The three groups of hypoxemic patients show an overexpression of hypoxia-sensitive transcription factors, primarily HIF-1α, compared to control subjects. In OSA there was an increase in plasma levels of NF-κB1 compared to COPD group. In situations of CIH, overexpression of NF-κB1 in plasma has been demonstrated in a cell culture model[6] with a selective activation of inflammatory pathways, unlike CCH hypoxia of patients with COPD and overlap, where the activation of adaptive pathways predominates. Oxidative stress driven by CIH may initiate systemic inflammation in OSA,[7] which inflammatory response in turn promoting the development of cardiovascular morbidities.[8,9] We have found a decrease in the plasma of SOD in OSA patients. In situations with a chronically oxidative stress due to overexpression of NF-κB1, there may be a decrease in SOD by a saturation of the antioxidant systems.

We found no differences between the three patient groups in the expression of transcription factors in peripheral musculature. However, in COPD there is a higher level of VCAM and lower SOD than in OSA, reflecting a more intense inflammatory state at the muscle, besides a lower ability to nullify the deleterious effect of free radicals. These findings match with the findings of other authors[10] and agree with that muscle dysfunction in COPD is clinically important. In patients with CCH, inflammatory and oxidative processes in plasma and in muscle fiber seem to be independent. In OSA, there is a correlation between the levels of the NF-KB in plasma and in muscle fiber, as well as between parameters of inflammatory and antioxidant status in plasma and peripheral muscle, suggesting that inflammation and oxidative stress at the systemic levels and in the muscle are interrelated processes.

In summary, the three groups of hypoxemic patients show an overexpression of hypoxia-sensitive transcription factors, with a higher expression of NF-κB in OSA. In plasma, an increase in oxidative stress is evident in the three groups, but the deficit in antioxidant substances is greater in OSA, which may be due to the overexpression of NF-κB. At peripheral muscle, there were no differences in inflammatory parameters, unlike the response to oxidative stress, with an increase in the production of free radicals and a decrease in antioxidant substances in COPD patients versus OSA patients. Inflammation and oxidative stress in plasma and muscle in COPD and COPD-OSA seem to be independent phenomena. In OSA, inflammatory and oxidative stress levels in muscle fiber are related to systemic levels.

## Funding Source

## Conflicts of Interest

None declared.

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## Is a mobile application useful for patients with moderate-severe asthma?☆

### ¿Es útil una aplicación móvil para los pacientes con asma moderada-grave?

*To the Editor:*

In Spain, up to 3.9% of patients with severe asthma have uncontrolled disease,[1–3] partly due to poor adherence to self-management plans or treatment (50 %–67%),[4,5] a situation that generates higher costs.[6]

Telemedicine has been proposed as a potentially useful tool in asthma management,[7,8] although some associated difficulties could impact on its usefulness in daily clinical practice. The current Covid-19 pandemic has highlighted the need for telemonitoring of patients who, given the situation, cannot attend face-to-face consultations. This approach is convenient, avoids travel, increases healthcare efficiency, and in certain situations is the only solution for patient care.[9–11]

We aimed to assess the degree of acceptance and use of a mobile application designed for the follow-up of moderate-severe, uncontrolled asthmatic patients.

In 2015, in conjunction with the Department of Computer Science of the Universidad Pública de Navarra, we developed an app

with two user profiles. The patient's profile gives access to 3 different tabs:

☐ *Control:* recorded daily by the patient using 4 dichotomous questions about symptoms, peak flow value of that day, last reported value of the Asthma Control Test (ACT), and 2 dichotomous questions about treatment administration and the need for rescue medication.
☐ *ACT:* completed monthly. Contains the 5 ACT questions.
☐ *Synchronization:* an additional, complementary tab for updating and refreshing data, for use only in the case of connection problems.

The doctor's profile includes another 2 tabs:

☐ *Diagnosis:* severity, control, spirometry, personal peak flow, comorbidities, and various questionnaire results recorded at inclusion:
   ☐ ACT: self-administered questionnaire to determine degree of asthma control. Consists of 5 questions stratified from 0 to 5 points: poor control is a score $\leq 19$ points.
   ☐ Anxiety and depression: Hospital Anxiety and Depression Scale. Self-administered 14-item questionnaire with subscales of 7 items each (anxiety in odd-numbered questions and depression in even-numbered questions). The score in each subscale ranges from 0 to 21. The higher the score, the higher the anxiety and depression. For both subscales, scores above 10 would indicate a "case", and scores above 7 would be considered a "probable case".
   ☐ Degree of functional dyspnea or hyperventilation (Nijmegen questionnaire): self-administered questionnaire consisting of 16 items scored on a scale from 0 to 4. A score of $\geq 23$ suggests a diagnosis of hyperventilation syndrome.
   ☐ Adherence to asthma treatment: Test of Adherence to Inhalers. Evaluates the degree of therapeutic adherence and identifies patterns of poor adherence (erratic, deliberate, and unconscious). A total of 54 points can be obtained; a score $\leq 45$ points is considered poor adherence.
   ☐ Health-related quality of life: quality of life questionnaire for patients with asthma, short version (Mini-Asthma Quality of Life Questionnaire) and EuroQol-5D. In the first, an average modification of 0.5 in the score obtained in each question, each dimension, or in the overall questionnaire is equivalent to "minimally important clinical change". Differences of about 1.0 represent moderate change and differences > 1.5 represent large changes.
☐ *Incidence:* record of exacerbations and need for additional treatment every 3 months.

Every day, the app automatically generates a color-coded control level (green, yellow, and red), and provides personalized instructions for treatment adjustment (at the discretion of the physician). In case of inadequate control (yellow and red), the physician receives an automatic alert and can respond immediately via the app.

Between December 2015 and December 2017, we successively enrolled 34 outpatients, aged between 18 and 75 years with a proven diagnosis of uncontrolled moderate or severe asthma (according to GINA-GEMA criteria),[1,2] defined as: ACT $\leq 19$ in 2 evaluations performed over a 6-month period and/or $\geq 2$ exacerbations during the previous year requiring systemic corticosteroids. The study was approved by the clinical research ethics committee of the hospital. Exclusion criteria were patient with no smartphone, a primary diagnosis other than asthma, and/or the existence of debilitating mental illness. Of the total number of preselected patients, only 5.7% were excluded because they did not have a smartphone.

**Table 1**
Comparison of variables between groups by app adherence.

|  | Adherence < 65% (n = 9) | Adherence $\geq$ 65% (n = 21) | p |
|---|---|---|---|
| *Age* | 48.1 ± 4.9 | 57.8 ± 8.4 | 0.001 |
| *Sex* | | | |
| Women | 7 | 14 | 0.2 |
| Men | 1 | 7 | |
| *BMI* | 29.6 ± 9.4 | 30.9 ± 7.5 | 0.4 |
| *ACT* | 14.5 ± 4.3 | 17.3 ± 5.5 | 0.2 |
| *TAI* | 48 ± 2.6 | 48 ± 3.2 | 0.1 |
| *Nijmegen* | 29.1 ± 11.7 | 16.7 ± 6.9 | 0.001 |
| *Mini-AQLQ* | 4.1 ± 1.2 | 4.9 ± 1.2 | 0.1 |
| *HAD even numbers* | 7.1 ± 4.8 | 4.5 ± 3.2 | 0.2 |
| *HAD odd numbers* | 11.8 ± 4 | 7.1 ± 2.9 | 0.002 |
| *Satisfaction 3 months* | 24.6 ± 3.7 | 25.9 ± 2.5 | 0.4 |
| *Satisfaction 12 months* | 25.4 ± 4.6 | 27.2 ± 2.3 | 0.4 |
| *GERD* | 5 (55.6) | 10 (47.6) | 0.1 |
| *Rhinitis* | 7 (78) | 13 (62) | 0.7 |

ACT: Asthma Control Test; BMI: body mass index; GERD: gastroesophageal reflux disease; HAD: Hospital Anxiety and Depression Scale; Mini-AQLQ: Mini Asthma Quality of Life Questionnaire; TAI: Test of Adherence to Inhalers.
The data are expressed as mean ± standard deviation or n (%).

Overall, 73% were women, mean age was 54.9 years, and mean baseline ACT was 16.5 points. The socioeconomic status of patients was not specifically assessed, but residence in rural areas was considered when assessing potential problems with the app or network connectivity, although no significant differences were identified.

Thirty patients (91%) completed the follow-up period of 1 calendar year. They attended face-to-face visits in the Severe Asthma Unit every 3 months and had access to the day hospital. The 4 lost-to-follow-up cases were patients who repeatedly failed to attend the face-to-face visits. Patients with low adherence to app use were not excluded from the analysis.

We measured the degree of satisfaction by means of a specifically designed questionnaire consisting of 6 questions scored from 1 ("strongly disagree") to 5 ("strongly agree") points. The mean score was 25.7 out of 30 possible points at 3 months, and was almost 1 point higher (26.5) at the end of the follow-up period. The lowest score was for app/network connectivity (mean 4.07 vs. 3.9 points at 12 months).

To evaluate the use of the app, each patient's input was summarized and the percentage was calculated from the theoretical annual value (365 inputs). Taking into account existing studies,[7,12–14] 65% or higher was considered good adherence. The overall mean was 70%, sustained over time (76% at 3 months and 68% at 6, 9, and 12 months).

An association was revealed between adherence (<65% and $\geq$65%) and age, Nijmegen questionnaire, and anxiety profile on the Hospital Anxiety and Depression Scale (Table 1).

A total of 805 alerts were generated for poor disease control, 87% of which were automatically resolved via the app itself, while remote medical intervention was necessary in 13%.

Although the number of visits to the primary care physician, to the emergency department, hospital and ICU admissions, exacerbations, and need for rescue medication were not the primary aim of this study, data from the preceding year were compared with those from the study year. We also collected data for an economic study of both direct and indirect costs, which will improve the quality of the study.

Access to the health system tailored for typical asthma variability is often difficult or impossible to achieve. Results on the effectiveness of telemedicine are inconclusive.[15]

Adherence to the app was reliably evaluated over a sufficiently long period, since recording was automatically performed on a daily basis, and changes in use over time could be determined (it only decreased by 8 percentage points between months 3 and 6). The

number of patients lost-to-follow-up (11.7%) was acceptable and not due to problems with the app. Satisfaction improved 1 point at completion of follow-up.

We found that less adherent patients scored higher on the anxiety (Hospital Anxiety and Depression Scale) and hyperventilation (Nijmegen) questionnaires, a finding that might aid the identification of individuals who need additional support to improve their use.

Only 13% of alerts generated during the entire follow-up period required medical intervention. This means that the app can be used in daily clinical practice and public health systems without overburdening resources. In addition, it would restrict face-to-face visits to those patients who really need them, while the remaining patients could be monitored in a daily virtual follow-up, essential in situations such as those experienced in the Covid-19 pandemic.

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## Sneeze-induced chylothorax☆

### *Quilotórax inducido por estornudo*

*To the Editor,*

Chylothorax, a pleural effusion with a high content of chylomicrons and triglycerides, is usually caused by surgical complications (esophagectomies, pulmonary resections), lymphomas, liver cirrhosis, or other causes.[1] It rarely occurs spontaneously in association with injuries that are considered "trivial". The only case of chylothorax attributable to sneezing published to date resolved rapidly within a few days.[2] We report, however, another similar case with a course that was not so favorable and required various interventional therapeutic techniques.

A 71-year-old man consulted for progressive dyspnea of two weeks' duration, with no general symptoms, orthopnea, fever, or previous trauma. His history was significant for arterial hypertension, permanent non-valvular atrial fibrillation, and aortic valve replacement with a mechanical prosthesis performed 8 years earlier. He was receiving treatment with acenocoumarol. Chest X-ray revealed left pleural effusion occupying half of the hemithorax. Thoracentesis showed a milky fluid with the following characteristics: leukocytes 1,875/µL (95% lymphocytes), proteins 3.8 g/dL (serum 6.91 g/dL), lactate dehydrogenase 373 U/L (serum 685 U/L), triglycerides 1,203 mg/dL (serum 93 mg/dL), cholesterol 62 mg/dL (serum 197 mg/dL), normal flow cytometry, and cytological studies negative for malignancy. A chest-abdominal CT only showed left pleural effusion with no pleural thickening or enlarged lymph nodes. Intranodal lymphangiography showed extravasation of contrast material (lipiodol) into the left pleural cavity (Fig. 1). The patient was interviewed again and reported several fits of intense sneezing during the days before the appearance of the present symptoms, an event confirmed by his wife. He required two therapeutic thoracenteses of 1 L and 1.25 L over the course of two weeks, so a tunneled pleural catheter (TPC) was inserted for controlled drainage at home. After two weeks of intensive (daily) drainage via the TPC and radiological confirmation of lung re-expansion, 4 g of talc in solution (slurry) were instilled through the TPC. A low-fat diet was also recommended and octeotride (50 mcg/12 h sc) was prescribed, which continued for six weeks. After 10 weeks of talc instillation through the TPC and when three successive drainage