

## RESEARCH LETTER

## Parameters recorded by software of non-invasive ventilators predict COPD exacerbation: a proof-of-concept study

**Objective** To assess whether daily variations in three parameters recorded by non-invasive ventilation (NIV) software (respiratory rate (RR), percentage of respiratory cycles triggered by the patient (%Trigg) and NIV daily use) predict the risk of exacerbation in patients with chronic obstructive pulmonary disease (COPD) treated by home NIV.

**Methods** Patients completed the EXACT-Pro questionnaire daily to detect exacerbations. The 25th and 75th percentiles of each 24 h NIV parameter were calculated and updated daily. For a given day, when the value of any parameter was >75th or <25th percentile, the day was marked as 'abnormal value' ('high value' >75th, 'low value' <25th). Stratified conditional logistic regressions estimated the

risk of exacerbation when  $\geq 2$  days (for RR and %Trigg) or  $\geq 3$  days (for NIV use) out of five had an 'abnormal value'.

**Results** Sixty-four patients were included. Twenty-one exacerbations were detected and medically confirmed. The risk of exacerbation was increased when RR (OR 5.6, 95% CI 1.4 to 22.4) and %Trigg (OR 4.0, 95% CI 1.1 to 14.5) were considered as 'high value' on  $\geq 2$  days out of five.

**Conclusions** This proof-of-concept study shows that daily variations in RR and %Trigg are predictors of an exacerbation.

## INTRODUCTION

Early detection of exacerbations to rapidly implement therapeutic interventions is a major goal in the management of patients with severe chronic obstructive pulmonary disease (COPD).<sup>1</sup> Respiratory rate (RR) is a physiological parameter that changes during an episode of exacerbation and may serve as the warning signal of a developing exacerbation.<sup>2</sup>

Home long-term non-invasive ventilation (NIV) is a modality of treatment for

patients with COPD at the end stage of chronic respiratory failure.<sup>3</sup> Home ventilators are now equipped with built-in software providing data such as RR, percentage of respiratory cycles triggered by the patient (%Trigg) and daily usage.

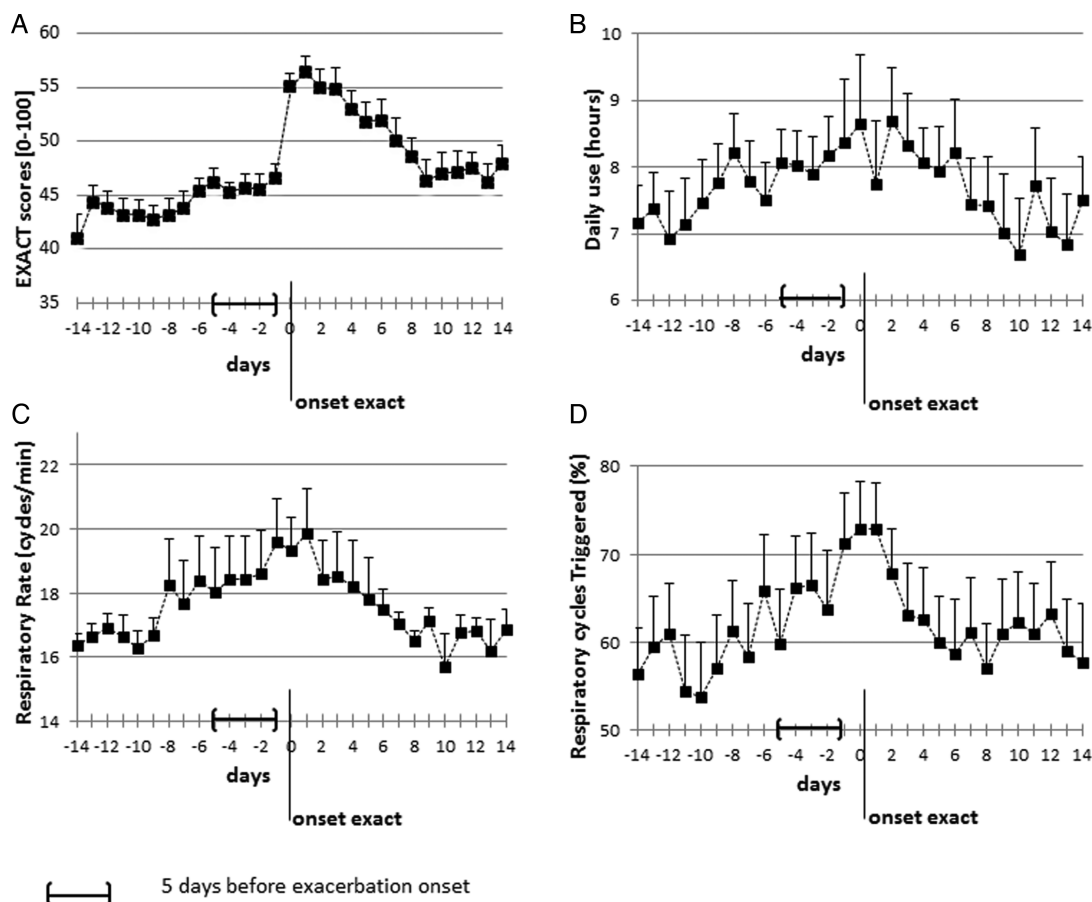
Our objective was to assess whether day-to-day variation in these three parameters recorded by the ventilators can predict an imminent exacerbation in patients with COPD treated at home with NIV.

## MATERIALS AND METHODS

Patients with COPD treated at home with NIV and oxygen therapy were eligible for this prospective observational study (see online supplement for details).

## Assessment of exacerbations

Patients filled in the EXACT-Pro questionnaire every day for a maximum of 6 months. This questionnaire was used to detect exacerbation events.<sup>4</sup> Each event detected using the EXACT-Pro score had to be validated by an event committee of two chest physicians.



**Figure 1** (A) EXACT-Pro score, (B) daily use of non-invasive ventilation, (C) respiratory rate and (D) percentage of respiratory cycles triggered by the patient in the 14 days preceding and following the onset of exacerbation (n=21). Data are reported as mean and SE.

**Analysis of data recorded by ventilators** RR, %Trigg and daily usage (h/day) were analysed as follows: 25th and 75th percentiles of each 24 h parameter recorded by the ventilator were calculated from the fourth day of follow-up onwards and updated daily. For a given day, when the value of a parameter was >75th or <25th percentile, the day was recorded as 'abnormal value' ('high value' >75th, 'low value' <25th).

Stratified (one stratum/patient) conditional logistic regression models were used to estimate the risk of exacerbation when  $\geq 2$  days (for RR and %Trigg) or  $\geq 3$  days (for NIV daily usage) out of 5 days had 'abnormal values'.

## RESULTS

Sixty-four patients were included, 44 of whom completed the study. EXACT-Pro detected 21 medically confirmed cases of exacerbation (mean (SD) age 72 (6) years, forced expiratory volume in 1 s/forced vital capacity 42 (12)%).

The risk of exacerbation was increased when RR (OR 5.6, 95% CI 1.4 to 22.4,  $p=0.01$ ; sensitivity 46.2%; specificity 89.7%) and %Trigg (OR 4.0, 95% CI 1.1 to 14.5,  $p=0.037$ ; sensitivity 53.8%; specificity 76.2%) were 'high value' on  $\geq 2$  days out of five. The variation in daily usage of NIV (>75th or <25th percentile) tended to be associated with a risk of exacerbation (OR 3.0, 95% CI 0.8 to 11.3,  $p=0.097$ ). Figure 1 shows, for the 21 exacerbations, the EXACT-Pro score, daily use of NIV, respiratory frequency and triggered cycles in the 14 days preceding and following the onset of the exacerbation (see online supplement for detailed results).

## DISCUSSION

Providing useful tools for detecting exacerbations is the cornerstone of COPD

management. This study presents the proof of concept that exacerbations of COPD can be detected by the time-course of respiratory parameters recorded by NIV software. RR and %Trigg increased in the days preceding exacerbation onset. Regarding daily NIV usage, some patients increased their usage of NIV, probably with the expectation of reducing breathlessness. Conversely, other patients reduced NIV usage, certainly reflecting intolerance and/or inadequacy of the ventilator settings during exacerbations.

The main advantage of this approach for detecting exacerbations is that it requires neither the patient's active involvement nor additional sensors in the patient's environment. Studies are needed to confirm these results and to investigate their clinical usefulness.

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**Contributors** Involvement in the conception, hypothesis delineation and design of the study: J-CB, J-LP, CP, RT, J-FT. Acquisition of data or analysis and

interpretation: J-CB, J-LP, JP, NT, AB, NA. Writing the article or substantial involvement in its revision prior to submission: J-CB, J-LP, JP, NT, RT.

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**Competing interests** J-CB is employed by Agir à dom, a non-profit home care company, and has received personal fees from Philips (outside the submitted work). NA and NT are employed by Agir à dom. CP has received grants from Agir à dom (outside the submitted work). J-CB, RT, J-LP, NT and NA have a patent pending on the algorithm to detect exacerbations.

**Patient consent** Obtained.

**Ethics approval** This study was approved by our institutional review board (IRB-6705).

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- 2 Murphy PB, Kumar A, Reilly C, *et al.* Neural respiratory drive as a physiological biomarker to monitor change during acute exacerbations of COPD. *Thorax* 2011;66:602–8.
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- 4 Leidy NK, Wilcox TK, Jones PW, *et al.* Standardizing measurement of chronic obstructive pulmonary disease exacerbations. Reliability and validity of a patient-reported diary. *Am J Respir Crit Care Med* 2011;183:323–9.

**ONLINE SUPPLEMENTARY MATERIAL TO - Parameters recorded by software of non-invasive ventilators predict COPD exacerbation: a proof of concept**

**MATERIALS AND METHODS**

*Study Design:* prospective observational study

*Study participants:* Patients were recruited through a regional home-care provider's database (AGIR à dom, Meylan, France).

*Inclusion criteria:*

- severe COPD patients ( $FEV_1/FVC < 70\%$  and  $FEV_1 < 50\%$  of predicted value)
- using home based long-term non-invasive ventilation and oxygen-therapy.

*Exclusion criteria:*

- Insufficient literacy to answer questionnaire
- Cognitive deficiency

*Data collected:*

- Day to day NIV use, respiratory rate (RR), and the percentage of inspiratory cycles triggered by the patients (%Trigg) using the ventilator's built-in software
- Anthropometric data at inclusion
- Medical history
- Lung function and arterial blood gas values from patients' medical charts (data from latest routine scheduled medical visit to ensure NIV efficacy).
- Smoking status
- COPD Assessment Test (CAT) questionnaire [Sup. Ref.1]

*Ethics approval and consent:*

Study approved by local IRB (IRB-6705). All included patients signed a written informed consent form.

***Assessment of COPD exacerbations:***

**Systematic follow-up:**

- 1) ***Inclusion visit (one to one interview):*** patients were instructed how to fill in the EXACT-Pro diary booklet, following guidelines from the EXACT-Pro manual, and were instructed to complete their diary every day for a maximum of 6-months.
- 2) ***Weekly follow-up by phone:*** to identify any deterioration in the patient's clinical status using 6 standard questions on: i) breathlessness, ii) sputum production, iii) cough, iv) visits to general practitioner (GP) for breathing problems, v) any feeling of deterioration in their health, vi) change in daily activities for health reasons.
- 3) ***Monthly home visit (if patient's clinical condition was stable):*** to collect the completed EXACT-Pro diaries, to deliver new EXACT-Pro diaries and to download data from the ventilator. Downloaded data covered the entire previous 4 weeks.

**Non-scheduled home visits by a nurse** due to deterioration in clinical status identified during the weekly phone call:

- Patients were asked to pursue their treatment or contact their GP if needed.
- Any change in medication was noted, data were downloaded from the ventilator, and the completed EXACT-Pro diary was collected and replaced with a new one.
- If the patient was hospitalised, the nurse visited the patient in hospital.

After home visits due to deterioration in the patient's clinical condition the EXACT-Pro record was analyzed and if the threshold of exacerbation (see below) was exceeded a second home visit was made 14 days later. If exacerbation was suspected a report by the GP was requested.

The clinical diagnosis of exacerbation was confirmed by two pneumologists (JP, AB) based on a review of the GP's report and the patient's medical chart.

**Definition of “Exacerbation”:** **Both** an EXACT-Pro score above the thresholds (given below) **and** a medical confirmation of exacerbation by 2 pneumologists. (If one of these two conditions was not respected, the patient was considered as “non-exacerbated”).

**End of follow-up:** 14 days after the onset of an exacerbation **or** after 6 months without exacerbation.

All NIV-related data downloaded by nurses were stored for subsequent analysis (see details below).

**Tools for COPD exacerbation detection:**

- *EXACT-Pro questionnaire*

The EXACT-Pro is a 14-item questionnaire to be filled in daily. It is scored on a scale from 0-100, with higher scores indicating a more severe condition. Changes in the total score are used to define onset and recovery, as well as the magnitude of the exacerbation. The three score domains ask about i) breathlessness, ii) cough and sputum, and iii) chest symptoms. We used a validated French version of this questionnaire in a booklet format covering a 30 day period. The EXACT-Pro is licensed through the United Biosource Corporation and the EXACT-Pro data were analyzed according to the recommendations of the developers. Events of exacerbation were defined in one of the two following ways: *Either*, an increase in the total score of  $\geq 12$  points above the patient's mean baseline score for 2 consecutive days (Day 1 of the 2 days serving as Onset), *or*, an increase of  $\geq 9$  points above the baseline scores for 3 consecutive days (Day 1 of the 3 days serving as Onset).

- *Analysis of data recorded by Built-In software of Home Ventilators*

Parameters given by NIV software included daily usage, leaks, minute ventilation, respiratory rate, tidal volume and percentage of respiratory cycles triggered by the patient. They were displayed as 24-hour values.

NIV-related data downloaded and stored during the follow-up period were analyzed as follows:

**Patients with exacerbation** (above Exact-Pro threshold + medically confirmed): for each patient, the follow-up period was divided into blocks of 5 days from the beginning of the follow-up to onset of exacerbation (as determined by the EXACT-Pro score). The five days before the onset of an exacerbation were *a priori* defined as the “**pre-exacerbation period**”.

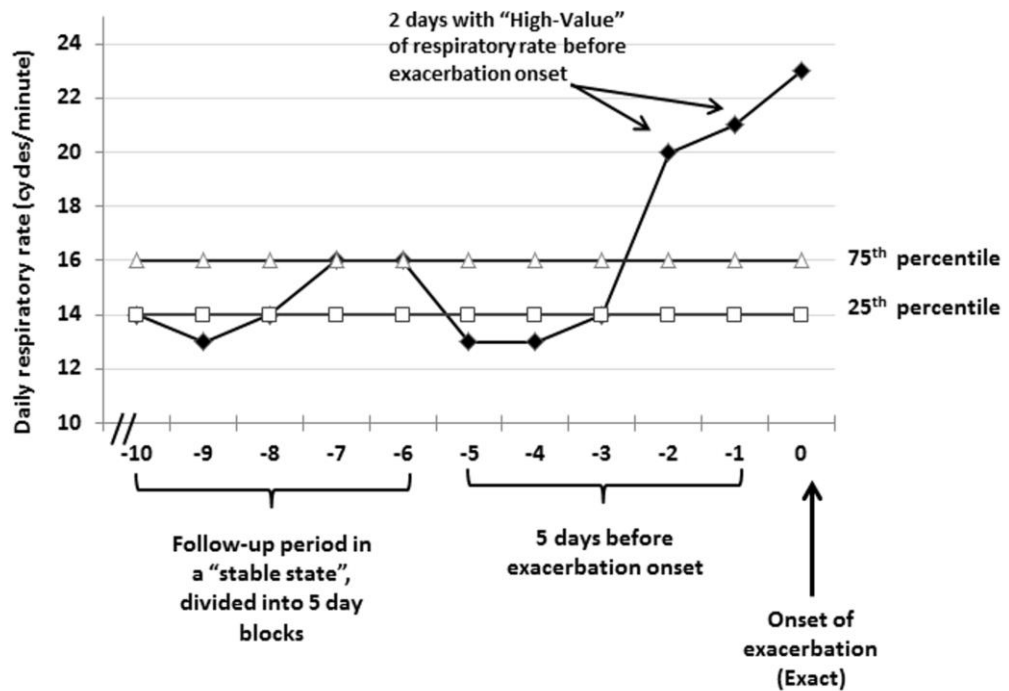
Three parameters from the NIV software were considered: *i*) Respiratory rate (number of breaths/minute); *ii*) percentage of respiratory cycles triggered by the patient (%) and *iii*) daily usage (hours/day). These NIV software parameters were analyzed as follows (see figure S1):

1) Twenty-fifth<sup>th</sup> and 75<sup>th</sup> percentiles of each 24-hour parameter (RR, %Trigg, daily use) were calculated from the fourth day of follow-up and updated on a daily basis.

2) For a given parameter, when a recorded 24-hour value for a given day was above the 75<sup>th</sup> percentile, the day was labelled as “High-Value”. Conversely, when the recorded 24-hour value was below the calculated 25<sup>th</sup> percentile, the day was labelled as “Low-Value”.

For respiratory rate and percentage of respiratory cycles triggered by the patient, only “High-Values” were considered as abnormal. For daily NIV use, “high-value” or “low-value” were both considered as abnormal as patients could respond to a clinical deterioration either by increasing NIV usage (in case of relief of dyspnea with NIV) or by decreasing NIV usage owing to a poor tolerance of the device at the preset settings of NIV during this period.

**Figure S1. Schematization of data analysis for detecting exacerbation (*representative trace of a patient’s respiratory rate*)**



The five days before exacerbation onset were *a priori* defined as the “*pre-exacerbation period*”. Black diamonds represent day to day values of each specific parameter (here respiratory rate). White squares and white triangles represent the 25<sup>th</sup> and 75<sup>th</sup> percentiles of 24- hour mean/median values for each specific parameter (here respiratory rate) which were updated on a daily basis.

For a given parameter, when a value recorded on a given day was above the 75<sup>th</sup> percentile value, it was marked as “High-Value”. Likewise, when the value recorded was below the 25<sup>th</sup> percentile of the 24- hour mean/median values, it was marked as “Low-Value”.

**Sample size estimation and statistical analysis:**

*Sample Size:* Since no published data were available regarding any changes in parameters recorded by built-in NIV software during an exacerbation, we chose to target the same number of exacerbations as in the study of Yanez et al (20 exacerbations) [Sup. Ref. 2]. Assuming comparable patient severity, we considered that the recruitment of at least 60 patients followed-up for 6 months would allow us to document at least 20 exacerbations.

*Statistical analysis:* Data were analyzed using Statistical Analysis System (SAS<sup>®</sup>) software version 9.1.3 (SAS Institute, Cary, NC, USA). Continuous data are expressed as mean (SD) or median (interquartile range) according to the distribution of each variable and categorical data as percentage. Unpaired *t*-tests or Mann-Whitney tests were used to compare anthropometric and clinical variables between patients who had presented an exacerbation (threshold of exacerbation calculated with EXACT-Pro score plus confirmation by the event committee) and those who had not. The same tests were used to compare patients who dropped-out versus those who completed the study.

Stratified (one strata/patient) conditional logistic regression models were used to estimate the risk of exacerbation when two or more days (for respiratory rate and % of cycles triggered) or three or more days (for NIV daily usage) out of five days were scored as “abnormal-values”. The choice of two or more days (for respiratory rate and % of cycles triggered) and three or more days (for NIV daily usage) was based on minimization of the Akaike Information Criterion (AIC) and maximization of sensitivity.



## RESULTS

### *Patients' characteristics*

Figure S2 shows the study flow chart. Among 96 eligible patients, 34 (35%) were not included or withdrew early-on from the study because they did not have sufficient reading skills or were embarrassed completing the EXACT-Pro questionnaire.

**Figure S2. Study Flow Chart**

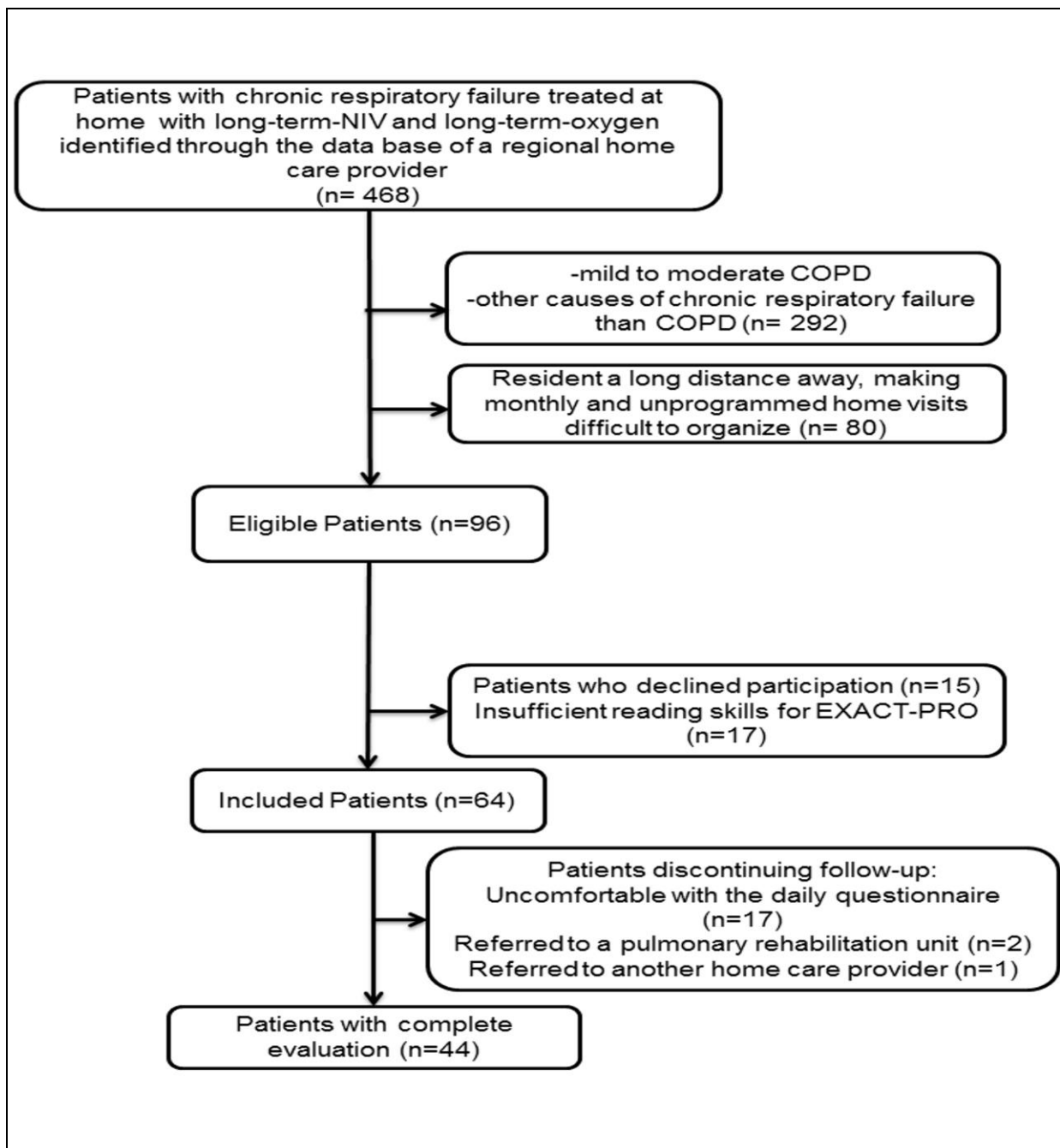


Table S1 shows patients' characteristics. Patients included had severe COPD (mean CAT score =  $18 \pm 6$ ). Forty-four patients completed the study and twenty patients dropped-out. Interestingly, this latter group of patients had lower daily oxygen-therapy compliance, exhibited a nearly significant trend of being worse compliers with NIV and reported a higher rate of current smoking than the group of patients that completed the study.

**Table S1. Baseline demographic and clinical characteristics**

Characteristics	total (n = 64)	Exacerbated (n = 21)	Non Exacerbated (n = 23)	Dropouts (n = 20)
Age, years	71 (9)	72 (6)	72 (10)	70 (10)
Male, n (%)	40 (63)	12 (57)	15 (65)	13 (65)
BMI, Kg/m <sup>2</sup>	27.2 [21.7;30.7]	23.9 [21.9;28.9]	27.4 [21.5;30.1]	28.4 [22.2;31.4]
Current smokers, n (%)	14 (21.9)	3 (14.3)	4 (17.4)	7 (35.0)
Former smokers, n (%)	36 (56.3)	14 (66.7)	13 (56.5)	9 (45.0)
Dyslipidemia, n (%)	21 (32.8)	3 (14.3)*	11 (47.8)	7 (35.0)
Diabetes, n (%)	15 (23.4)	5 (23.8)	5 (21.7)	5 (25.0)
Hypertension, n (%)	35 (54.7)	13 (61.9)	13 (56.5)	9 (45.0)
FEV <sub>1</sub> /FVC, (%)	44.6 (13.0)	42.4 (12.0)	44.1 (13.8)	47.7 (13.2)
FEV <sub>1</sub> , L	0.8 [0.6;0.9]	0.7 [0.5;1.0]	0.8 [0.5;0.9]	0.9 [0.7;1.0]
FEV <sub>1</sub> , % predicted	31.2 [23.9;39.7]	30.5 [22.4;38.6]	29.6 [20.9;38.1]	35.0 [29.0;48.2]
PaO <sub>2</sub> (kPa)	8.6 [7.7;10.3]	8.4 [7.4;10.6]	9.4 [8.2;10.8]	8.3 [7.3;9.6]
PaCO <sub>2</sub> (kPa)	6.0 [5.5;6.7]	5.9 [5.4;6.6]	6.0 [5.4;6.5]	6.0 [5.5;7.2]
pH	7.42 (0.04)	7.43 (0.03)	7.43 (0.03)	7.40 (0.04)
Months on domiciliary oxygen therapy	47 [24;82]	52 [27;99]	49 [29;80]	40 [18;50]
Oxygen therapy use (hours/day)	14.1 [8.1;23.0]	19.5 [9.8;23.2]	16.7 [10.0;23.0]	9.0 [6.5;18.6]‡
Months on NIV	36 [15;60]	38 [8;71]	38 [21;68]	28 [9;55]
NIV use (hours/day)	7.5 (2.9)	7.6 (3.0)	8.0 (2.3)	6.9 (3.5)
CAT score	18 (6)	20 (6)	17 (6)	18 (7)

Continuous data are presented as mean (SD) or median [25<sup>th</sup>, 75<sup>th</sup> Inter Quartile Range ], depending on validation of normality of data distribution.

Categorical data are expressed as percentage.

Definition of abbreviations:

CAT = COPD Assessment Test™; COPD = chronic obstructive pulmonary disease; BMI = body mass index; SD = standard deviation; FEV<sub>1</sub> = forced expiratory volume in 1 second

\*: p-value < 0.05 between Exacerbated and Non-Exacerbated.

‡: p-value < 0.05 between Dropouts and "Exacerbated plus Non-Exacerbated".

### *NIV parameters predicting a risk of exacerbation*

Table S2 reports NIV settings and data recorded by NIV software during the “stable state” period and the “pre-exacerbation period” for the 21 patients who had an exacerbation.

**Table S2: NIV settings and Parameters recorded by NIV software during “stable state” period and “pre-exacerbation period” (n=21 patients).**

	<b>Stable State (from inclusion to Day-6 before onset of exacerbation)</b>	<b>5 days preceding onset of exacerbation (EXACT-score)</b>
<b>NIV settings</b>		
IPAP ( <i>cmH<sub>2</sub>O</i> )	15 [14; 16]	
EPAP ( <i>cmH<sub>2</sub>O</i> )	6 [6; 6]	
Pressure support ( <i>cmH<sub>2</sub>O</i> )	11 [8;13]	
Back-up rate ( <i>number/min</i> )	14 [13;16]	
<b>Parameters recorded by NIV software</b>		
<b>NIV Daily use, hours/day</b>	<b>8.2 [6.4; 9.3]</b>	<b>7.8 [6.5; 9.3]</b>
Respiratory rate; cycles/min	16 [15; 18]	17 [15; 19]
Respiratory cycles triggered by patient, %	64 [31; 81]	68.0 [44; 89]
Unintentional Leaks, L/min	1.2 [0.0; 26.1]	2.4 [0.0; 19.5]
Ventilation, L/min	8.8 [7.3; 10.9]	8.7 [7.7; 11.8]
Tidal Volume, mL	468 [393; 633]	476 [360; 615]

Data are presented as median [25<sup>th</sup>; 75<sup>th</sup> Inter Quartile Range] of the values recorded by NIV software.

**Table S3: NIV settings and Parameters recorded by NIV software over the entire follow-up period (n=23 patients).**

<b>NIV settings</b>	
IPAP ( <i>cmH<sub>2</sub>O</i> )	18 [17;19]
EPAP ( <i>cmH<sub>2</sub>O</i> )	6 [5;8]
Pressure support ( <i>cmH<sub>2</sub>O</i> )	12 [10;14]
Back-up rate ( <i>number/min</i> )	13 [12;15]
<b>Parameters recorded by NIV software</b>	
	<b>Entire follow-up period</b>
NIV Daily use, hours/day	8.2 [6.3; 9.8]
Respiratory rate; cycles/min	16 [14; 18]
cycles triggered by patient, %	69 [16; 89]
Unintentional leaks, L/min	1.2 [0.0; 8.4]
Ventilation, L/min	10.1 [8.5; 11.6]
Tidal Volume, mL	650 [550; 720]

During stable periods, Tidal volume and Ventilation were significantly lower in “exacerbated patients” than “non-exacerbated patients” with respectively  $p = 0.0117$  and  $p = 0.035$  (Wilcoxon tests)

Table S4 shows that the risk of exacerbation increased when the respiratory rate and the percentage of respiratory cycles triggered by the patient increased when one of these two parameters was considered as a “High Value” (i.e. above the 75<sup>th</sup> of a moving window value) for two or more days out of the five day window. The variation in daily usage of NIV (above the 75<sup>th</sup> or below the 25<sup>th</sup> percentile of moving values) also tended to be associated with a risk of imminent exacerbation.

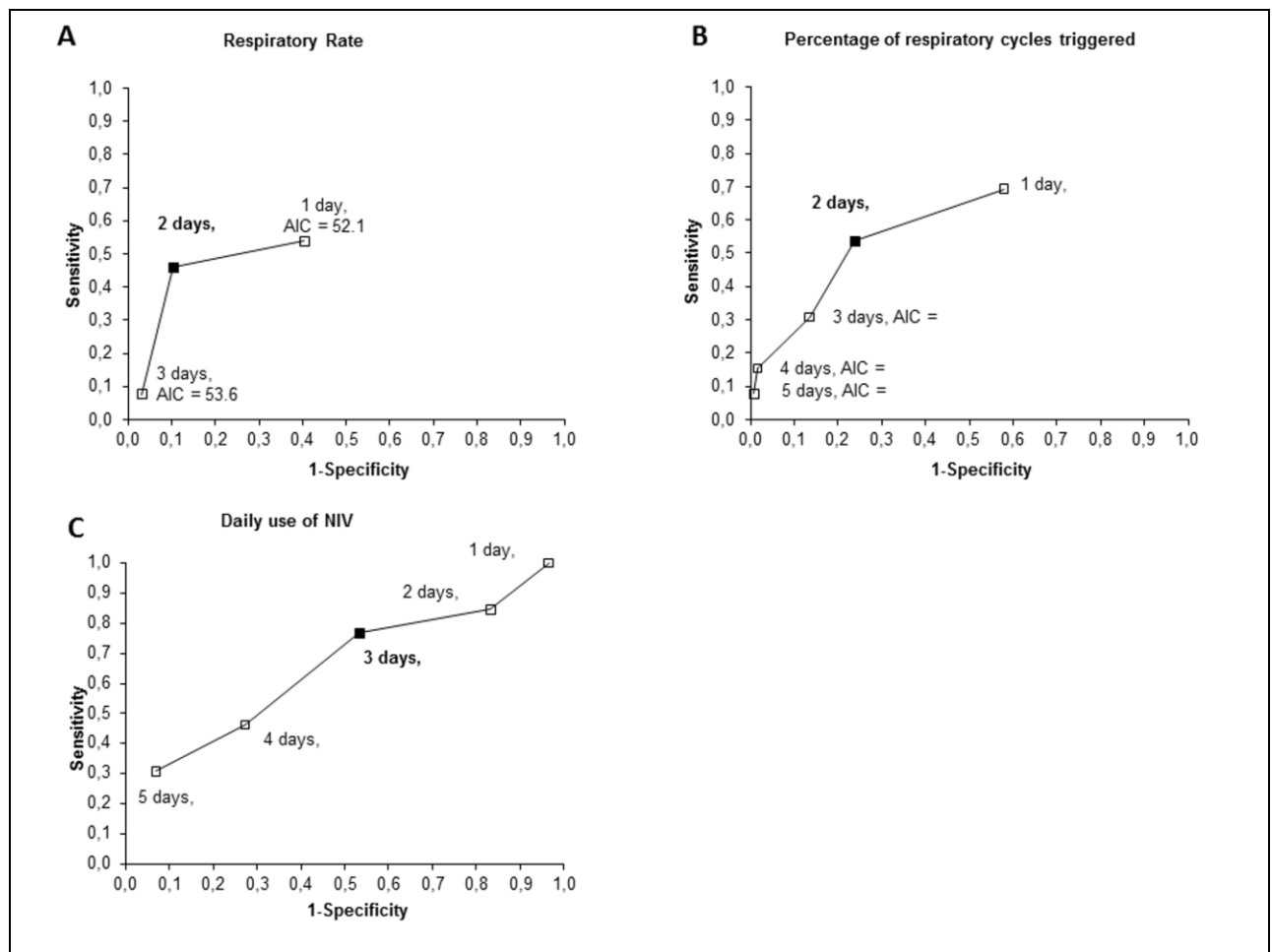
**Table S4: Changes in NIV parameters associated with the risk of exacerbation.**

	Odd Ratio [95% CI]	P-value	Sensitivity	Specificity	PPV	NPV
<b>Respiratory rate</b>	5.6 [1.4; 22.4]	0.01	46.2	89.7	31.6	94.2
<b>% of respiratory cycles triggered</b>	4.0 [1.1; 14.5]	0.037	53.8	76.2	18.9	94.1
<b>Daily use of NIV</b>	3.0 [0.8; 11.3]	0.097	-	-	-	-

PPV= positive predictive value, NPV= negative predictive value

*Stratified conditional logistic regression models*

Figure S3 shows ROC analysis for the 3 parameters tested.



**Roc curves for each parameter tested: (A) Respiratory rate. (B) Percentage of respiratory cycles triggered by the patient, (C) Daily use of NIV**

ROC curves exhibit sensitivity, specificity and Akaike Information Criterion (AIC) in detecting exacerbation according to the number of days (1day, 2days, 3 days etc..) scored as “abnormal-value” for each parameter. The choice of two or more days (for respiratory rate and % of cycles triggered) and three or more days (for NIV daily usage) out of five days scored as “abnormal-values” was based on minimization of the Akaike Information Criterion (AIC) and maximization of sensitivity.

## **REFERENCES TO ONLINE SUPPLEMENTARY MATERIAL**

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- Sup. Ref. 2. Yanez AM, Guerrero D, Perez de Alejo R, et al. Monitoring breathing rate at home allows early identification of COPD exacerbations. *Chest* 2012; 142: 1524-9.