Original Article on Novel Insights into Chronic Cough

A smartphone-based application for cough counting in patients with acute asthma exacerbation

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Background: While tools exist for objective cough counting in clinical studies, there is no available tool for objective cough measurement in clinical practice. An artificial intelligence (AI)-based cough count system was recently developed that quantifies cough sounds collected through a smartphone application. In this prospective study, this AI-based cough algorithm was applied among real-world patients with an acute exacerbation of asthma.

Methods: Patients with an acute asthma exacerbation recorded their cough sounds for 7 days (2 consecutive hours during awake time and 5 consecutive hours during sleep) using Coughy™ smartphone application. During the study period, subjects received systemic corticosteroids and bronchodilator to control asthma. Coughs collected by application were counted by both the AI algorithm and two human experts. Subjects also provided self-measured peak expiratory flow rate (PEFR) and completed other outcome assessments [e.g., cough symptom visual analogue scale (CS-VAS), awake frequency, salbutamol use] to investigate the correlation between cough and other parameters.

Results: A total of 1,417.6 h of cough recordings were obtained from 24 asthmatics (median age =39 years). Cough counts by AI were strongly correlated with manual cough counts during sleep time (rho =0.908, P<0.001) and awake time (rho =0.847, P<0.001). Sleep time cough counts were moderately to strongly correlated with CS-VAS (rho =0.339, P<0.001), the frequency of waking up (rho =0.462, P<0.001), and salbutamol use at night (rho =0.243, P<0.001). Weak-to-moderate correlations were found between awake time cough counts and CS-VAS (rho =0.313, P<0.001), the degree of activity limitation (rho =0.169, P=0.005), and salbutamol use at awake time (rho =0.276, P<0.001). Neither awake time nor sleep time cough counts were significantly correlated with PEFR.

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Conclusions: The strong correlation between cough counts using the AI-based algorithm and human experts, and other indicators of patient health status provides evidence of the validity of this AI algorithm for use in asthma patients experiencing an acute exacerbation. Study findings suggest that Coughy™ could be a novel solution for objectively monitoring cough in a clinical setting.

Keywords: Cough; asthma exacerbation; artificial intelligence (AI); objective cough frequency

Submitted Oct 20, 2022. Accepted for publication May 19, 2023. Published online Jun 09, 2023.
doi: 10.21037/jtd-22-1492
View this article at: https://dx.doi.org/10.21037/jtd-22-1492

Introduction

Cough is a normal defense mechanism of the human body and many diseases like respiratory infections, airway inflammatory diseases, and pulmonary malignancy present with cough as a primary symptom (1). In particular, cough is the most distressing symptom in patients with asthma during an acute exacerbation, and it is also the only symptom in cough variant asthma (2). Cough may precede dyspnea or wheezing in an acute asthma exacerbation, and evidence has been found that monitoring nocturnal coughs may detect asthma exacerbations earlier (3,4). While it is known that cough improves as patients recover from an acute exacerbation of asthma, the detailed natural course of cough in the convalescent phase of acute exacerbation has not been well studied. This is partly because validated objective measures of cough are not yet available for use in clinical practice (5). Thus, physicians have to rely on patient self-report of the pattern, intensity, and frequency of their coughs despite the significance of coughs from asthmatics (5).

Since the 1950s, quantifying cough frequency over prolonged periods has been explored, and only two systems, VitaloJAK™ and the Leicester Cough Monitor (LCM), are currently used in cough research (5,6). These monitoring systems have been found to be effective and accurate in objectively quantifying cough frequency. Specifically, the VitaloJAK™ has been used in the phase 3 clinical trial for the Gefapixant, a novel antitussive agent that antagonize P2X3 receptor, while the LCM was used in the phase 2 clinical trial for PA101, which was a novel formation of inhaled sodium cromoglicate to treat idiopathic pulmonary fibrosis and chronic cough (7). The VitaloJAK™ has also been widely used in clinical trials of various cough medications such as TRPV1 antagonists, sodium channel blockers, neurokinin-1 receptor antagonists, and selective P2X3 receptor antagonists including BLU-5937, sivopixant, and eliapixant (8-13). The VitloJAK™ has a two-step process involving an algorithm to initially filter out non-cough sounds, which results in a shorter file for analysis. Recently, the performance of this VitaloJAK™ filtering algorithm was assessed on 143 patients with refractory chronic cough, showing high sensitivity and reliability (14). Although the VitaloJAK™ is only approved system for monitoring cough for clinical trials of newly developed medications, this cough monitoring system is dependent on manual counts by trained human cough counters, which is labor intensive to quantify the data. It needs manual labor time of 87 (15) and 5 min (16) per 24-h recording for the VitaloJAK™ and LCM, respectively (17). In addition, it requires a special device for recording that is generally bulky and may be uncomfortable for patients to wear for extended periods of time.

Recently, artificial intelligence (AI) and a machine learning-based approach to cough monitoring emerged to address these deficiencies (18-21). Applications that analyze cough sounds and objectively quantify cough from

Highlight box

Key findings

- In a real-world setting with acute asthma exacerbation, the Coughy™ smartphone application, which utilizes an AI training algorithm, demonstrated a significant correlation with trained human cough counters for both awake and sleep time cough counts.

What is known and what is new?

- Conventional cough monitoring systems require significant time and cost due to their reliance on human labor, while the Coughy™ could effectively monitor real-world coughs without human manual counts.

What is the implication, and what should change now?

- The results of this study shed light on the potential clinical utility of a smartphone application with a cough recording and AI analyzing algorithm for monitoring and follow-up of patients with acute asthma exacerbation.

a smartphone recording in near real time through an AI algorithm have substantial advantages over the above-mentioned monitoring systems (22,23). These solutions do not require additional equipment for use like separate microphones or machinery, which could improve patient compliance and convenience. Further, since there is no need for trained human cough counters, which is labor-intensive and time-consuming, costs are lower, and analysis is more efficient. Thus, this AI-based approach for objectively counting cough can improve monitoring for research purposes, as well as clinical use, as treatment response of patients can be monitored in real time. In a previous study, the usefulness of AI-based cough counts was evaluated in patients with acute asthma exacerbation, however cross-sectional measurement of only five voluntary or spontaneous coughs was conducted (22).

In this prospective study, the objective was to evaluate whether cough counts measured by the Coughy™ AI algorithm are in concordance with those measured by humans and assess the correlation of these cough counts with clinical indicators among acute-exacerbated asthmatic patients during their treatment with systemic steroids and bronchodilator. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-1492/rc).

Methods

Study population

Adults (19 to 80 years) experiencing an acute exacerbation of asthma were recruited from eight university hospitals in Korea from May to October 2021. Subjects were eligible to participate if they predominantly presented with cough and needed short-term systemic steroids and a short-acting bronchodilator for symptom control. The presence of asthma was defined as follows: (I) having one or more typical asthmatic symptoms, such as cough, dyspnea, or wheezing, and (II) established airway hyperresponsiveness (AHR) or reversible airway obstruction. AHR was considered positive when PC_{20} [provocative concentration eliciting a 20% decline in forced expiratory volume in 1 second (FEV1)] was less than 16 mg/mL, or the dose of dry mannitol causing a 15% fall in the FEV1 (PD_{15}) was less than 625 mg/mL, in a bronchial provocation test using methacholine chloride or mannitol, respectively. Airway reversibility was confirmed by an increase in FEV1 of at least 200 mL and 12% above baseline following the inhalation of 400 μg of salbutamol or several days or weeks of anti-inflammatory treatment with systemic or inhaled steroids.

Subjects were excluded from the study if they met any of the following criteria: having a disease or condition other than asthma that may cause cough or dyspnea, such as pneumonia, tuberculosis, interstitial lung disease, heart failure, renal failure, pulmonary arterial hypertension, suspected gastroesophageal reflux (GERD) symptoms (e.g. heart burn, regurgitation), proven GERD by gastric endoscopy in the past year, and upper airway disease other than allergic rhinitis and sinusitis which are common comorbid diseases in asthma patients.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Boards of Ewha Womans University Seoul Hospital (No. 2021-05-006-010), Gachon University Gil Medical Center (No. GAIRB2021-258), Korea University Anam Hospital (No. 2021AN0245), SMG-SNU Boramae Medical Center (No. 20-2020-311), Seoul National University Bundang Hospital (No. B-2106-693-403), Seoul National University Hospital (No. J-2008-078-1148), Kangwon National University Hospital (No. KNUH-A-2021-06-021), and Kyungpook National University Chilgok Hospital (No. KNUCH 2021-05-010-001). Written informed consent for participation was obtained from all patients.

Study design

On Day 1, the study subjects were prescribed 7-day of systemic corticosteroids and a short-acting bronchodilator after they underwent baseline pulmonary function test (PFT) including forced vital capacity (FVC) and FEV1. At the discretion of the attending physician, an antitussive and other inhaled or oral medication were permitted to be administered in combination for asthma exacerbation. During the 7-day treatment period, the subjects used Coughy™ to record coughing sounds for 2 h during the day and 5 h during sleep (at a time selected by subjects) for a total of 49 h, using the provided smartphone (iPhone XR, Apple, Cupertino, CA, USA). When recording, the subjects were instructed to place their smartphone 50 to 70 cm away from their face, with the microphones on their smartphones pointing towards their mouths by attaching the smartphone to an armband during awake time and positioning it near the bed during sleep. The smartphone was charged during sleep time to record for consecutive days. Subjects were also instructed to record in an environment without loud living

noises or other person's noises including voices, coughs, and breathing sounds. During the recording, subjects slept alone and did not wear a mask or cover their mouths. On Day 7, each subject visited a clinic and was asked to undergo a follow-up PFT.

Recorded sound files from the smartphone application were collected and uploaded hourly to a secure server. The sound files were sequentially analyzed by both the AI algorithm and trained human cough counters and compared. To protect participant privacy, the cough analysts could only listen to the 0.5-s cough-like audio segments and additional 1 s around the segments if clarification is needed. When analyzed by the human experts, two trained experts independently labelled coughs and non-coughs following the protocol. A supervisor then reviewed any samples where the two trained experts disagreed and adjudicated to make the final decision.

Additional study measures

Each subject was provided a portable peak flow meter (Mini-wright standard PFM 3103085, Clement Clarke International Ltd.) and was instructed to measure their peak expiratory flow rate (PEFR) right after waking up and before sleep. Subjects were also asked to complete a number of patient-reported outcome (PRO) measures daily on the Coughy™ app, including: (I) cough symptom visual analogue scale (CS-VAS), which is a measure of overall daily cough symptom severity ranging from 0 cm (not at all) to 10 cm (extremely), (II) frequencies of wake-up during sleep time, (III) salbutamol use (during awake time and sleep time), (IV) degree of activity limitation (0, not at all; 1, a little; 2, moderate; 3, quite a bit; 4, extremely) at awake time, and (V) degree of asthma-related symptoms including cough, wheezing, dyspnea, and chest tightness at sleep time and awake time (0, not at all; 1, mild; 2, moderate; 3, severe; 4, very severe) (24).

Statistical analyses

Sociodemographic and clinical characteristics were shown in median [interquartile range (IQR)] or frequency (%). Missing data were omitted, and the remaining data were analyzed. Changes in parameters during the study period was assessed using paired Wilcoxon signed rank test. To assess the validity of the Coughy™ AI-based algorithm, Spearman's rank correlations (rho) were calculated between sleep and awake cough counts derived from the AI algorithm and the trained human counters. Further assessments of the validity of cough count measured by Coughy™ was assessed via correlations with the CS-VAS, the frequencies of wake up, salbutamol use, the degree of activity limitation, and PEFR. The strength of the correlations was defined as weak (≥0.1 to <0.30), moderate (≥0.30 to <0.50), and high (≥0.50) according to Cohen guidelines (25). All statistical analyses were performed with SPSS version 19.0 (IBM, Armonk, NY) and GraphPad Prism 8.0 software (GraphPad Software, San Diego, CA, USA).

Results

Characteristics of the study sample

A total of 24 subjects with an acute asthma exacerbation were enrolled, and their sociodemographic and clinical characteristics are presented in *Table 1*. The median age of study subjects was 39 years (IQR, 26.0–49.5), 62.5% were female, and 75.0% were never smokers. The median duration after asthma diagnosis was 46 months (IQR, 9.5–108.0), and 62.5% of subjects had an asthma exacerbation in the past year. Among those enrolled, 54.2% and 29.2% of subjects showed reversible airway obstruction after salbutamol inhalation and anti-inflammatory asthma treatment, respectively, and 20.8% and 4.2% presented AHR in methacholine and mannitol challenge test, respectively. Before treatment for acute asthma exacerbation, the median lung functions at enrollment were 80.0 (IQR, 64.0–93.0) for FVC (% predicted) and 69.0 (IQR, 59.0–82.0) for FEV1 (% predicted). After seven-day treatment for acute asthma exacerbation, the median lung functions were 81.0 (IQR, 72.0–105.0) for FVC (% predicted) and 79.0 (IQR, 75.0–81.0) for FEV1 (% predicted).

All subjects had received low dose inhaled corticosteroid and long-acting beta 2 agonist for their asthma. Among them, 5 (20.8%), 1 (4.2%), 3 (12.5%) had also received leukotriene receptor antagonist, anticholinergics, and oral corticosteroid for their asthma, respectively. Three (12.5%) additionally had taken antihistamine for their comorbid rhinosinusitis.

Changes in study parameters from Day 1 to 7

Compared to Day 1, sleep time cough counts measured by the AI algorithm and human cough counters decreased significantly from Day 5 to 7, while awake time cough

Table 1 Characteristics of study participants.

Characteristics	Subjects (n=24)
Age, years	39 (26.0–49.5)
Female	15 (62.5)
Smoking status	
Never smoker	18 (75.0)
Former smoker	2 (8.3)
Current smoker	4 (16.7)
Asthma duration	
First symptom, months	60 (8.5–120.0)
Diagnosis, months	46 (9.5–108.0)
Treatment, months	36 (0.0–108.0)
Asthma exacerbation in the last year	15 (62.5)
Asthma control status	
Uncontrolled	20 (83.3)
Partly controlled	4 (16.7)
Controlled	0 (0.0)
Comorbid allergic disease	
Allergic rhinitis	19 (79.2)
Sinusitis	8 (33.3)
Atopic dermatitis	5 (20.8)
Urticaria	4 (16.7)
Food allergy	3 (12.5)
Drug allergy	5 (20.8)
Family history of allergic disease	11 (45.8)
Reversible airway obstruction	
After salbutamol inhalation	13 (54.2)
After asthma treatment	7 (29.2)
Airway hyperresponsiveness	
Methacholine challenge test	5 (20.8)
Mannitol challenge test	1 (4.2)
Lung function (before treatment)	
FVC (% predicted)	80.0 (64.0–93.0)
FEV1 (% predicted)	69.0 (59.0–82.0)
Lung function (after treatment)	
FVC (% predicted)	81.0 (72.0–105.0)
FEV1 (% predicted)	79.0 (75.0–81.0)
Serum total IgE, IU/L	265.0 (72.1–569.0)
Peripheral blood eosinophil, /μL	177.0 (81.7–415.9)
Medication	
Low dose ICS/LABA	24 (100.0)
LTRA	5 (20.8)
Anticholinergics	1 (4.2)
OCS	3 (12.5)
Antihistamine	3 (12.5)

Data are shown in median (interquartile range) or frequency (%). FVC, forced vital capacity; FEV1, forced expiratory volume in 1 second; IgE, immunoglobulin E; ICS, inhaled corticosteroid; LABA, long-acting beta2 agonist; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroid.

counts measured by the AI algorithm and human cough counters deceased earlier on Day 2 (*Figure 1A*, Table S1). Sleep time cough counts per hour measured by the AI algorithm and human cough counters decreased significantly on Day 5 and 7, whereas awake time cough counts measured by the AI algorithm and human cough counters deceased earlier on Day 3 (*Figure 1B*, Table S2). The overall CS-VAS also decreased significantly from Day 3 to 7 (*Figure 2A*, Table S3). The frequencies of wake-up decreased significantly on Day 5 and 7, whereas salbutamol use at sleep time and awake time did not change significantly (*Figure 2B*). The degree of activity limitation decreased significantly from Day 3 to 7 (*Figure 2C*), and morning and evening PEFR improved significantly since Day 3 and 2, respectively (*Figure 2D*). The degrees of cough and other symptoms at sleep time decreased significantly since Day 4 and 5, respectively (Table S4). The degrees of cough or wheezing and other symptoms at awake time decreased significantly even earlier since Day 2 and 3, respectively.

Performance characteristics of AI-based cough counting algorithm

A total of 1,417.6 h audio data were collected including 353.7 and 1,063.9 h for awake and sleep, respectively. The median start time of recording was A.M. 08:59 (IQR, 07:21–09:55) for awake time and A.M. 00:01 (IQR,

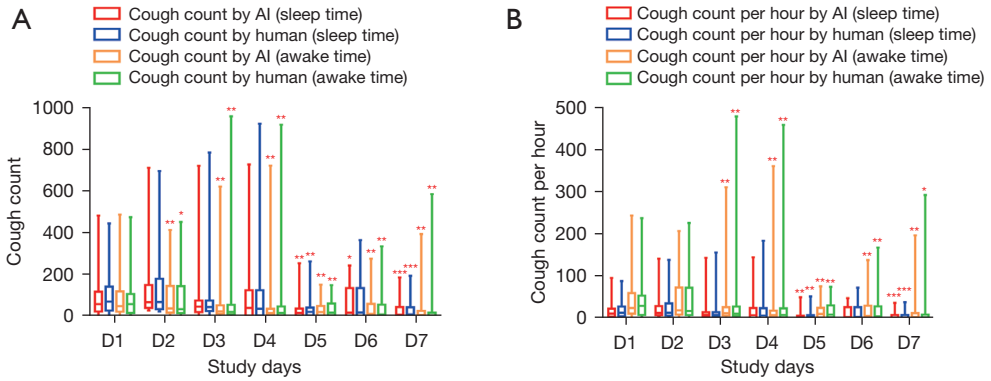

Figure 1 Changes in sleep/awake cough counts measured by human and AI. (A) Total cough counts; (B) cough count per hour. Box plots show median (line), 25 and 75 percentiles (box), and range (whiskers). *P<0.05, **P<0.01, ***P<0.001 compared to Day 1 using paired Wilcoxon singed rank test. AI, artificial intelligence.

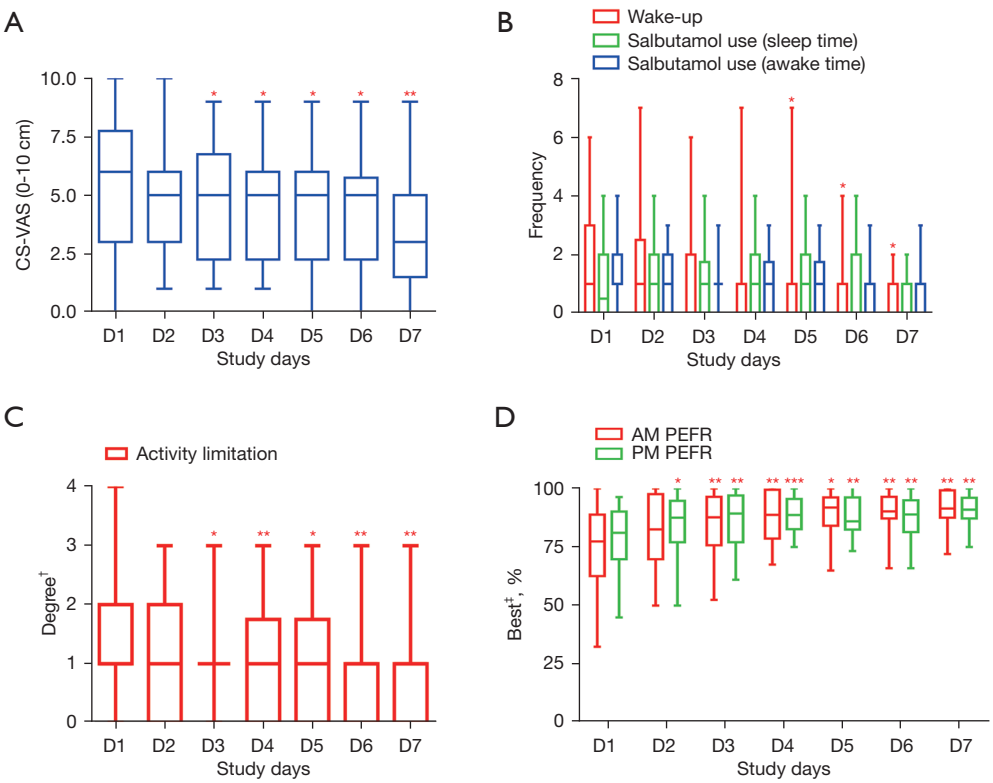

Figure 2 Changes in the clinical parameters through the study period. (A) Changes in overall symptom score using CS-VAS; (B) changes in frequencies of wake-up, and salbutamol use at sleep time and awake time; (C) changes in degree of activity limitation. Changes in A.M. and P.M. PEFR (D). Box plots show median (line), 25 and 75 percentiles (box), and range (whiskers). *P<0.05, **P<0.01, ***P<0.001 compared to Day 1 using paired Wilcoxon singed rank test. †, the degree of activity limitation consists of 0 (not at all), 1 (a little), 2 (moderately), 3 (quite a bit), and 4 (extremely). ‡, the percent of the best values measured during study period in each subject. CS-VAS, cough symptom visual analogue scale; PEFR, peak expiratory flow rate.

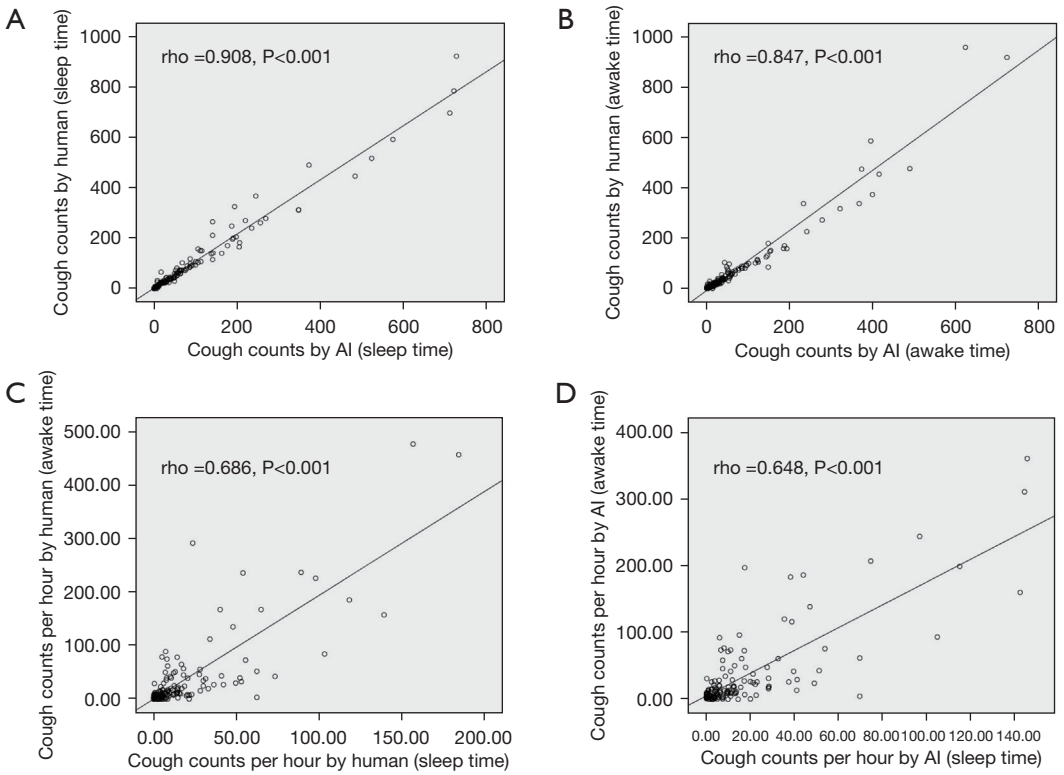

Figure 3 Correlation between cough counts measured by human and AI at sleep time (A) and awake time (B) correlation between awake and sleep cough counts per hour measured by human (C) and AI algorithm (D). AI, artificial intelligence.

22:40–00:57) for sleep time. The median recording hours per subject were 58.0 h (IQR, 56.2–63.0), 14.3 h (IQR, 14.1–15.0) and 43.8 h (IQR, 41.4–47.6) for total, awake and sleep time. From the audio data, total 655,986 cough-like sounds were extracted and classified by human and AI algorithm. The cough count results using human count and from the AI algorithm were compared and it showed 82.3% of sensitivity, 99.1% of specificity and 98.5% of accuracy.

Sleep time and awake time cough counts measured collectively during 7-day study period by trained human cough counters and the AI algorithm were strongly correlated to each other (rho =0.908, P<0.001 and rho =0.847, P<0.001, respectively; *Figure 3A*,*3B*). Interestingly, sleep time and awake time cough counts per hour for each subject were strongly correlated to each other, irrespective of being counted by humans (rho =0.686, P<0.001; *Figure 3C*) or AI (rho =0.648, P<0.001; *Figure 3D*).

In addition, weak or moderate to strong correlations were found between sleep time cough counts measured by AI and CS-VAS (rho =0.339, P<0.001; *Figure 4A*), the frequencies of wake-up (rho =0.462, P<0.001; *Figure 4B*), and salbutamol use at night (rho =0.243, P<0.001; *Figure 4C*), but not with A.M. PEFR (rho =–0.007, P=0.901; *Figure 4D*). Weak to moderate correlations were observed between sleep time cough counts measured by AI and degrees of asthma-related symptoms including cough (rho =0.444, P<0.001; *Figure 4E*), wheezing (rho =0.299, P<0.001; *Figure 4F*), dyspnea (rho =0.318, P<0.001; *Figure 4G*), chest tightness (rho = 0.314, P<0.001; *Figure 4H*) at sleep time, and FEV1 (rho =0.481, P=0.032; *Figure 4I*), but not with FVC (rho =0.171, P=0.447; *Figure 4J*). Weak to moderate correlations were evidenced between awake time cough counts measured by AI and with CS-VAS (rho =0.313, P<0.001; *Figure 5A*), the degree of activity limitation (rho =0.169, P=0.005; *Figure 5B*), and the frequency of salbutamol use at awake time (rho =0.276, P<0.001; *Figure 5C*), but not with P.M. PEFR (rho =–0.085, P=0.115; *Figure 5D*). Moderate to high correlations were seen between awake time cough counts measured by AI and degrees of asthma-related symptoms including cough (rho =0.423, P<0.001; *Figure 5E*), wheezing (rho =0.544, P=0.005; *Figure 5F*), dyspnea (rho =0.320, P<0.001; *Figure 5G*), but not chest tightness (rho =0.318, P=0.115; *Figure 5H*) at

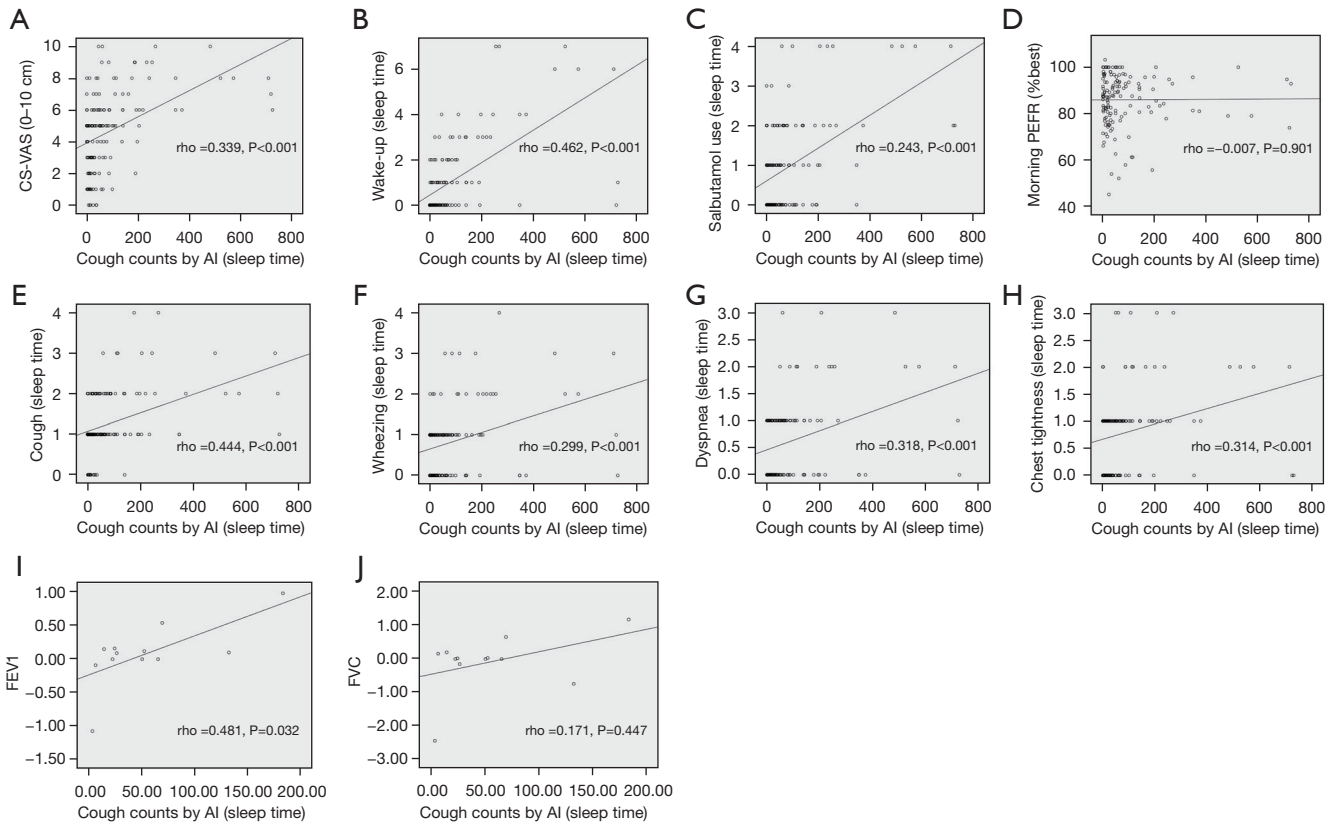

Figure 4 Correlation of sleep cough counts measured by AI with overall symptom score using CS-VAS (A), frequencies of wake-up (B), salbutamol use (C) at sleep time, and A.M. PEFR (D), degrees of asthma-related symptoms including cough (E), wheezing (F), dyspnea (G), chest tightness (H) at sleep time, changes in FEV1 (I), and FVC (J). CS-VAS, cough symptom visual analogue scale; AI, artificial intelligence; PEFR, peak expiratory flow rate; FEV1, forced expiratory volume in 1 second; FVC, force vital capacity.

awake time, FEV1 (rho =0.376, P=0.205; *Figure 5I*), or FVC (rho =0.431, P=0.142; *Figure 5J*).

Discussion

The purpose of this study was to evaluate the recently developed Coughy™ AI algorithm to objectively quantify cough counts among patients in clinical practice. In this study, awake time and sleep time cough sound recordings were obtained using a smartphone application from adults experiencing an acute exacerbation of asthma while receiving systemic corticosteroids for 7 days. Cough sounds were counted by trained human cough counters and compared to results using the Coughy™ AI algorithm. To support the validity of the AI-based algorithm in a real-world setting in patients with asthma, cough counts were significantly correlated with those by trained cough counters both for awake time and sleep time. Further, cough counts using AI algorithm were also moderately to strongly correlated with cough severity as measured by the CS-VAS and the frequencies of wake-up, and rescue medication use, as well as the degree of activity limitation and asthma-related symptom other than cough.

Recently, AI cough monitors have emerged with high sensitivity and specificity, some achieving sensitivity of 86.78% and specificity of 99.42% (26,27). Based on advances in cough sound processing and AI technology, AI-based diagnosis of various respiratory diseases has been investigated (28). In particular, a smartphone-based cough monitoring system is emerging, which includes continuous sound collection with a smartphone application, subsequent signal processing, and noise removal, and finally cough sound identification through machine learning (29,30). There have been studies conducted for detection cough among 7 children hospitalized for respiratory disease, coronavirus disease 2019 screening, and early recognition of

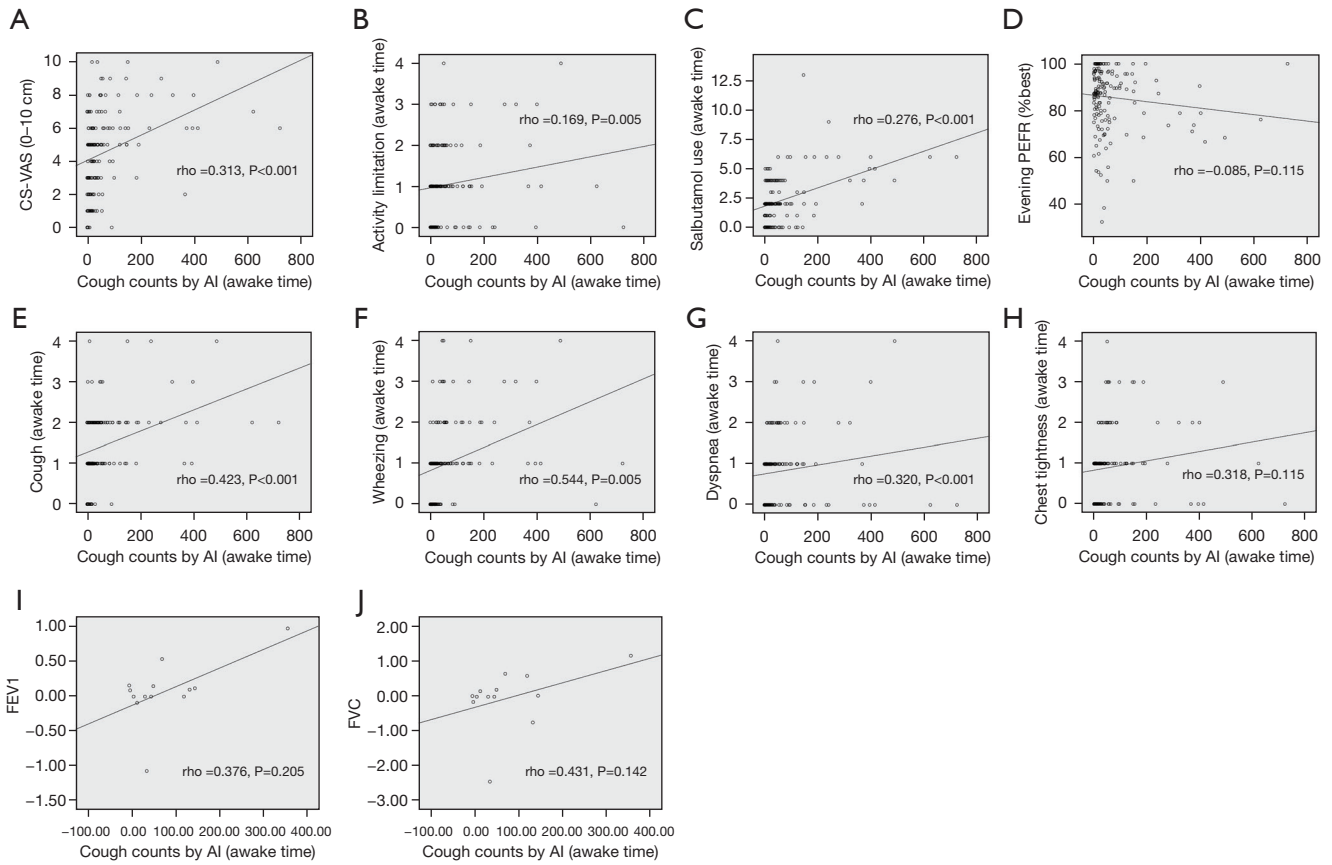

Figure 5 Correlation of awake cough counts measured by AI with overall symptom score using CS-VAS (A), degrees of activity limitation (B), frequency of salbutamol use (C) at awake time, and P.M. PEFR (D), degrees of asthma-related symptoms including cough (E), wheezing (F), dyspnea (G), chest tightness (H) at awake time, changes in FEV1 (I), and FVC (J). CS-VAS, cough symptom visual analogue scale; PEFR, peak expiratory flow rate; FEV1, forced expiratory volume in 1 second; FVC, force vital capacity.

exacerbation of chronic obstructive lung disease and chronic heart failure (31-34).

Although not many, there are also several previous studies on asthma, from a basic study to distinguish voluntary coughs from 12 asthmatics and 12 healthy controls (35), to a recent study which recorded voluntary cough sounds from 89 asthmatics and 89 healthy controls on a smartphone, and analyzed by their audio-based classification model, showing sensitivity and specificity of 83% and 85% in classifying cough between two groups (19). Moreover, the latest prospective diagnostic accuracy study enrolled 119 asthmatics and recorded five voluntary or spontaneous coughs from each subject using a smartphone, to differentiate acute exacerbation of asthma and controlled asthma in these asthmatic patients by AI-based cough sound analysis (22). This study showed that a positive percent agreement between the clinical diagnosis and AI-based detection of asthma exacerbation was 89%. However, it differs from our study in that cross-sectional measurement of only five voluntary or spontaneous coughs rather than cough sound monitoring.

In the current study, the recently developed Coughy™ AI algorithm was used to objectively measure cough counts. The core of AI algorithm consists of two phases: detecting cough-like sounds and classifying events into cough or other sounds. At the cough-like sound detection, the time stamps of cough-like events are saved, and an 0.5 s length audio is extracted from each time stamp. Next, the audios are classified into cough sounds or non-cough sounds by deep learning model based on 2D-convolutional neural network (CNN). To establish this AI cough recognition system, cough data from 130 patients with cough lasting

3 weeks or more were obtained at allergy or pulmonology clinics in Korea. The cough data was divided into training set and test set consisting of 122 subjects (30,786 coughs) and 8 subjects (2,214 coughs), respectively, and the AI algorithm achieved sensitivity of 92% and specificity of 96% in ambulatory setting. Establishment of AI algorithm was previously described (23). The current study analyzed cough sounds from actual asthma patients during an acute asthma exacerbation, and showed a high accordance in cough counts between AI measurements and manual measurement by two trained human experts, which is regarded as the gold standard. Overall, we found that the Coughy™ AI algorithm also worked well in real-world asthma patients.

Awake time and sleep time cough counts showed a significant correlation with CS-VAS. It is interesting to note that the patient's overall cough symptom score continued to improve despite of temporary worsening of the sleep time parameters on Day 2. These findings may suggest that there may be factors other than the cough frequencies or waking up from cough in explaining the discomfort of coughing reported by subjects. It can be another explanation that one or more days would be required for systemic corticosteroids and bronchodilators to relieve nocturnal aggravation of symptoms in patients with acute asthma exacerbation.

There was no significant correlation between either awake time and sleep time cough frequencies and PEFR. This finding is consistent with a previous report, though it was a study of a different setting (36). A post hoc analysis of double-blind, randomized trial regarding the efficacy of beclomethasone/formoterol as a reliever reported no association between self-report questionnaire-based cough or wheezing and lung function including FEV1 and PEFR. This seems to support the involvement of different pathways in cough and bronchoconstriction in the human airway, which needs to be further studied (37,38).

Another noteworthy finding of this study was that the awake time and sleep time cough frequencies were significantly correlated in asthma exacerbation patients. Instead of monitoring the patient for the entire 24 h, we instructed patients to record their coughing sounds for 2 h during the day and select a time for their recording. Although it may be ideal to record cough sounds for 24 h, it may cause considerable inconvenience to patients because there is a risk of interrupting the patient's privacy by recording additional background noises and conversations outside of patients' cough. In this regard, as revealed in our study, it would be very useful at least in asthmatic patients if we could estimate the patient's overall cough symptoms including awake time only by analyzing sleep time cough sounds, which are relatively easy to record. Further research is needed to determine whether this correlation is reproduced not only in asthma but also other respiratory diseases.

Unlike previous studies, the current study did not record voluntary or forced coughs cross-sectionally, but serially monitored involuntary or natural coughs from asthma patients for at least 7 h a day throughout the 7-day treatment period for acute exacerbation of asthma. Thus, the results of this study demonstrate that the Coughy™ AI-based cough analysis recorded by a smartphone could be used for monitoring acute exacerbated asthma treatment response. The AI-based cough count monitoring with a smartphone has benefits in convenience of recording, near real-time analysis, and cost reduction compared to conventional methods like the VitaloJAK™ or LCM. This study has illuminated the possibility of clinical application of the cough recording and AI analyzing algorithm using a smartphone app to monitor and follow-up of the patients with acute exacerbation of asthma. We now plan to evaluate whether light-weight devices like smartwatches can serve as a substitute for smartphone-based cough recordings to improve patient acceptability and usability.

There are several limitations with this study. First, we did not conduct 24-h cough monitoring. We designed this study to record cough sounds for 2 h during the day based on each patient's own selection, and this 2-h of recording may not be sufficient to represent the entire period of awake time. Furthermore, the recording time was not controlled by study protocol but selected by each patient, which may weaken the power of our study. It would be helpful to investigate the most proper and efficient time of the day that represents the patient's overall coughs by examining the correlation between the 24-h recording and the awake time/sleep time recordings by performing the 24-h recording simultaneously. In addition, only 24 patients with asthma were included in the study and further work is needed to generalize the findings to asthma.

Conclusions

Cough monitoring was performed in adult asthma patients with an exacerbation of asthma using the Coughy™ smartphone-enabled AI-based cough monitor technology. Strong correlations have been observed between AI cough counts and trained cough counters, as well as with other patient-reported endpoints, which supports the usefulness

of this technology as an objective measurement of cough frequency in patients with asthma.

Acknowledgments

We thank Soundable Health, Inc. for providing Coughy™ AI algorithm.
Funding: This work was supported by Institute for Information & Communications Technology Promotion (IITP) grant funded by the Korea government (MSIP) (No. 2020-0-02111), Development of Acoustic AI Platform Technology for Monitoring and Managing Respiratory.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editors (Woo-Jung Song and Kian Fan Chung) for the series "Novel Insights into Chronic Cough" published in *Journal of Thoracic Disease*. The article has undergone external peer review.

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-1492/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-1492/dss

Peer Review File: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-1492/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-1492/coif). The series "Novel Insights into Chronic Cough" was commissioned by the editorial office without any funding or sponsorship. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Boards of Ewha Womans University Seoul Hospital (No. 2021-05-006-010), Gachon University Gil Medical Center (No. GAIRB2021-258), Korea University Anam Hospital (No. 2021AN0245), SMG-SNU Boramae Medical Center (No. 20-2020-311), Seoul National University Bundang Hospital (No. B-2106-693-403), Seoul National University Hospital (No. J-2008-078-1148), Kangwon National University Hospital (No. KNUH-A-2021-06-021), and Kyungpook National University Chilgok Hospital (No. KNUCH 2021-05-010-001). Written informed consent for participation was obtained from all patients.

References

1. Lee JH, Song WJ. Perspectives on chronic cough in Korea. J Thorac Dis 2020;12:5194-206.
2. Niimi A. Narrative Review: how long should patients with cough variant asthma or non-asthmatic eosinophilic bronchitis be treated? J Thorac Dis 2021;13:3197-214.
3. Tinschert P, Rassouli F, Barata F, et al. Smartphone-based cough detection predicts asthma control – description of a novel, scalable digital biomarker. Eur Respir J 2020;56:4569.
4. Chang AB, Harrhy VA, Simpson J, et al. Cough, airway inflammation, and mild asthma exacerbation. Arch Dis Child 2002;86:270-5.
5. Hall JI, Lozano M, Estrada-Petrocelli L, et al. The present and future of cough counting tools. J Thorac Dis 2020;12:5207-23.
6. Smith J, Woodcock A. New developments in the objective assessment of cough. Lung 2008;186 Suppl 1:S48-54.
7. Birring SS, Wijsenbeek MS, Agrawal S, et al. A novel formulation of inhaled sodium cromoglicate (PA101) in idiopathic pulmonary fibrosis and chronic cough: a randomised, double-blind, proof-of-concept, phase 2 trial. Lancet Respir Med 2017;5:806-15.
8. Smith JA, McGarvey LPA, Badri H, et al. Effects of a novel sodium channel blocker, GSK2339345, in patients with refractory chronic cough. Int J Clin Pharmacol Ther 2017;55:712-9.
9. Morice A, Smith JA, McGarvey L, et al. Eliapixant (BAY

1817080), a P2X3 receptor antagonist, in refractory chronic cough: a randomised, placebo-controlled, crossover phase 2a study. Eur Respir J 2021;58:2004240.
10. Smith J, Morice A, Birring S, et al. Improvements in Cough Frequency Over 24 Hours with BLU-5937, a Selective P2X3 Antagonist, in Patient Subgroups Defined by Baseline Awake Cough Frequencies. Am J Respir Crit Care Med 2021;203:A1019.
11. Smith J, Allman D, Badri H, et al. The Neurokinin-1 Receptor Antagonist Orvepitant Is a Novel Antitussive Therapy for Chronic Refractory Cough: Results From a Phase 2 Pilot Study (VOLCANO-1). Chest 2020;157:111-8.
12. Smith JA, Murdoch R, Newlands A, et al. P152 the impact of a selective oral TRPV1 antagonist in patients with chronic cough. Thorax 2012;67:A128.
13. Niimi A, Saito J, Kamei T, et al. Randomised trial of the P2X(3) receptor antagonist sivopixant for refractory chronic cough. Eur Respir J 2022;59:2100725.
14. Smith JA, Holt K, Dockry R, et al. Performance of a digital signal processing algorithm for the accurate quantification of cough frequency. Eur Respir J 2021;58:2004271.
15. Barton A, Gaydecki P, Holt K, et al. Data reduction for cough studies using distribution of audio frequency content. Cough 2012;8:12.
16. Lee KK, Matos S, Evans DH, et al. A longitudinal assessment of acute cough. Am J Respir Crit Care Med 2013;187:991-7.
17. Spinou A, Birring SS. An update on measurement and monitoring of cough: what are the important study endpoints? J Thorac Dis 2014;6:S728-34.
18. Porter P, Abeyratne U, Swarnkar V, et al. A prospective multicentre study testing the diagnostic accuracy of an automated cough sound centred analytic system for the identification of common respiratory disorders in children. Respir Res 2019;20:81.
19. Hee HI, Balamurali B, Karunnakaran A, et al. Development of Machine Learning for Asthmatic and Healthy Voluntary Cough Sounds: A Proof of Concept Study. Appl Sci 2019;9:2833.
20. Zimmer AJ, Ugarte-Gil C, Pathri R, et al. Making cough count in tuberculosis care. Commun Med (Lond) 2022;2:83.
21. Santosh KC, Rasmussen N, Mamun M, et al. A systematic review on cough sound analysis for Covid-19 diagnosis and screening: is my cough sound COVID-19? PeerJ Comput Sci 2022;8:e958.
22. Porter P, Brisbane J, Abeyratne U, et al. A smartphone-based algorithm comprising cough analysis and patient-reported symptoms identifies acute exacerbations of asthma: a prospective, double blind, diagnostic accuracy study. J Asthma 2023;60:368-76.
23. Shim JS, Kim MH, Lee SM, et al. An artificial intelligence algorithm-based smartphone application for daily cough monitoring. Allergy 2023;78:1378-80.
24. Globe G, Wiklund I, Lin J, et al. Psychometric Properties of the Asthma Symptom Diary (ASD), a Diary for Use in Clinical Trials of Persistent Asthma. J Allergy Clin Immunol Pract 2016;4:60-6.e4.
25. Cohen J. Statistical Power Analysis for the Behavioral Sciences. 2nd ed. New York (NY): Lawrence Erlbaum Associates; 1988.
26. Adhi Pramono RX, Anas Imtiaz S, Rodriguez-Villegas E. Automatic Identification of Cough Events from Acoustic Signals. Annu Int Conf IEEE Eng Med Biol Soc 2019;2019:217-20.
27. Liu JM, You M, Wang Z, et al., editors. Cough detection using deep neural networks. 2014 IEEE International Conference on Bioinformatics and Biomedicine (BIBM); 2014. 2-5 Nov. 2014.
28. Alqudaihi KS, Aslam N, Khan IU, et al. Cough Sound Detection and Diagnosis Using Artificial Intelligence Techniques: Challenges and Opportunities. IEEE Access 2021;9:102327-44.
29. Kvapilova L, Boza V, Dubec P, et al. Continuous Sound Collection Using Smartphones and Machine Learning to Measure Cough. Digit Biomark 2019;3:166-75.
30. Hoyos-Barceló C, Monge-Álvarez J, Pervez Z, et al. Efficient computation of image moments for robust cough detection using smartphones. Comput Biol Med 2018;100:176-85.
31. Kruizinga MD, Zhuparris A, Dessing E, et al. Development and technical validation of a smartphone-based pediatric cough detection algorithm. Pediatr Pulmonol 2022;57:761-7.
32. Zhang X, Pettinati M, Jalali A, et al. Novel COVID-19 Screening Using Cough Recordings of A Mobile Patient Monitoring System. Annu Int Conf IEEE Eng Med Biol Soc 2021;2021:2353-7.
33. Ponomarchuk A, Burenko I, Malkin E, et al. Project Achoo: A Practical Model and Application for COVID-19 Detection From Recordings of Breath, Voice, and Cough. IEEE J Sel Top Signal Process 2022;16:175-87.
34. Windmon A, Minakshi M, Bharti P, et al. TussisWatch: A Smart-Phone System to Identify Cough Episodes as Early Symptoms of Chronic Obstructive Pulmonary Disease and

Congestive Heart Failure. IEEE J Biomed Health Inform 2019;23:1566-73.
35. Al-Khassaweneh M, Bani Abdelrahman R. A signal processing approach for the diagnosis of asthma from cough sounds. J Med Eng Technol 2013;37:165-71.
36. Morjaria JB, Rigby AS, Morice AH. Asthma phenotypes: do cough and wheeze predict exacerbations in persistent asthma? Eur Respir J 2017;50:1701366.
37. Choudry NB, Fuller RW, Anderson N, et al. Separation of cough and reflex bronchoconstriction by inhaled local anaesthetics. Eur Respir J 1990;3:579-83.
38. Fuller RW, Karlsson JA, Choudry NB, et al. Effect of inhaled and systemic opiates on responses to inhaled capsaicin in humans. J Appl Physiol (1985) 1988;65:1125-30.

Cite this article as: Shim JS, Kim BK, Kim SH, Kwon JW, Ahn KM, Kang SY, Park HK, Park HW, Yang MS, Kim MH, Lee SM. A smartphone-based application for cough counting in patients with acute asthma exacerbation. J Thorac Dis 2023;15(7):4053-4065. doi: 10.21037/jtd-22-1492

Supplementary

Table S1 Changes in sleep/awake cough counts measured by artificial intelligence (AI) and human through the study period

Cough counts (total)	Study period						
	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
AI (/sleep time)	58 (20, 104.5)	52 (7.5, 105)	49 (14.8, 76.5)	23.5 (0, 80)	12 (1.3, 37.8)**	17 (0, 100)*	11 (3.8, 46.8)***
Human (/sleep time)	68 (27, 130.5)	47.5 (6.3, 105)	45 (26.5, 76.8)	22.5 (0.3, 80.3)	18.5 (2.3, 42.3)**	21 (0, 107)	12 (3.75, 46.5)***
AI (/awake time)	51.5 (24.8, 122)	40 (17.8, 132)**	26.5 (14.5, 55.8)**	18 (7.3, 38.5)**	21.5 (5, 52)**	14 (8, 62)**	8 (2.5, 28)**
Human (/awake time)	61 (18.8, 109.8)	35 (15.8, 130.3)*	24 (13.3, 57.8)**	19 (6.5, 49.8)**	18.5 (7, 63.3)**	12 (4, 59)**	12 (3.8, 46.5)**

Data are presented as median (interquartile ranges). *P<0.05, **P<0.01, ***P<0.001 compared to Day 1 using paired Wilcoxon singed rank test.

Table S2 Changes in sleep/awake cough counts per hour measured by artificial intelligence (AI) and human through the study period

Cough counts (per hour)	Study period						
	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
AI (/sleep time)	12.3 (5.1, 24.1)	14.1 (8.6, 30.4)	9.8 (4.6, 15.6)	8.6 (1.0, 25.5)	3.8 (1.2, 7.9)**	4 (0.4, 27.6)	2.2 (0.8, 9.4)***
Human (/sleep time)	14.5 (6.0, 28.9)	14.3 (7.4, 36.4)	9.4 (5.6, 15.6)	7.7 (1.1, 25.4)	4.7 (1.2, 8.9)**	4.2 (0.4, 27.6)	2.4 (0.8, 9.3)***
AI (/awake time)	25.8 (12.4, 61.0)	20.0 (10.0, 74.0)	13.3 (7.3, 27.9)**	9.0 (3.7, 19.3)**	11.5 (2.5, 26.0)**	7.0 (4.0, 31)**	3.8 (0.8, 13.5)**
Human (/awake time)	30.5 (9.4, 54,9)	18.5 (9.0, 73.5)	12.0 (6.6, 28.9)**	9.5 (3.3, 24.9)**	10.0 (3.5, 32.0)**	6 (2.0, 29.5)**	3.3 (2.0, 10.1)*

Data are presented as median (interquartile ranges). *P<0.05, **P<0.01, ***P<0.001 compared to Day 1 using paired Wilcoxon singed rank test.

Table S3 Changes in CS-VAS, the frequency of wake up and salbutamol use, the degree of activity limitation, and morning and evening PEFR through the study period

Variables	Study period						
	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
CS-VAS	5 (3, 7)	5 (3, 6)	5 (2.25, 6.75)*	5 (2.25, 6)*	5 (2.25, 6)*	5 (2.25, 5.75)*	3 (1.5, 5)**
Wake up	1 (0, 2.75)	1 (0, 2)	0 (0, 1.75)	0 (0, 1)	0 (0, 0.75)*	0 (0, 1)*	0 (0, 1)*
Salbutamol use (/sleep time)	0.5 (0, 2)	0.5 (0, 2)	1 (0, 1.75)	1 (0, 2)	1 (0, 1.75)	0 (0, 2)	0 (0, 1)
Salbutamol use (/awake time)	2 (1, 4)	2 (1, 3.75)	2 (2, 4)	2 (1.25, 4)	2 (0.25, 4)	2 (0, 3.5)	2 (0, 2.75)
Activity limitation[†] (/awake time)	1 (1, 2)	1 (0, 2)	1 (1, 1)*	0 (0, 1.75)**	1 (0, 1.75)*	1 (0, 1)**	1 (0, 1)**
AM PEFR, %best[‡]	81.0 (69.8, 90.1)	85.0 (66.2, 94.3)	89.4 (77.1, 97.1)**	88.6 (82.6, 95.5)**	85.7 (82.2, 96.1)*	88.9 (81.4, 95.0)**	91.0 (87.2, 96.0)**
PM PEFR, %best[‡]	77.4 (62.6, 88.9)	82.6 (69.8, 97.6)*	87.7 (75.7, 96.5)**	88.8 (78.6, 99.5)***	91.9 (84.2, 96.2)**	90.2 (87.2, 96.4)**	91.5 (87.5, 99.2)**

Data are presented as median (interquartile ranges). *P<0.05, **P<0.01, ***P<0.001 compared to Day 1 using paired Wilcoxon singed rank test. [†]The degree of activity limitation consists of 0 (not at all), 1 (a little), 2 (moderately), 3 (quite a bit), and 4 (extremely). [‡]The percent of the best values measured during study period in each subject. CS-VAS, cough symptom visual analogue scale ranging from 0 cm (not at all) to 10 cm (extremely); PEFR, peak expiratory flow rate.

https://dx.doi.org/10.21037/jtd-22-1492

Table S4 Changes in the degree of asthma-related symptoms including cough, wheezing, dyspnea, and chest tightness through the study period

Variables	Study period						
	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Sleep time							
Cough							
Grade 0	0 (0.0)	1 (4.2)	0 (0.0)	5 (20.8)	7 (29.3)	4 (16.7)	4 (16.7)
Grade 1	14 (58.3)	12 (50.0)	13 (54.2)	12 (50.0)	12 (50.0)	15 (62.5)	13 (54.2)
Grade 2	7 (29.2)	7 (29.2)	9 (37.5)	6 (25.0)	4 (16.7)	3 (12.5)	3 (12.5)
Grade 3	2 (8.3)	2 (8.3)	2 (8.3)	1 (4.2)	0 (0.0)	1 (4.2)	1 (4.2)
Grade 4	1 (4.2)	1 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Wheezing							
Grade 0	6 (25.0)	5 (20.8)	8 (33.3)	9 (37.5)	0 (37.5)	12 (50.0)	11 (45.8)
Grade 1	12 (50.0)	14 (58.3)	12 (50.0)	11 (45.8)	12 (50.0)	8 (33.3)	7 (29.2)
Grade 2	4 (16.7)	2 (8.3)	2 (8.3)	3 (12.5)	2 (8.3)	3 (12.5)	2 (8.3)
Grade 3	2 (8.3)	1 (4.2)	2 (8.3)	1 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)
Grade 4	0 (0.0)	1 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Dyspnea							
Grade 0	7 (29.2)	8 (33.3)	12 (50.0)	13 (54.2)	13 (54.2)	14 (58.3)	12 (50.0)
Grade 1	15 (62.5)	11 (45.8)	9 (37.5)	9 (37.5)	8 (33.3)	7 29.2)	7 (29.2)
Grade 2	1 (4.2)	4 (16.7)	2 (8.3)	1 (4.2)	2 (8.3)	2 (8.3)	1 (4.2)
Grade 3	1 (4.2)	0 (0.0)	1 (4.2)	1 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)
Grade 4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Chest tightness							
Grade 0	6 (25.0)	5 (20.8)	9 (37.5)	9 (37.5)	11 (45.8)	11 (45.8)	8 (33.3)
Grade 1	13 (54.2)	13 (54.2)	12 (50.0)	12 (50.0)	12 (50.0)	9 (37.5)	11 (45.8)
Grade 2	3 (12.5)	3 (12.5)	2 (8.3)	2 (8.3)	0 (0.0)	3 (12.5)	1 (4.2)
Grade 3	2 (8.3)	2 (8.3)	1 (4.2)	1 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)
Grade 4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Awake time							
Cough							
Grade 0	0 (0.0)	0 (0.0)	2 (8.3)	1 (4.2)	3 (12.5)	5 (20.8)	4 (16.7)
Grade 1	4 (16.7)	13 (54.2)	12 (50.0)	13 (54.2)	12 (50.0)	12 (50.0)	13 (54.2)
Grade 2	16 (66.7)	9 (37.5)	8 (33.3)	10 (41.7)	8 (33.3)	6 (25.0)	5 (20.8)
Grade 3	1 (4.2)	1 (4.2)	2 (8.3)	0 (0.0)	1 (4.2)	1 (4.2)	1 (4.2)
Grade 4	3 (12.5)	1 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.2)
Wheezing							
Grade 0	5 (20.8)	5 (20.8)	7 (29.2)	9 (37.5)	10 (41.7)	8 (33.3)	12 (50.0)
Grade 1	7 (29.2)	14 (58.3)	13 (54.2)	9 (37.5)	10 (41.7)	13 (54.2)	9 (37.5)
Grade 2	9 (37.5)	1 (4.2)	3 (12.5)	4 (16.7)	2 (8.3)	1 (4.2)	2 (8.3)
Grade 3	1 (4.2)	2 (8.3)	1 (4.2)	2 (8.3)	2 (8.3)	2 (8.3)	0 (0.0)
Grade 4	2 (8.3)	2 (8.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.2)
Dyspnea							
Grade 0	5 (20.8)	10 (41.7)	8 (3.3)	11 (45.8)	12 (50.0)	12 (50.0)	13 (54.2)
Grade 1	12 (50.0)	10 (41.7)	12 (50.0)	8 (33.3)	7 (29.2)	9 (37.5)	8 (33.3)
Grade 2	4 (16.7)	3 (12.5)	3 (12.5)	3 (12.5)	5 (20.8)	3 (12.5)	3 (12.5)
Grade 3	1 (4.2)	1 (4.2)	1 (4.2)	2 (8.3)	0 (0.0)	0 (0.0)	0 (0.0)
Grade 4	2 (8.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Chest tightness							
Grade 0	5 (20.8)	7 (29.2)	7 (29.2)	7 (29.2)	9 (37.5)	10 (41.7)	12 (50.0)
Grade 1	13 (54.2)	12 (50.0)	12 (50.0)	13 (54.2)	12 (50.0)	11 (45.8)	9 (37.5)
Grade 2	3 (12.5)	3 (12.5)	4 (16.7)	2 (8.3)	2 (8.3)	3 (12.5)	2 (8.3)
Grade 3	2 (8.3)	2 (8.3)	1 (4.2)	2 (8.3)	1 (4.2)	0 (0.0)	1 (4.2)
Grade 4	1 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Data are presented as frequency (percent). The degree of asthma-related symptoms consists of 0 (not at all), 1 (mild), 2 (moderate), 3 (severe), and 4 (very severe).

https://dx.doi.org/10.21037/jtd-22-1492