Smartphone-based cough monitoring as a near real-time digital pneumonia biomarker

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Shareable abstract (@ERSpublications)
Smartphone-based cough monitoring delineates individual cough trajectories of hospitalised pneumonia patients correlating with disease activity. Cough count levels depend on daytime and are associated with clinical markers of oxygenation and inflammation. https://bit.ly/3klUBqf

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Abstract

Background Cough represents a cardinal symptom of acute respiratory tract infections. Generally associated with disease activity, cough holds biomarker potential and might be harnessed for prognosis and personalised treatment decisions. Here, we tested the suitability of cough as a digital biomarker for disease activity in coronavirus disease 2019 (COVID-19) and other lower respiratory tract infections.

Methods We conducted a single-centre, exploratory, observational cohort study on automated cough detection in patients hospitalised for COVID-19 (n=32) and non-COVID-19 pneumonia (n=14) between April and November 2020 at the Cantonal Hospital St Gallen, Switzerland. Cough detection was achieved using smartphone-based audio recordings coupled to an ensemble of convolutional neural networks. Cough levels were correlated to established markers of inflammation and oxygenation.

Measurements and main results Cough frequency was highest upon hospital admission and declined steadily with recovery. There was a characteristic pattern of daily cough fluctuations, with little activity during the night and two coughing peaks during the day. Hourly cough counts were strongly correlated with clinical markers of disease activity and laboratory markers of inflammation, suggesting cough as a surrogate of disease in acute respiratory tract infections. No apparent differences in cough evolution were observed between COVID-19 and non-COVID-19 pneumonia.

Conclusions Automated, quantitative, smartphone-based detection of cough is feasible in hospitalised patients and correlates with disease activity in lower respiratory tract infections. Our approach allows for near real-time telemonitoring of individuals in aerosol isolation. Larger trials are warranted to decipher the use of cough as a digital biomarker for prognosis and tailored treatment in lower respiratory tract infections.

Introduction

Lower respiratory tract infections are prevalent, have a high rate of in-hospital mortality, and represent a significant economic and resource-demanding burden worldwide. This could be witnessed first-hand during the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic associated with coronavirus disease 2019 (COVID-19) [1], which virtually stretched healthcare systems to their limits. The course of lower respiratory tract infection is heterogeneous and can involve complications including co-infections or empyema. Thus, it is important to rely on accurate markers of disease activity. Nowadays, apart from classical clinical examination and the evaluation of vital signs, the assessment of disease activity is primarily based on laboratory-based, biochemical markers. Such markers, however, require blood sampling, only provide a snapshot of the disease, depend on laboratory equipment and staff, have technical and biological time delays, and might be cost-intensive. It would therefore be of high relevance

to have a noninvasive, quantitative real-time measurement of disease activity in pneumonia. In this context, digital biomarkers would be desirable to personalise treatment approaches and enable better timing of hospital admission and medical emergency interventions such as invasive ventilation [2, 3].

Referred to as "the watchdog of the lungs" almost 100 years ago [4], the cough reflex repels potentially dangerous material to prevent lung access and further helps to clear the lungs from invading pathogens and particles. In lower respiratory tract infections, including COVID-19, cough represents a cardinal symptom whose level is thought to be associated with disease activity and progressively decline towards resolution of the infection. Cough levels, therefore, might hold biomarker potential in COVID-19 and other lower respiratory tract infections. Of note, in communicable respiratory diseases, cough is of additional importance considering that coughing contributes to pathogen aerosolisation and, thus, increases the contamination of surrounding air, which fosters onward transmission [5].

While it is easy to recognise a single cough event or note that a patient is coughing (*e.g.* "sporadically" or "a lot"), the objective, reproducible and clinically relevant quantification of cough over extended periods of time has remained challenging [6]. In fact, no standardised technology for cough assessment and quantification thoroughly validated in a clinical setting is available to date even though several automated cough monitors have been developed [7, 8]. Of note, the potential value of cough/sound detection for COVID-19 pre-screening, diagnosis and classification is increasingly recognised [9, 10]. However, to our knowledge, no study has so far analysed cough frequencies in hospitalised COVID-19 patients over days to weeks and correlated cough count evolution with the course of disease and clinical and laboratory parameters.

In our previous work we developed a dedicated smartphone-based cough detection system successfully used to assess disease control and predict attacks in asthma [11–13]. Here, we harnessed this groundwork for further technological development and applied our machine learning-based technology to acute cough caused by lower respiratory tract infections during the SARS-CoV-2 pandemic, after optimisation and validation specifically in COVID-19 cough [14]. The aim of the current study was to prove the feasibility of automated, near real-time, noninvasive, smartphone-based cough detection in hospitalised patients, and to assess the correlation of cough frequency measures with pneumonia disease activity.

Material and methods

Study subjects

In total, 46 patients were enrolled in the study, of which 32 (70%) had COVID-19 pneumonia and 14 (30%) had non-COVID-19 pneumonia (table 1). Males were over-represented in the study cohort (83%), and 87% of patients had pre-existing medical conditions. 28 patients (61%) were 60 years or older, and only four patients (9%) were younger than 50 years. Two patients (4%) clinically deteriorated during the study, which resulted in one intensive care unit (ICU) admission and one death. All other patients recovered in the general ward and could be finally discharged after a median length of hospital stay of 9.5 days and a median length of cough detection of 7 days. In the absence of contraindications, patients received low-molecular-weight heparin (enoxaparin) by default. Within the COVID-19 cohort, 12 patients (38%) received treatment with remdesivir, hydroxychloroquine or aviptadil, each of which was given off-label at the time of study. Patients gave written informed consent to participate in the study and be audio-recorded during their hospital stay. The study was reviewed by the Ethikkommission Ostschweiz (EKOS) and approved under BASEC number 2020-00741.

Study design

The study was designed as a prospective, observational, single-centre, exploratory cohort study. Between April and November 2020 (during the initial COVID-19 waves in Switzerland) we recruited a total of 46 patients hospitalised for pneumonia at the Cantonal Hospital St Gallen, a tertiary care centre located in Eastern Switzerland. The target sample size was defined in the study protocol and calculated based on assumptions from an early retrospective cohort study on risk factors for COVID-19 mortality from Wuhan, China [15], using an indirect proxy for cough. According to protocol, the primary study end-point was treatment outcome as defined as secondary ICU admission or death. However, as both of these events occurred only once, we had to focus our analyses on more exploratory end-points and ultimately targeted clinical and laboratory markers of disease activity. Inclusion criteria for study participation were: 1) hospitalisation due to a lower respiratory tract infection; 2) age $\geqslant$18 years; and 3) willingness and ability to provide written informed consent. Direct admission to the ICU was the sole exclusion criterion. Depending on the final diagnosis, patients were subdivided into COVID-19 and non-COVID-19 pneumonia, in which inclusion/exclusion criteria were equally applicable to both groups. Some baseline characteristics were statistically different between COVID-19 and non-COVID-19 pneumonia cases (table 1).

TABLE 1 Characteristics of patients enrolled in this study (n=46)

Parameter	COVID-19	Non-COVID-19	p-value
Patients, n	32	14	
Age, years	63 (29–85)	57.5 (30–84)	0.796
Length of cough detection, days	7 (2–23)	5 (2–17)	0.157
Length of hospital stay, days	11 (4–25)	6 (3–20)	0.074
BMI, kg·m^{-2}	31.8 (21–46)	25.3 (17.4–33)	<0.001
Female/male	6 (19)/26 (81)	2 (14)/12 (86)	1
Clinical deterioration/adverse outcome			
ICU admission	1 (3)	0 (0)	1
Death	0 (0)	1 (7)	1
Frequent comorbidities			
Type 2 diabetes and prediabetes	16 (50)	1 (7)	0.015
Hypertension	10 (31)	3 (21)	0.268
Obesity	10 (31)	0 (0)	0.010
Cancer of any kind	3 (9)	6 (43)	0.026
COPD	1 (3)	4 (29)	0.041
Asthma	3 (9)	1 (7)	1
Sleep apnoea	3 (9)	2 (14)	1
Smoking status			
Never	14 (44)	4 (28)	0.521
Former	16 (50)	5 (36)	0.566
Current	2 (6)	5 (36)	0.035
Off-label medication for COVID-19			
Hydroxychloroquine	4 (13)	NA	NA
Remdesivir	4 (13)	NA	NA
Aviptadil	4 (13)	NA	NA

Data are presented as median (range) or n (%) unless otherwise stated. BMI: body mass index; ICU: intensive care unit; NA: not applicable.

Methods

An automated, unobtrusive, near real-time, contact-free, smartphone-based cough detection system was developed using data from previous studies [11–13]. We continuously monitored cough frequencies by counting the expulsive phases of cough over extended periods of time (2–23 days) from a distance of 1–2 m from the patients' bedsides. We used Samsung Galaxy A3 2017 SM-A320FL Android smartphones running the cough detection app and additionally equipped with secure digital cards (ScanDisk Ultra microSDXC A1 64GB 100 MBs Adapt) to increase the memory capacity for local backup data storage. The cough detection app essentially records audio tracks (sounds) using the built-in microphone of the smartphone and detects coughing events on-device in a time-resolved manner based on a convolutional neural network approach. The cough detection data are continuously received by the app's backend and sent in near real-time to a secure server (here, a dedicated server from ETH Zurich) for display on a web client. Further details on the technology as well as system performance and validation specifically for COVID-19 cough are summarised in a separate article [14].

Analysis

Cough frequency is shown as the "number of coughs per hour", the "mean number of coughs per hour", or the "number of coughs per 6 hours". Cough counts were descriptively analysed as a function of time both in the whole study cohort and in stratified patient subgroups. Correlations among baseline clinical parameters and cough counts were investigated using principal component analysis (PCA) computed using the nonlinear iterative partial least squares (NIPALS) algorithm [16]. Generalised linear mixed Poisson regression models were used to analyse the association between cough counts and various explanatory clinical and laboratory parameters, considering within-patient repeated measurements. Cough frequency followed circadian cycles which were modelled by adjusting for hour of the day using harmonic sine and cosine terms. Independent variables were included in the models in order to test the association between clinical variables and cough counts. Data were analysed using the R statistical software (www.r-project.org) and the nominal significance level was 0.05.

Results

Feasibility of in-hospital automated cough detection

The cough-recording smartphones were placed in close proximity to the patients' bedsides in recording/transmitting mode (figure 1). Of the recruited 46 patients, we had to exclude one patient from analysis because of poor data quality (extensive background noise) and another one because the patient's roommate did not consent to the audio recording. Thus, cough recording and analysis was ultimately feasible in 44 out of 46 (96%) patients, including 31 patients with laboratory-confirmed COVID-19. Cough data of good quality were reliably received by a secure ETH Zurich server for all these individuals and could be viewed in near real-time by the study investigators from remote locations, demonstrating 100% technical feasibility. A total of 120 012 individual coughs were recorded during the whole study.

Cough trajectories during hospital stay

In previous cases where our cough detection technology was used, we focused on nightly cough clusters, *i.e.* episodes of at least two individual coughs with a maximum allowed time interval of 2 s between the expulsive phases of the individual coughing events [11, 12]. However, in the current study with a different indication for acute lower respiratory tract infections, we sought to focus on all-day cough counts to: 1) take full advantage of the power of continuous monitoring; 2) have a more granular analysis of cough evolution during pneumonia recovery; and 3) potentially identify clinical changes in disease course more rapidly.

First, using a biomarker development analysis targeting important surrogate markers of oxygenation (*i.e.* ROX index) and inflammation (*i.e.* C-reactive protein (CRP)), we found that the hourly cough count was

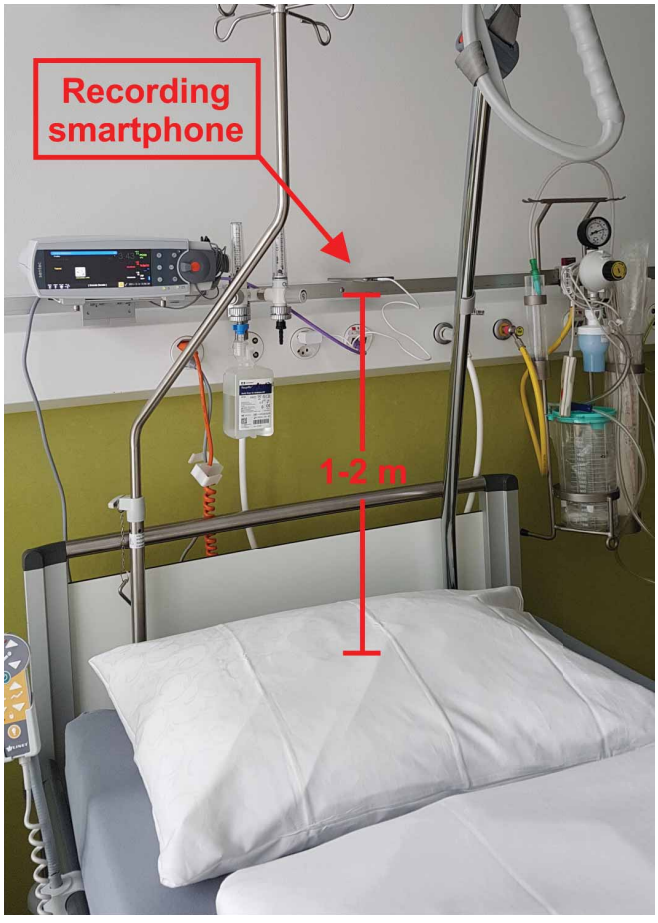

FIGURE 1 Standard study setup in the hospital room. The recording smartphones were placed within 1–2 m of the patients' bedsides and transmitted near real-time cough data to a secure server provided by ETH Zurich. Cough levels were continuously monitored over days to weeks and all-day cough recordings were considered for the final data analysis.

the most strongly correlated parameter of cough (supplementary figure S1). As shown in figure 2a based on a patient with COVID-19 pneumonia, hourly cough counts were highest on day 1 of study and then steadily declined during hospital stay. In another COVID-19 patient, cough levels were initially low but later peaked coinciding with a clinically suspected bacterial superinfection, which was successfully treated with antibiotics (figure 2b). Although inter-patient variation in cough frequency and trajectories was high (supplementary figure S2), our continuous monitoring approach allowed us to discern a particular pattern of cough fluctuations during the day, with peaks coinciding with morning and evening activities at around lunch- and dinnertime, and little cough activity during the night (figure 2c). When stratifying the cohort according to laboratory-confirmed COVID-19 status, we found that cough evolution was similar between COVID-19 and non-COVID-19 patients (incident rate ratio 1.07, 95% CI 0.86–1.33, p=0.548), suggesting cough as a conserved pneumonia symptom irrespective of viral *versus* bacterial aetiology. Collectively, hourly cough counts of patients hospitalised for an acute respiratory tract infection decreased steadily over time but were immediately responsive to clinical worsening as observed during bacterial superinfection.

Correlation of cough counts with pneumonia disease activity

Aside from two unfortunate exceptions (one death and one ICU admission), all patients clinically improved and could be discharged from hospital; prediction of clinical deterioration was therefore not an eligible end-point for cough analysis. We thus analysed the association of hourly cough counts with various clinical and laboratory markers routinely used to assess disease activity in pneumonia. As shown in figure 3a, PCA drew a global picture of the biomarker constellation neighbouring cough counts. We statistically tested these purely descriptive data using linear mixed models implemented in a repeated measures design. We found that hourly cough counts were significantly associated with the composite oxygenation marker ROX index as well as with other clinical markers of oxygen demand (*i.e.* inspiratory oxygen fraction, breathing rate and oxygen saturation measured by pulse oximetry) (figure 3b). In addition, hourly cough counts were significantly correlated to body temperature and biochemical markers of inflammation such as CRP and ferritin (figure 3c). Of note, taking into account circadian fluctuations of coughing activity (figure 2c), a 10% decrease in hourly cough count was associated with an increase of 1.2 units ROX (figure 3b) and a decrease of 36 mg·L^{-1} CRP (figure 3c).

Taken together, cough levels correlated with various clinical and laboratory markers of disease activity, suggesting cough as a surrogate of disease in lower respiratory tract infections.

Discussion

Remote monitoring of patients and digital health interventions using state-of-the-art technology are a healthcare priority having gained further momentum during the SARS-CoV-2 pandemic [17, 18]. Principally suited for screening, diagnostic, treatment and follow-up purposes, telemedicine (or digital health) provides unprecedented opportunities for patient-centric care in both acute and chronic settings, in a hospital environment or at home, to complement and extend classical care and improve the patients' quality of life. However, potential digital biomarkers need to be clinically tested and carefully validated for

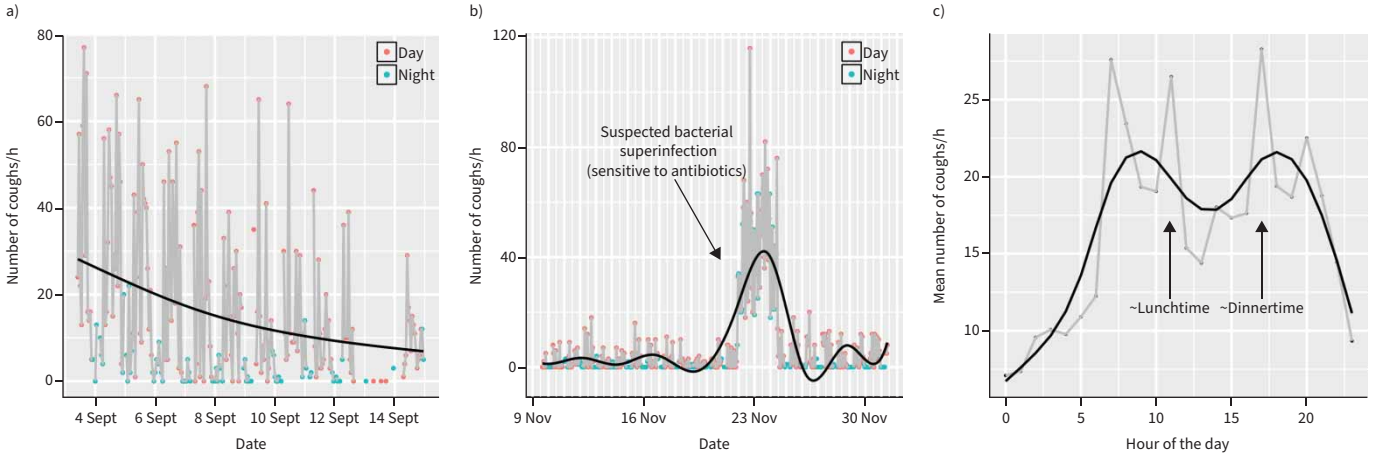

FIGURE 2 Patterns of cough in hospitalised pneumonia patients. a) Time-dependent decline of hourly cough counts in a patient with COVID-19. b) Evolution of hourly cough counts in a patient with COVID-19 experiencing a suspected bacterial superinfection. c) Hourly pattern of cough fluctuations over 24 h in the whole study cohort.

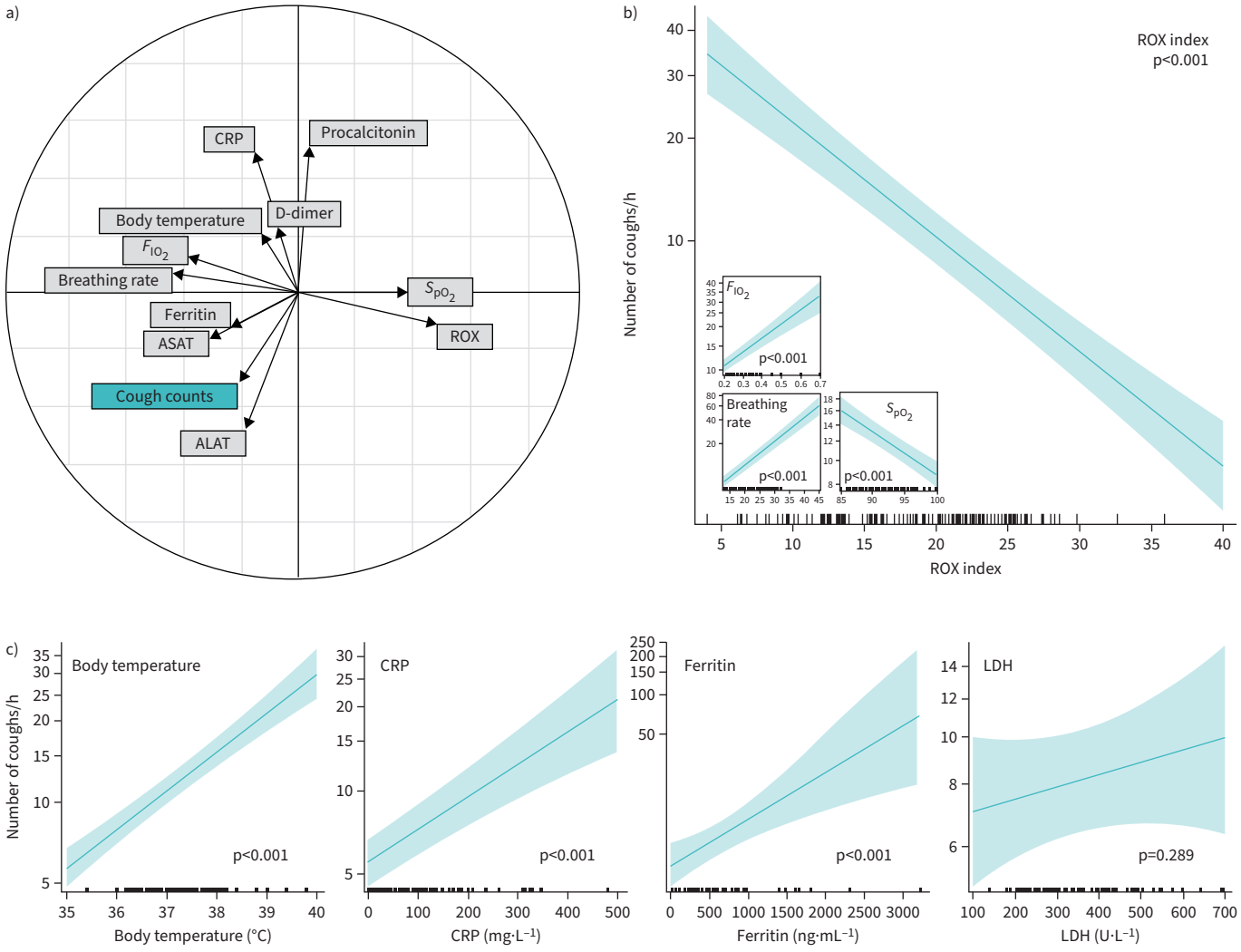

FIGURE 3 Clinical and laboratory correlates of cough frequency in pneumonia. a) Descriptive principal component analysis (PCA) correlation plot of hourly cough count associations generated using the nonlinear iterative partial least squares (NIPALS) algorithm. b) Linear mixed model analyses of the association of hourly cough counts with clinical markers of oxygenation/the requirement for oxygen supplementation. c) Linear mixed model analyses of the association of hourly cough counts with clinical and laboratory markers of inflammation. ALAT: alanine aminotransferase; ASAT: aspartate aminotransferase; CRP: C-reactive protein; F_{IO_2}: inspiratory oxygen fraction; LDH: lactate dehydrogenase; S_{pO_2}: oxygen saturation measured by pulse oximetry.

their robustness. Here, we employed a smartphone-based technology for passive, unobtrusive cough detection [11–13] to continuously monitor hospitalised, non-critically ill patients with pneumonia during the early days of the SARS-CoV-2 pandemic. It was the primary goal of our study to assess the suitability of cough frequency as a potential digital biomarker for disease activity in lower respiratory tract infections.

The current study is the first to demonstrate the feasibility of automated, unobtrusive, audio-based, near real-time cough detection in a hospital environment in the setting of an acute respiratory tract infection. Hourly cough frequencies correlated with both clinical markers of disease activity and laboratory markers of inflammation. The positive association with oxygen demand and inflammatory markers as well as the negative association with the degree of oxygenation/saturation suggests hourly cough counts as a potential digital biomarker in lower respiratory tract infections. Moreover, we discerned a characteristic pattern of daytime-dependent fluctuations in cough levels [19, 20], which further highlights the importance of continuous monitoring for reducing the possibility of non-representative, less temporally resolved ("snapshot") data. It is also important to note that our approach allowed us to determine clinical "effect sizes" of cough changes, with a defined decline in cough counts predicting a certain unit change of reference markers such as ROX index and CRP.

While the study focus was on COVID-19, we also included non-COVID-19 pneumonia patients for both practical reasons (a final diagnosis was not always available at the time of study inclusion) and control purposes. Our analyses showed no apparent differences of cough frequencies between COVID-19 and non-COVID-19 pneumonia, thus demonstrating the usefulness and validity of cough telemonitoring in both settings. While the non-COVID-19 cohort represents cases of classical bacterial pneumonia, the advent of SARS-CoV-2 gave us the unique opportunity to study cough in viral pneumonia, an otherwise less common type of lower respiratory tract infection. As such, this study represents a valuable resource and results might be translatable to other forms of viral pneumonia as well.

Several limitations are applicable to our study. First, case numbers were limited and inter-patient variation in cough frequency was high. These circumstances largely precluded correction for potential confounding variables such as comorbidities (*e.g.* COPD) and tobacco consumption. Second, there was only one ICU admission and one death, such that the prediction of clinical deterioration based on cough counts (the initial primary objective) was not possible. Third, the individual patients were hospitalised (hence, enrolled in the study) at different relative time-points in disease evolution, with highly dissimilar cough levels. Fourth, the employed cough detection technology works reliably yet not perfectly in terms of sensitivity and specificity [14]. Moreover, different cough qualities (*e.g.* productive/wet *versus* non-productive/dry cough) were not discriminated as corresponding tools are not yet available or lack accuracy. However, a future re-analysis of the current data with a reliable, cough quality-discriminating algorithm is envisaged. Fifth, as a non-randomised (cohort) study, we cannot exclude the possibility of patient selection bias. In view of these limitations, larger trials are warranted to prove the validity of cough detection for guidance of treatment decisions and the identification of secondary deteriorations/complications. It is hoped that continuous cough detection can capture more rapid incident changes of disease activity to enable faster medical response and personalisation of the therapeutic path in both viral and bacterial pneumonia.

Taken altogether, we here report the successful use of an automated, noninvasive, smartphone-based cough counter in hospitalised, non-critically ill patients with lower respiratory tract infections including COVID-19. Cough levels declined with the length of hospital stay and correlated with established markers of disease activity, suggesting cough as a useful digital pneumonia biomarker. Study findings need to be reproduced in validation trials.

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Conflict of interest: Three of the authors (P. Tinschert, I. Shih and D. Cleres) have co-founded or hold shares in Resmonics AG, Zurich, Switzerland. The other authors have no conflicts of interest to declare. No medical writer was involved in the preparation of the manuscript.

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