prognostic information about COPD patients. However, the test is performed only once or a few times per year in most cases. Since changes in patient's status can occur any time between these measurements, a continuous monitoring system able to predict major 6MWT outcomes would have a clinically relevant impact. Concretely, the present study aims to propose a novel predictive regression model for major 6MWT outcomes (such as distance and HR recovery), using anthropometric information, clinical parameters such as measures of pulmonary function and HR indices derived from data acquired during rest. Different regression models were integrated into a multivariate BN, enabling the prediction of all relevant outcomes simultaneously. Likewise, it also allows to make inferences about the progression of a patient's functional status, by updating any change that occurs in the patient's clinical variables or the outcomes derived from the 6MWT. The final model could serve to reinforce the home-monitoring of COPD patients by tracking relevant parameter changes over time. Its potential application in a digital healthcare system will enable a more personalized assessment of the patients' status on a daily basis.

Table 1
Demographic and anthropometric data for the study population.

Clinical characteristics	$n = 46$
Male (Female)	34 (12)
Age, yr	65.00 (60.00 - 69.00)
Height, cm	169.50 (164.00 - 178.00)
BMI, kg/m^2	24.85 (22.27 - 29.04)
Smoker, n (%)	
Current smoker	9 (19.57)
Former smoker	37 (80.43)
Comorbidities, n (%)	43 (93.48)
Asthma	10 (21.74)
Lung cancer	9 (19.57)
Cardiovascular disorders	14 (30.43)
Obstructive sleep apnea syndrome	8 (17.39)
6MWD, m	435 (370 - 498)
FVC% pred	86.45 (72.20 - 110.90)
FEV_1% pred	52.15 (42.80 - 68.60)
$80\% \leq FEV_1\%$ pred, n (%)	5 (10.87)
$50\% \leq FEV_1\%$ pred $< 80\%$, n (%)	20 (43.48)
$30\% \leq FEV_1\%$ pred $< 50\%$, n (%)	18 (39.13)
$FEV_1\%$ pred $< 30\%$, n (%)	3 (6.52)

The data are presented as median (first - third quartile) and in the case of grouping, as the number and percentage of patients. BMI: body mass index; FVC: forced vital capacity; FEV_1: forced expiratory volume in one second.

2. Methods

2.1. Sample population and experimental protocol

Fifty COPD patients were recruited during their consultation at Ziekenhuis Oost-Limburg (Genk, Belgium). The institutional medical ethics committee from Ziekenhuis Oost-Limburg approved the study (reference 18/0047 U). The study follows the World Medical Association of Helsinki on Ethical Principles for Medical Research Involving Humans Subjects. All subjects were diagnosed with COPD before study inclusion and provided written informed consent prior to study participation. The exclusion criteria applied to the patient's recruitment were: younger than 18 years old, inability to give informed consent, no previous consultation or rehabilitation sessions, pregnant women, suffering from cognitive diseases and being unable to perform the experiment. The protocol included three phases, a five-minute resting phase, a walking phase, and a five-minute recovery phase. During the resting and recovery phases, the patients were seated in a wheelchair. The walking phase consisted of the execution of the 6MWT by the patients. During the test, the patients were asked to walk as far as possible along a 45-meter corridor for six minutes [10], while none of them used supplementary oxygen during the walk. The distance was measured as the total number of laps completed by the patients along the corridor plus the meters of the last non-completed lap.

Anthropometric data and spirometry parameters were collected for each patient by a clinical technician as well as relevant clinical information from the patient's record. A summary of the main clinical parameters is listed in Table 1. In particular, the spirometry parameters comprised the most commonly used parameters in COPD patients, the forced vital capacity (FVC), the forced expiratory volume in one second (FEV_1), and the ratio between these parameters (FEV_1/FVC). All these parameters expressed as a per-

centage of the predicted value for a healthy person with similar anthropometrics measures.

2.2. Physiological data

At the end of the resting phase and shortly after the walking phase, the peripheral capillary oxygen saturation (SpO_2) and the heart rate (HR) were measured by a pulse oximeter (Model 3230, Nonin Medical Inc.). The patients were also asked to score their level of dyspnea and fatigue, using the modified Borg scale (mBorg) [23] before and after exercise.

Electrocardiogram (ECG) was recorded during the entire resting and recovery phases. The ECG recording was continuously measured using lead II by a wearable prototype device (Stichting imec the Netherlands) using Ag/AgCl electrodes (Kendall H92SG, Covidien Inc.). The ECG signals were sampled at 512 Hz.

2.3. Extraction of HRV indices from ECG

The R-peaks from the ECG signals were detected using a wavelet-based technique, using the resampled signal at 500 Hz by spline interpolation [24], followed by manual rejection of misdetections and ectopic beats after visual inspection. The selection of only normal heartbeats aimed to obtain normal-to-normal intervals (NN intervals) from the RR time series before any further processing. This correction step was performed by a trained/specialized researcher. The RR intervals were computed by the time differences for each pair of R detections to get the RR time series. All the RR time series were selected to have the same length, 255.75 s, and 322.25 s, for the last part of resting and the first part of recovery phases, respectively.

The series of RR intervals were used to compute classical heart rate variability (HRV) indices which provide information about different aspects of the cardiovascular system, like autonomic regulation or adjustment. In particular, we computed time-domain, frequency-domain, and non-linear HRV indices only for the resting phase where stationarity in the RR time-series is guaranteed.

2.3.1. Time-domain HRV indices

We computed Standard Deviation of NN intervals (SDNN), the Percentage of successive NN intervals that differ by more than 50 ms (pNN50), and the Root Mean Square of Successive NN interval Differences (RMSSD) [25].

2.3.2. Frequency-domain HRV indices

Before computing the frequency HRV indices, we applied cubic spline interpolation to the NN time series to 4 Hz to get a uniform sampling. The spectral density of the series was estimated by the Welch periodogram of the resampled NN series using windows of 64 s. The frequency-domain indices consisted of the absolute and normalized energy of the time series in different frequency bands. Particularly, we computed the energy in the low-frequency band between 0.04 and 0.15 Hz (LF) and the energy in the high-frequency band, between 0.15 and 0.40 Hz (HF). The former reflecting sympathetic and the latter the parasympathetic activity of the nervous system [25]. The LF and HF indices were divided by the sum of the two energy bands to get also normalized indices (nLF and nHF). Moreover, the ratio between LF and HF energy was calculated (HF/LF).

2.3.3. Non-linear index

The non-linear index was a common HR fragmentation index computed as the percentage of inflection points (PIP) of the NN time series, that is the percentage of zero-crossing points in the first derivative of the NN series [26].

2.3.4. Heart rate recovery

We analyzed the heart rate recovery (HRR) using a biexponential approach [27] applied to the NN time series of the recovery phase, after the 6MWT. In particular, we computed the decay in heart rate after the test at minute 1, 2, and 3 of recovery (HRR_1, HRR_2 and HRR_3). These decays in HR have been investigated in many studies, commonly after an exercise peak, as a predictor of cardiovascular death [28].

2.4. Modeling 6MWT outputs

The aim of the study was to implement a predictive model able to estimate relevant outputs of the 6MWT from baseline clinical information, without the need of performing the test. In particular, the 6MWT outputs to be modeled were: the total distance walked by the patient (i.e., 6MWD), the maximum heart rate achieved when completing the test (i.e., HR_{max}), and the heart rate recovery index evaluated after 3 min of the patient's recuperation (i.e., HRR_3). To estimate the 6MWT outputs, a total of 32 features (see Appendix A, Table A.1) including clinical markers of disease severity, patients' anthropometric characteristics, and HRV indices obtained during the pre-walking period were included to the initial feature space.

2.4.1. Feature selection with lasso regularization

Firstly, we modeled each 6MWT output independently before integrating them in a global model. The initial feature space served as input to a multivariate regression analysis, that includes least absolute shrinkage and selection operator (LASSO) regularization to retain the most predictive parameters [29]. This regularization technique allows to obtain sparse models and thus a better interpretation of the final outcomes.

The LASSO approach was applied individually for each 6MWT output to obtain three independent multivariate regression models which are described below. The most predictive features retained after the LASSO regularization were then used to obtain the final models, this time through ordinary least square (OLS) regression. Detailed information about this two-stage procedure can be found in Appendix A.

2.4.2. Model for estimating the walked distance

For COPD patient assessment using the 6MWT, the distance walked by the patients represents one of the most important clinical outputs beyond spirometer tests. Many studies proposed equations to empirically predict the 6MWD for healthy subjects. The following equation, including physical characteristics of the subject, is commonly used [30]

$$6MWD_{pred} = 218 + [5.14*height - 5.32*age] - [1.80*weight + 51.36*sex] \quad (1)$$

However, the above equation applies to healthy subjects and does not consider other factors associated with the patient's condition like clinical parameters, that can affect the walked distance, as it may happen in COPD patients. Therefore, apart from the covariates in Eq. (1), we introduced other factors to the model. In particular, the multivariate model included new potential features from the following categories:

1. Clinical parameters associated with the patient's diagnosis: FEV_1, FVC, FEV_1/FVC ratio, Borg-scale index
2. Parameters measured during rest and before the test: HR, HRV indices, SpO_2
3. Parameters obtained after exercise: HR_{max}

Although the maximum heart rate, HR_{max}, reached by the patient can only be measured when the test is completed, we have added it as a potentially useful variable closely related to the

walked distance. Finally, the most predictive features retained via the LASSO were used in the final 6MWD model retrained on the whole population.

2.4.3. Model for the maximum heart rate HR_{max}

Following the same procedure as for the distance model, we determined the best feature subset that explains the variance in the values of HR_{max}, using LASSO regularization. Unlike the distance estimation, only the parameters measured during the baseline period and related to the clinical status of the patient (features listed in categories 1 and 2) are considered in this model, which means that the distance walked, and the recovery heart rate were not included among the input covariates. This strategy will facilitate the further coupling of the individual models, described in later sections.

2.4.4. Model for heart rate recovery index HRR_3

In the case of the HRR_3 model, both the distance walked, and the maximum heart rate reached were used as input covariates of the LASSO procedure, in addition to the aforementioned baseline features (categories 1 and 2). It was expected that the HRR_3 marker could be influenced by both markers, especially by HR_{max}, as it is measured during the stage following the end of the test. Likewise, parameters assessed during baseline, especially those of cardiac origin, are expected to contribute significantly to the recovery response.

2.5. Coupling individual models using a Bayesian network

2.5.1. Converting individual 6MWT models into Bayesian network

Except for the HR_{max} output, the models obtained for HRR_3 and 6MWD might depend on each other and thus on certain features only known after the test execution (i.e., HR_{max}). However, if these features are unknown, the 6MWT outputs can simultaneously be estimated by coupling the previous individual models through a Bayesian network (BN). That is possible because this probabilistic approach makes it possible to infer any variable within the network, once it has been trained with the original dataset.

In general, the structure of a BN can be learned from data, or manually constructed based on expert knowledge. In this study, we designed our network by coupling the predictive models obtained previously for each 6MWT output. Therefore, we can obtain a sparse BN just focused on predicting the quantities of interest (6MWD, HR_{max}, HRR_3). Moreover, the feature selection step based on the LASSO guarantees a good trade-off between simplicity and model performance.

2.5.2. A versatile, two-way 6MWT model, using Bayesian network

The above strategy would be sufficient to predict the results of the 6MWT test. However, this solution by itself might not allow to infer, if unknown, the severity of the patients in case of knowing the results of the test.

To add this functionality to the network, we first explored which features are the most relevant to accurately predict FEV_1 values, using a similar approach as for the previous models. Then, the new relevant selected variables were included when learning the global structure of the network as new observed nodes, without affecting the previous models obtained for the 6MWT outputs. For this step, the global structure of the network was designed by fixing some arcs according to the sparse models obtained for each 6MWT output, while other relevant arcs or relationship between the input variables including the FEV_1, were learned from data using the Hill-Climbing (HC) learning algorithm [31,32].

At this point, the global Bayesian network would also permit the prediction of disease severity based on the 6MWT outputs and other inputs, that is, running the model in reverse to predict an unknown input by the observed outputs. All the above is possible because the information can flow in any direction in BNs, depending on which variables are observed or unknown [33]. Therefore, we developed a unified global model to estimate the outputs of the 6MWT based on the baseline parameters, or to predict disease severity after the execution of the test if unknown for a particular patient. A global overview of this versatile tool is illustrated in Fig. 1.

2.5.3. Parameter learning

After the definition of the network structure (final variables and arcs), the next step was to estimate the network parameters. This step can be performed automatically for the entire network using the maximum likelihood estimator (MLE), which is equivalent to apply linear regression for continuous nodes [34]. However, the parameters can also be defined manually, by setting the node coefficients obtained from the LASSO or any other regularization technique, while root nodes (i.e., nodes without parents) are fixed with the distribution parameters of their associated continuous variables. In this work, we used the MLE method, since the LASSO was mainly applied for feature selection. Once the parameters of the BN are learned, it is possible to generate new random synthetic observations from the conditional distribution of the nodes, conditional on the evidence. The simulations are performed using an approximate inference algorithm (logic sampling) based on Monte Carlo particle filters [33]. This allows, for instance, to generate more representative samples for those patient groups with fewer cases. Consequently, a more balanced dataset can be obtained and used to retrain the network, thus improving its robustness and accuracy.

2.6. Model assessment and validation

The metrics used to assess the performance of individual models included root mean squared error (RMSE) and predictive correlation (R), while for model selection we applied leave-one-out cross-validation. The RMSE and R were used for the prediction of continuous variables represented by the 6MWT outputs. In the case of FEV_1, we aimed to predict which group each patient belonged to, rather than estimating the absolute values of FEV_1. Therefore, the overall performance was estimated by the weighted accuracy (Acc) metric, representing the average accuracy over all classes, considering the fraction of correct predictions in each class. Different grouping strategies were also applied when assessing the model accuracy, in order to get more balanced data among severity groups. It was achieved by merging some of the initially defined four groups ($G = 4$), thus generating fewer groups ($G = 3$ and $G = 2$). The reason for these strategies was the reduced number of patients presented in some of the initial groups, which were defined according to the patients' FEV_1 values.

2.7. Sensitivity analysis

Finally, we performed a sensitivity analysis to quantify the relative effect of the input parameters on the 6MWT model outputs, 6MWD, HR_{max} and HRR_3. In particular, we applied a variance-based sensitivity analysis presented by Sobol, which measures the uncertainty of model output because of the input's variance [35]. We computed the main effect indices, S_i, defined as the effect of varying x_i on the output y,

$$S_i = \frac{Var[E[y|x_i]]}{Var[y]} \tag{2}$$

In addition, we also computed the total-order effect indices which consider the impact of the variation of two or more parameters. We followed the approach presented in the study of Satelli

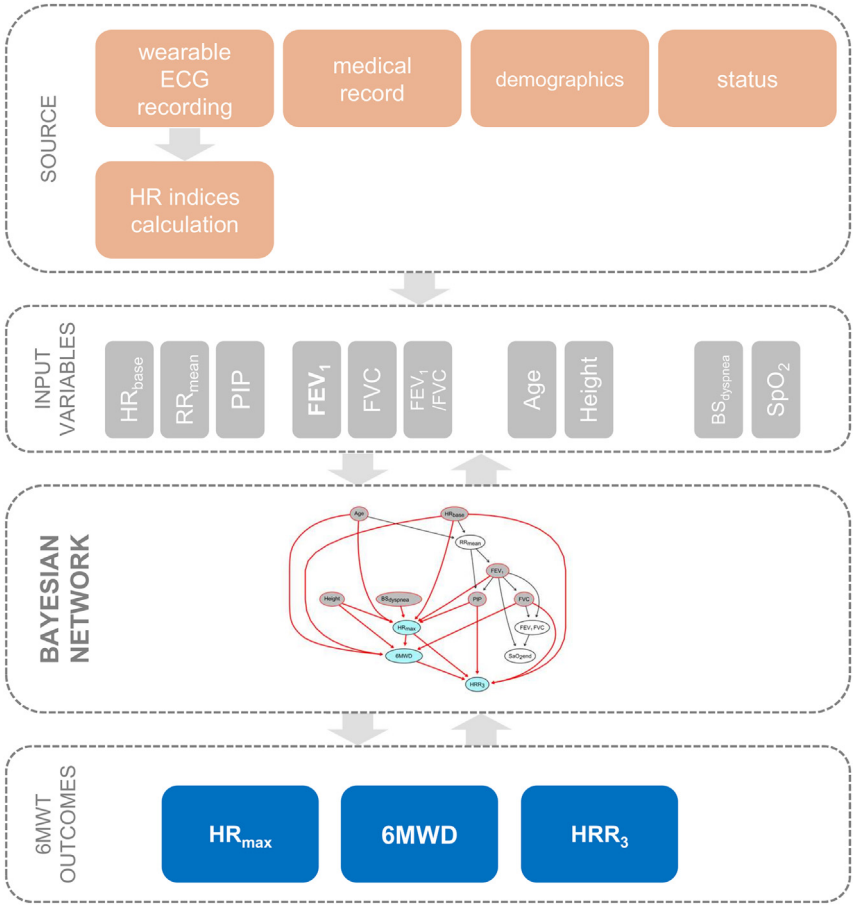

Fig. 1. Flowchart of the final system used in this study. BSdyspnea: Dyspnea score of the patient before the test, based on the mBorg scale; FEV_1: forced expiratory volume in one second, FVC: forced vital capacity, HR_{base}: Heart rate of the patient before the test, HR_{max}: Heart rate maximum after the test, HRR_3: the heart rate recovery index evaluated after 3 min of patient's recovery, PIP: percentage of inflection points in RR time seires, RR_{mean}: mean RR interval before the test, SpO_2: peripheral capillary oxygen saturation.

et al. [36] to reduce the number of combinations. Consequently, the total-order indices, ST_i were calculated as:

$$ST_i = S_i + \sum_{i \neq j} S_{ij} + \sum_{i \neq j \neq l} S_{ijl} + \ldots + S_{123\ldots k} = 1 \quad (3)$$

The main difference between the main and total-order indices is that the main effect indices, S_i quantify the variability of the output by the input parameters alone, whereas, the total-order indices, ST_i, consider the parameter and its interactions. The indices were calculated for each model output and its corresponding inputs. These indices provide better knowledge about the input and output relations and measure the robustness of the model in case of variance.

3. Results

3.1. Study population

The cohort for this study includes 50 COPD patients, 38 males and 12 females. Four patients were excluded from the analysis because of the presence of a pacemaker interfering with the ECG signal (one patient) or a low signal-to-noise ratio (three patients). Table 1 shows the patients' demographic and anthropometric data.

On average patients walked 431 m during the 6MWT. During the test, 7 patients paused and resumed walking at least once. These patients have a low FEV_1% pred, being below 50%, thus indicating a greater severity.

3.2. Complete Bayesian network scheme highlighting 6MWT outputs

The schemes in Fig. 2 represent the global Bayesian network obtained for modeling the 6MWT outputs. This network resulted in part from the coupling of the three individual models obtained after the LASSO regularization step. More details on the coefficients of the final models and the variables selected for each 6MWT output are described in Appendix A. The remaining variables, FEV_1/FVC, RR_{mean} and SpO_2, not included in the aforementioned models, are mainly related to the FEV_1 parameter, and allow inferring the patient's severity group based on the actual 6MWT results. Nodes with gray background (Age, Height, PIP, FVC, FEV_1 $BS_{dyspnea}$, HR_{base}) represent the input variables from which the outputs (6MWD, HR_{max} and HRR_3) were obtained, and defined by the red arcs. Black arcs define the direct relationship between inputs. Therefore, by instantiating just all the gray nodes with evidence, the values of 6MWD, HR_{max} and HRR_3 can be simultaneously predicted using the maximum a posteriori (MAP) queries.

3.3. Performance metrics for the individual and global models

The performance of the individual models was measured by the correlation coefficient R and the RMSE using leave-one-out cross-validation. The performance metrics for the 6MWD, HR_{max} and HRR_3 are presented in Table 2. The individual models showed a moderate correlation (above 0.60) for the 6MWD, and a strong correlation for the HR- related outputs, specifically, 0.8360 and 0.8763 for the HR_{max} and HRR_3 predictions, respectively. On the other

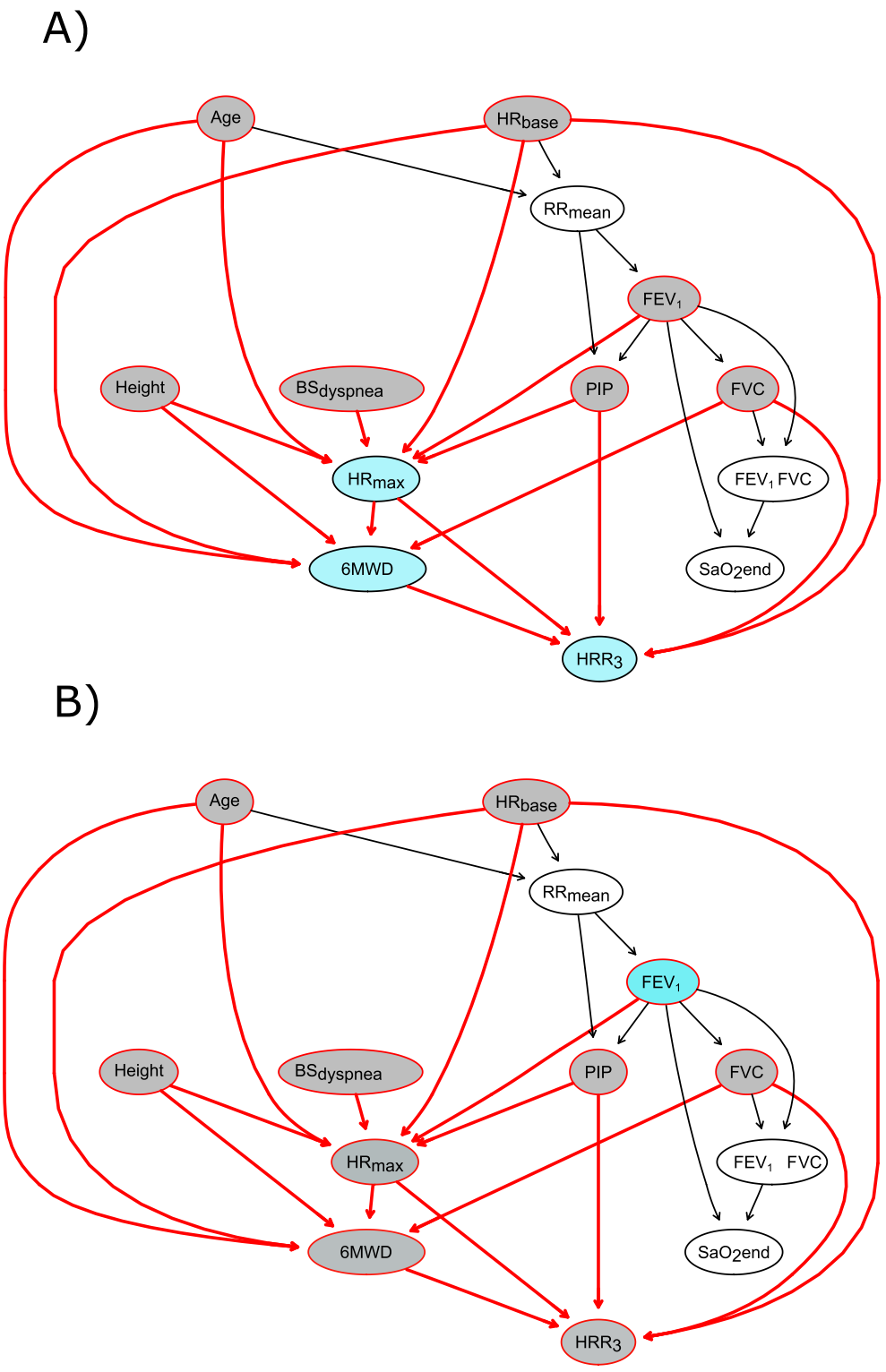

Fig. 2. Bayesian networks obtained for modeling the main outputs of the 6-minute walking test (6MWT) and disease severity (FEV_1). A) Network highlighting in gray those nodes (variables) needed to estimate 6MWD, HR_{max} and HRR_3 according to individual models obtained. B) Network highlighting the most relevant nodes for estimating the spirometry related variable, FEV_1, and thus the patient's severity, assuming that both FVC and FEV_1/FVC are unknown. In both networks, blue nodes indicate the dependent variables, while nodes in white stand for the unknown variables. Arcs in red are related to the models obtained for individual 6MWT outputs. Black arcs mean interactions between input variables that are useful for the accurate prediction of FEV_1 if the 6MWT outputs are known. $BS_{dyspnea}$: Dyspnea score gave by the patient before the test based on the mBorg scale, FEV_1: forced expiratory volume in one second, FVC: forced vital capacity, HR_{base}: Heart rate of the patient before the test, HR_{max}: Heart rate maximum after the test, HRR_3: the heart rate recovery index evaluated after 3 min of recovery, PIP: percentage of inflection points, RR_{mean}: mean time difference between beats before the test, SpO_2: peripheral capillary oxygen saturation.

Table 2
Average performance metrics for the 6MWD, HR_{max} and HRR_3 models selected by leave-one-out cross-validation.

	Individual models			Bayesian network		
	R(95%CI)	RMSE	MAPE	R(95%CI)	RMSE	MAPE
6MWD [m]	0.602 (0.38–0.76)	75.90	15.60	0.583 (0.35–0.75)	77.16	15.43
HR_{max} [bpm]	0.836 (0.72–0.90)	10.29	8.10	0.8369 (0.72–0.91)	10.26	8.10
HRR_3 [bpm]	0.876 (0.79–0.93)	4.34	18.29	0.577 (0.34–0.74)	7.36	32.49

The performance metrics, correlation (R), Root Mean Squared Error (RMSE) and Mean Absolute Percentage Error (MAPE) were computed for the individual models and the Bayesian network.

hand, the RMSE and MAPE values were, respectively, 75.9 m and 15.60% for the 6MWD, 10.29 bpm and 8.10% for the HR_{max} and 4.34 bpm and 18.29% for the HRR_3. Note that these values were measured for the individual models, while the values for the complete Bayesian network of Fig. 2 are also shown in Table 2. The performance metrics obtained for the output nodes when the outputs are all unknown, slightly worsened for 6MWD and to a greater extent for HRR_3, due to the error propagation occurring between the links connecting these model outputs. Nevertheless, the correlation, RMSE and MAPE values still exhibited a moderate performance in such a situation.

3.4. Relationship between relevant inputs and 6MWT outputs

After training of the Bayesian network, synthetic samples were simulated for each variable within the network. The aim of the new randomly generated samples is not to get strong correlations between variables, but to increase understanding of their existing relationships, especially increasing the understanding between inputs and outputs. Fig. 3 displays the 6MWT outputs against selected relevant inputs from both the 5000 simulated samples and the 46 original samples used for training the network. Correlation values (Pearson's coefficient) between variables and the associated P values are added to each graph. All correlations were statistically significant ($P<.001$). The results indicate an inverse relationship, that is a negative correlation, between 6MWD, and HR_{base}, Age, and HR_{max}, while the correlation between 6MWD and FVC was positive.

Regarding HR_{max}, its relationship with HR_{base} was positive as expected. On the other hand, the relationship of HR_{max} with Age and the spirometry values, FEV_1 and FVC, was inverse. Finally, the recovery output, HRR_3 had a positive correlation with the other outputs, 6MWD and HR_{max} whereas its correlation with HR_{base} was negative. Note that there is no correlation between HRR_3 and PIP.

3.5. Sensitivity analysis

Fig. 4 shows the results obtained from the sensitivity analysis performed for the analyzed 6MWT outputs. Both the main effect (S_i) corresponding to each individual input alone, and total effect (ST_i) considering also the interactions with other inputs are shown. For all models, values of S_i and ST_i are almost similar, indicating that interactions between inputs are negligible and thus the models are mostly additive.

The HR_{max} is significantly influenced by the heart rate at baseline, HR_{base}, with a contribution above 50%. Spirometry results measured through the FEV_1 and the Borg-scale index related to the lungs each contribute more than 10% to HR_{max}. The remaining variables associated with patient physical characteristics such as Age and Height together with PIP have a smaller contribution.

Regarding the total distance walked, HR_{base} is again the component with the largest effect (40%). Its influence is more than 2-fold larger than the influence of both Age and Height (less than 20% each). Age and Height are commonly used in clinical models for distance estimates for healthy subjects. FVC and HR_{max} had a more modest effect on 6MWD but still notable (>10%). The model predicting 6MWD was the most heterogeneous among all, its variables are related to the cardiorespiratory system and the physical properties of the subject.

Finally, the recovery dynamic of heart rate during the post-walking phase was mostly modulated by the effects of HR_{max} and HR_{base} as expected. Both inputs together accounted for more than 95% of the total output variance, while the effects of the other inputs accounted for the remaining 5%. Hence, we can proceed by pruning all the others and keep only these 2 dominant markers.

3.6. Inferring disease severity from 6MWT outputs

In the previous sections, we described the results predicting the outputs of the walking test. However, a BN also allows to infer the inputs (i.e., pulmonary status) of the network from the outputs (6MWD, HR_{max}, HRR_3). The Bayesian network designed in this study allows to estimate the severity of the patients by knowing the 6MWT outputs and the relevant clinical variables. Fig. 2-B highlights in gray color, which nodes are more relevant to this specific task. Despite the fact that they were acquired before the test, variables FVC and FEV_1/FVC are assumed to be unknown together with FEV_1. On the other hand, the node RR_{mean} depends on Age and HR_{base}. Therefore, by instantiating the gray nodes, the conditional probability of belonging to a particular severity group can be estimated for any patient.

Fig. 5 (top chart) shows the classification results by grouping the patients into four classes: Very severe ($FEV_1 \leq 30\%$), Severe (FEV_1: 30% – 50%), Moderate (FEV_1: 50% – 80%), and Mild ($FEV_1 > 80\%$). Since some classes had very few samples in the original database, the Bayesian network was retrained using simulated samples distributed uniformly among all classes. This allows for improved performance when classifying patients from minority classes. The overall weighted accuracy achieved for the initial four classes was Acc = 67.4% (95%CI: 52.0 – 80.5). As the Very severe group had only three individuals, the overall performance was also reported for three and two classes, being Acc=78.3% (95%CI: 63.6 - 89.1) using three groups, while for two groups was Acc=84.8% (95%CI: 71.1 – 93.7). With three classes, the groups were defined by merging the Very severe and Severe patients ($n = 21$), while Moderate and Mild remained identical. When only two classes were used, the groups are formed by joining Very severe with Severe class, and Moderate with Mild class, with $n = 21$ and $n = 25$, respectively (see Fig. 5 bottom chart). The classification results obtained for the two and three groups are summarized in Table 3 and Table 4, respectively.

3.7. Inferring patient progression for personalized therapy

In addition to estimating patient severity, the proposed network would make it possible to infer the progression of the patients if

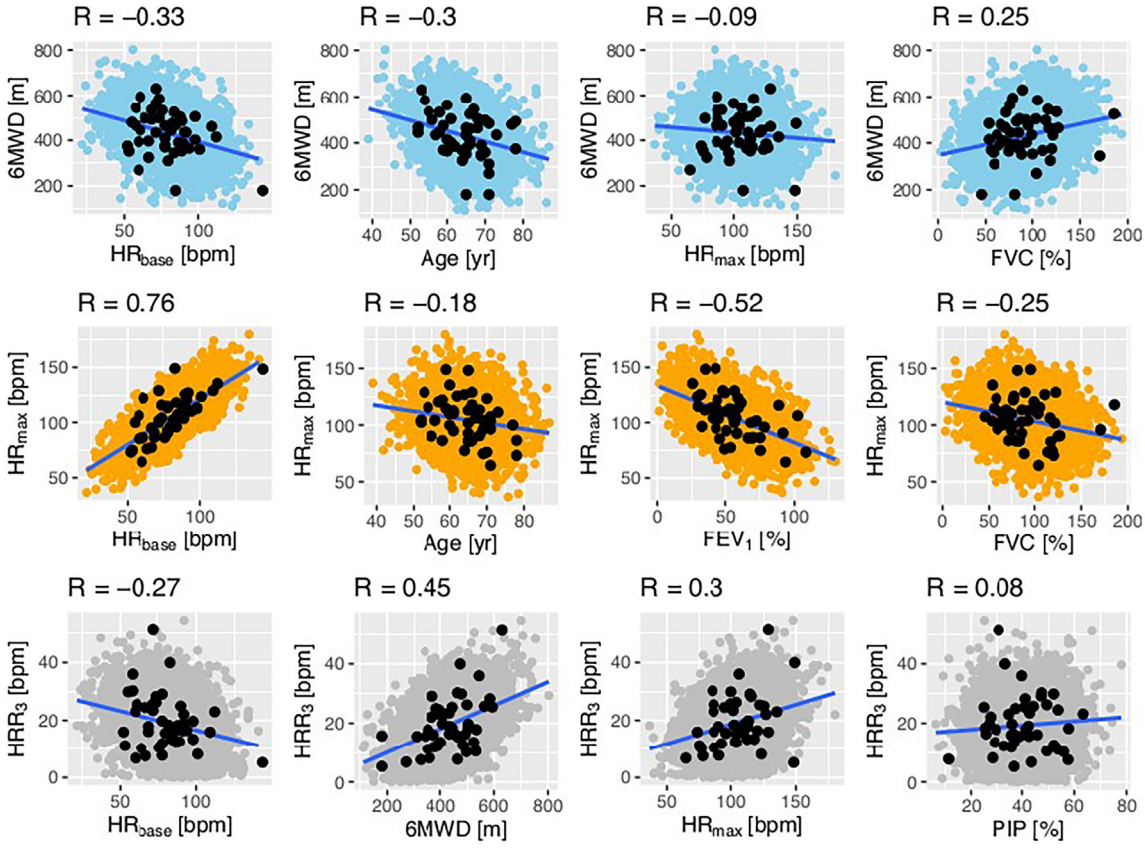

Fig. 3. Relationship between the model inputs and outputs, 6MWD, HR_{max} and HRR_3. The colored points represent the simulated data, whereas the black points are the real data used in the model. The blue lines are the linear regression resulting from the simulated and real data. 6MWD: six-minute walking distance, FEV_1: forced expiratory volume in one second, FVC: forced vital capacity, HR_{base}: Heart rate of the patient before the test, HR_{max}: Heart rate maximum after the test, HRR_3: the heart rate recovery index evaluated after 3 min of recovery, PIP: percentage of inflection points.

Table 3
Confusion matrix associated with the classification results obtained for only three classes (Very Severe + Severe, Moderate and Mild) according to disease severity.

Population ($N = 46$)		True class			
		Very severe + Severe	Moderate	Mild	Total
Predicted class	Very severe + Severe	15	1	0	16
	Moderate	6	17	1	24
	Mild	0	2	4	6
	Total	21	20	5	46

Table 4
Confusion matrix associated with the classification results obtained for only two classes (Very Severe + Severe and Moderate + Mild) according to disease severity.

Population ($N = 46$)		True class		
		Very severe + Severe	Moderate + Mild	Total
Predicted class	Very severe + Severe	15	1	16
	Moderate + Mild	6	24	30
	Total	21	25	46

one or more parameters change over time. For instance, we could infer how a patient would evolve as he or she gets older, or if the heart rate decreases, or both. Such a tool would be of great clinical value for tailoring the most effective treatment for each patient. Fig. 6 shows the estimate of the conditional probability (CP) belonging to each severity group in two patients, as a function of varying one of the parameters. That is, only one parameter is modified at a time, while the rest remains fixed. The example in Fig. 6-A corresponds to a patient diagnosed as Severe; whose actual parameter values are highlighted with vertical blue lines. Based on these graphics, it can be deduced that an increase in HR_{base} or HR_{max} above 110 bpm and 150 bpm, respectively, can result in a worsening of the patient. The same occurs when the PIP exceeds 60%. On the contrary, an increase in $FVC\%_{pred}$ above 110% could improve the patient's condition as expected, while the remaining parameters (not shown in the figure) had little influence.

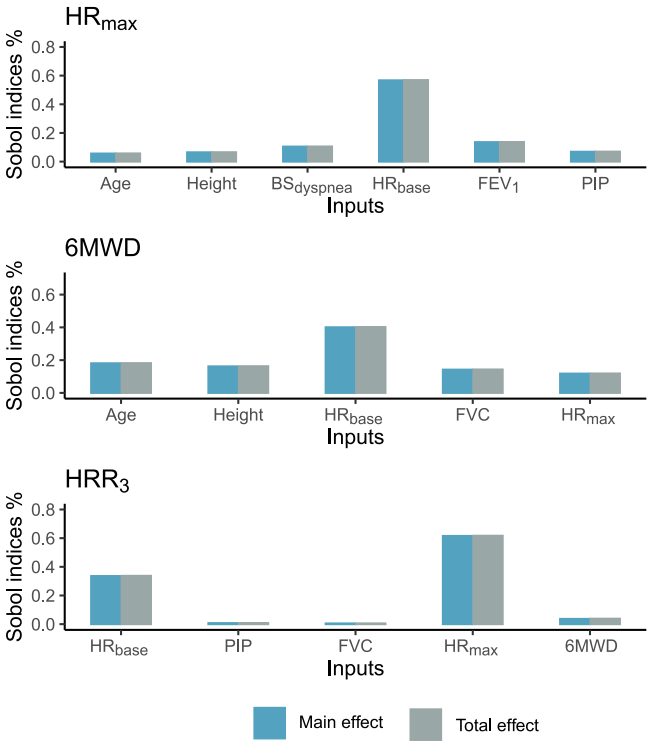

Fig. 4. Global sensitivity analysis using Sobol indices for HR_{max}, 6MWD and HRR_3. First-order (main) effects S_i (sensitivity to individual parameter variations) are represented by red bars and while green bars indicate total-order effects ST_i (sensitivity to parameter interactions).

The same analysis is conducted in Fig. 6-B for a Moderate diagnosed patient. In that case, the influence of each parameter is very similar to that of the Severe patient, with the actual values being within the expected region. Note that any desired combination of parameters changes can be tested as well, and more than one may be unknown when estimating the CP. However, such inference examples are only based on what the network has learned from our small study population.

4. Discussion

This study proposes a novel comprehensive tool for the assessment of walking capacity by modeling the 6MWT outcomes using Bayesian networks. To the best of our knowledge, it is the first time that Bayesian networks are used for modeling the 6MWT within a unified framework. The results showed that the prediction of the 6MWT outcomes, including 6MWD, HR_{max} and HRR_3, was good by only using clinical and physiological patient data. Furthermore, the implemented Bayesian network has the capacity of inferring the input variables from other known or measured data, and consequently, the pulmonary function parameters can be inferred from the 6MWT data. Therefore, our model provides a dual-function tool. Firstly, the trained model allows the prediction of the 6MWT outcomes and thus, the evaluation of the functional exercise capacity of the patients. And secondly, it can assess the disease severity and progression by inferring the predefined $FEV_1\%_{pred}$ groups, and how disease severity might progress (i.e., improved or worsened) by modifying the available patient data. Both capabilities enable the proposed model to be used for more personalized monitoring of COPD patients in their home environment, where only the results of the analysis are reported occasionally to the medical doctors supervising them.

Previous studies have proposed different models to predict the 6MWD [16,17,30,37] and compare the test performance of the patients to spirometry values. Many of these studies were, however, focused on healthy subjects. On the contrary, we modeled the 6MWD in COPD patients to obtain a more reliable characterization, considering the disease condition beyond the standard physical characteristics. We found that age, height, HR at baseline, HR_{max}, and $FVC\%_{pred}$ of the COPD patients are significantly associated with 6MWD and consequently, they were included in the multivariate regression model. Unlike our study, the most frequent parameters presented in previous 6MWD models include

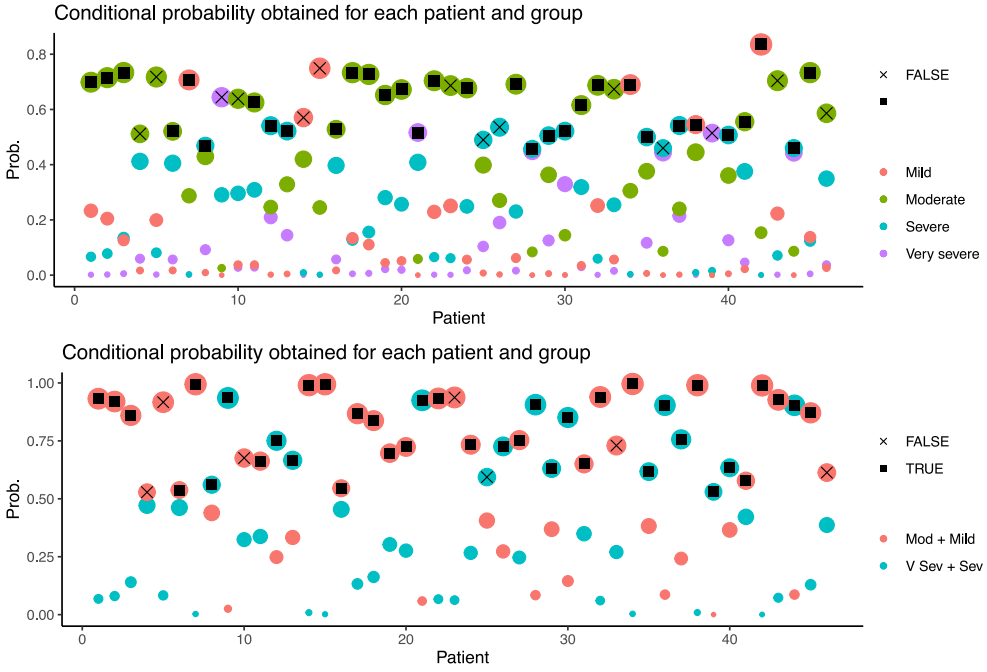

Fig. 5. Conditional probability associated with each class estimated for all patients. Top: all patienst grouped in four classes; Bottom: all patients grouped in two classes. Solid black squares (TRUE) indicate patients that were correctly classified while colors represent the classes.

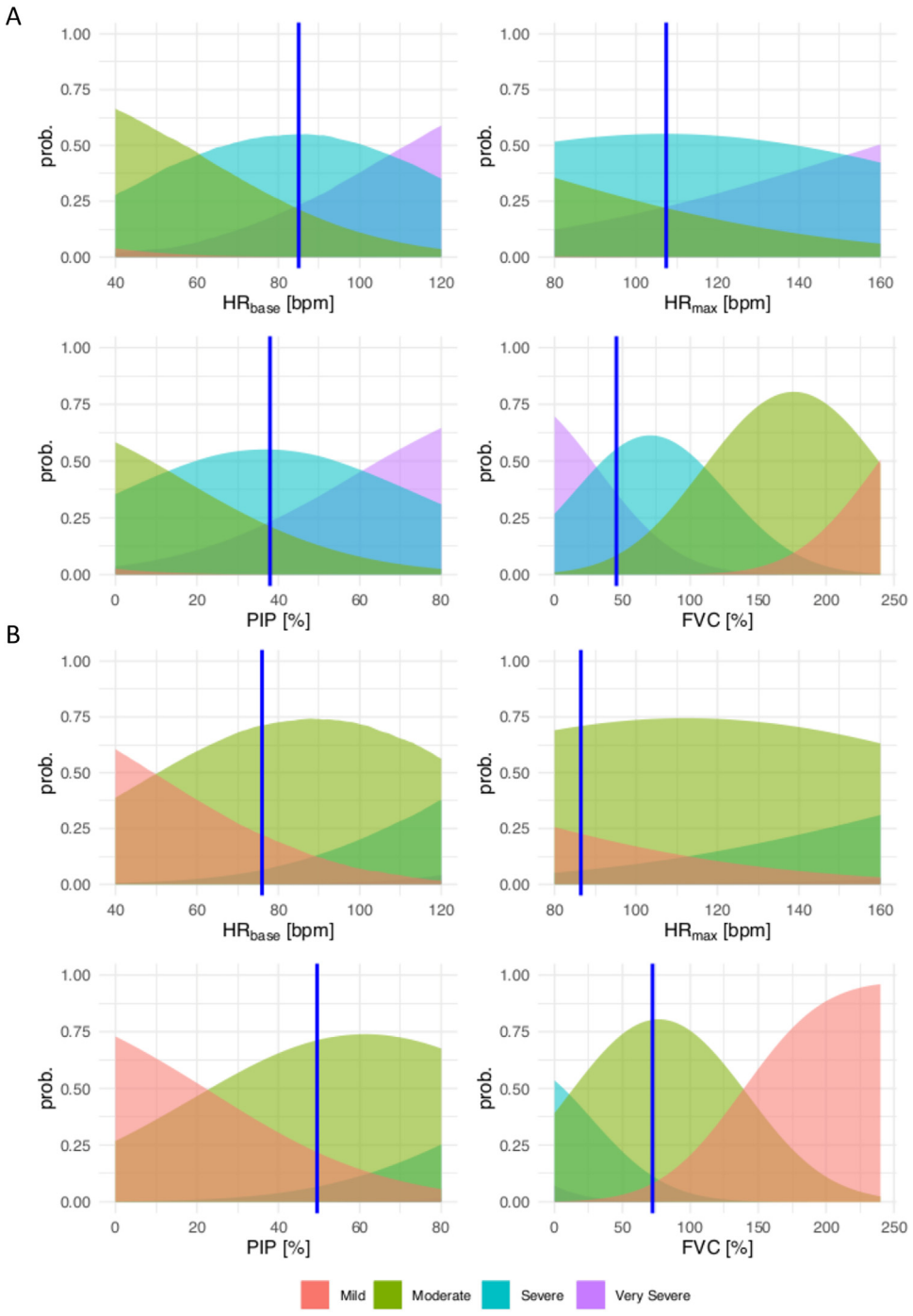

Fig. 6. Conditional probability (CP) estimated for each of the four disease severity groups as a function of parameters HR_{base} HR_{max}, FVC, and PIP. A) Example of the four CP trends computed for a Severe patient and, B) for a Moderate patient. The colored areas represent the probability of the actual patient to belong to a specific severity group: Mild ($FEV_1 \geq 80\%$), Moderate ($50\% \leq FEV_1 < 80\%$), Severe ($30\% \leq FEV_1 < 50\%$), Very severe ($FEV_1 < 30\%$), when shifting the analyzed parameter towards higher or lower values. Vertical blue lines indicate the actual values corresponding to the analyzed parameters at the time of measurement, which usually fall within the patient's actual group. FEV_1: forced expiratory volume in one second, FVC: forced vital capacity, HR_{base}: Heart rate of the patient before the test, HR_{max}: Heart rate maximum after the test, PIP: percentage of inflection points.

age and height, while some studies also included HR information, whose findings partially agree with our results [15–17]. In particular, Poh et al. [17] reported an inverse and direct relationship between 6MWD and both the age and height, respectively, in line with our results (see Fig. 3). That study also included in the model a measure of HR_{max}, but the authors did not report the same inverse relationship that we observed between 6MWD and HR_{max}. It was probably as a result of the different ways the measure was expressed. Here, we used absolute HR values expressed in bpm, while they used a percentage of the theoretical maximum HR, estimated as $220 - age$. However, the same behavior seen in our study regarding HR_{max} and 6MWD relationship was also observed in the study of Casanova et al. [16].

On the other hand, only a few studies focused on healthy subjects included spirometry values. Camarri et al. [37] reported that height and FEV_1 were the only significant parameters in the mul-

tivariate regression in healthy subjects. On the contrary, although FEV_1 was not significant in this study, a closely related parameter like FVC was included in our model. These differences in the models might be due to differences in the populations and consequently, the ranges and distribution of the FEV_1 values are different. Regarding COPD populations, Zeng et al. [38], investigated the relationship between 6MWD and COPD severity. This study reported the relationships between 6MWD and both the age and $FVC\%_{pred}$, which agree with our results, displayed in Fig. 3. As expected, both results suggest that a reduced FVC or an older patient implied a lower 6MWD. Moreover, we found an inverse relation of 6MWD with HR_{base} and HR_{max}, suggesting that larger HR increases during the test are linked to shorter 6MWD, and thus with a reduced functional exercise capacity.

The primary aim of the previous studies was to model the 6MWD whereas the other test outcomes have been investigated as modulators of it or to provide relevant information about disease prognosis. We additionally modeled HR_{max} and HRR_3 because previous studies suggested them as predictors of disease worsening and mortality in respiratory diseases [11–13]. Furthermore, HRR_3 after the 6MWT provided valuable information about severity and comorbidities in COPD patients [39,40]. Importantly, unlike the 6MWD model, the models obtained for both the HR_{max} and HRR_3 included a HRV index, namely a marker representative of the heart rate fragmentation (PIP). Consequently, the proposed additional models contribute to a more complete model of the 6MWT performance in COPD.

The relationships exhibited in Fig. 3 were expected based on previous studies and theoretical equations. On the other hand, the direct relationship between 6MWD and HRR_3 was also observed in previous studies that evaluated the heart rate recovery in respiratory diseases [11–13]. Therefore, the proposed models are in part supported by previous findings from other studies. But they are novel in the way they are integrated within a BN for assessing COPD patients, either by estimating the 6MWT outcomes, or by inferring disease severity from the test performance measures.

Results derived from the variance-based sensitivity analysis performed on the 6MWT models highlighted the most important input variables affecting the output variance. Several factors modulated almost equally the 6MWD except for HR_{max} which accounted for 40% of its total variance. As expected, this model shows that the prediction of 6MWD depends on both the cardiac and respiratory systems, as well as physical metrics. Therefore, it allows us to obtain a cardiopulmonary assessment of patients rather than just a pulmonary assessment. The other two models were, as expected, modulated mostly by HR-related measures, such as the HR measured at baseline and maximum HR achieved at the end of the walking phase. These two inputs alone represented more than 90% of the HRR_3 variance. Other variables associated with physical characteristics and pulmonary function had a smaller influence yet were not negligible, notably for the HR_{max} model. Overall, the models were mostly additive, and the results provide a hint to which variables should be prioritized over the rest when not all can be measured.

To bring all models together in one single tool, the versatility of Bayesian networks was leveraged for this purpose. Using Bayesian networks, we were able to represent causality between the different 6MWT output variables, as well as between the inputs. By combining the use of regression techniques with regularization, prior clinical knowledge, and available data, we defined the structure and learned the parameters of the final network. This overcomes the limitations of purely data-driven approaches that usually fail in representing disease mechanisms complexity, and in making complex clinical decisions even if trained on very large datasets [41,42]. On the other hand, Bayesian networks have some advantages compared to standard regression models, which can model associations but not causal structure and operate under restrictive assumptions about the variables' relationships. For instance, BNs can model multiple outcomes in a single model, deal with small datasets through data extension and constraints-based approaches [43], and in the presence of missing or incomplete data (i.e., by modeling the joint probability distributions using the two-step Expected Maximization (EM) algorithm) [44]. Moreover, they provide a mechanism for updating knowledge when new evidence is available. Therefore, by using the same scheme, we could add other new potential outcomes in the network and according to physicians' needs, in order to have a more comprehensive tool for COPD patients' assessment. Alternatively, another important score of death risk like the BODE index can be easily obtained from the patient's clinical parameters, including the BMI, FEV_1 pred, and dyspnea assessed by the modified Medical Research Council (MMRC) score, while exercise walked distance (6MWD) can be obtained from the model estimates [45].

The models reported for the 6MWD by previous studies are mainly based on standard regression analysis [30,37]. However, to design our BN network, we first applied multivariate linear regression with LASSO regularization to identify the most predictive features for each 6MWT output using cross-validation. While doing this we obtained a sparse, easily explainable network, where several variables are shared among the three defined multivariate models. Our approach provides an important alternative towards the integration of individual but closely related models into BNs, which is not possible with the available automatic algorithms used for network structure learning. Furthermore, the use of BN not only allows the prediction of the results of the 6MWT simultaneously under uncertain conditions, but it also enables inferring disease severity from actual 6MWT measures and clinical parameters. Indeed, the results obtained in both cases are promising considering the size of the database. Certainly, the more evidence becomes available, the more accurate estimation of the parameters of interest could be. That is supported by the results obtained when estimating the CP for fewer disease severity groups, defined as a function of $FEV_1\%$ pred. Finally, it was possible to estimate the most probable patient disease condition, and thus the path of its progression, if some change occurs in any of the network parameters. However, this particular capability should be further tested and validated by using follow-up information about the patients' clinical outcomes.

Given all its different functionalities, our model represents thus a versatile tool for COPD patient assessment and monitoring. More importantly, the cardiopulmonary patient's assessment could be performed several times a year, without the need to perform the actual physical test, which is typically done yearly. Besides, the ambulatory application of this model can provide relevant information on the patient's status that can aid in defining specific personalized treatments. Therefore, its potential use in digitalized healthcare systems as a decision support tool would reinforce the home-monitoring of COPD patients.

4.1. Limitations

Although Bayesian networks have some advantages when dealing with small datasets and in the presence of incomplete data, our study has been mostly limited by the small size of the population. This limitation becomes even more pronounced in some subgroups, such as those belonging to the very severe and mild classes. The classes are defined as a function of disease severity considering the FEV_1 values, therefore, including more patients in these two minority groups would increase the overall classification performance. Nevertheless, it is possible to merge the minority groups into those groups with more patients, which could still be suitable for clinical practice and warrant a higher prediction ac-

curacy. On the other hand, it should be noted that in our database, the patients conducted the six-minute walk test only once. In many studies, the test is performed two or more times, where the results are averaged or retained from the best-of-multiple attempts, minimizing the impact on the test outcomes of several factors such as the learning effect, path layout, or the patient fatigue and pauses [46,47]. In that sense, our results regarding the prediction of the walked distance ($R \sim 0.60$) could be improved, if at least two walks were performed for each patient. This will be helpful because of the less propensity to execute a poor first attempt due to lack of learning, or a poor second walked distance due to patient fatigue or eventual pauses during the test. Moreover, the presence of comorbidities in these patients may also influence the 6MWT outcomes. However, it was not considered in the study due to the diverse nature of these comorbidities, making it difficult to pool patients in nearby similarly distributed groups. Finally, the lack of a control group does not allow us to define significant differences that can be detected between individual models obtained for healthy and COPD patients.

5. Conclusions

A comprehensive model was developed for the assessment of the standardized 6-min walk test outcomes in COPD patients without physical performance measures. Our model represents a first approximation that would become a powerful tool to continuously monitor the COPD patient's condition and disease progression at home, without physical performance measures. The tool could also be suitable for being implemented together with wearable devices or even embedded. Moreover, it might serve to schedule or planning personalized therapies for the patients, that can be easily adjusted in accordance with their evolution. Further studies requiring larger patient cohorts, with equally distributed groups of disease severity and follow-up information, are needed to validate and refine the model, as well as to improve the overall performance, especially for extreme low or high FEV_1% measures.

Declaration of Competing Interest

None.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cmpb.2022.107020.

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