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VECTOR: An algorithm for the detection of COVID-19 pneumonia from velcro-like lung sounds

Fabrizio Pancaldi [a,b,*], Giuseppe Stefano Pezzuto [c], Giulia Cassone [d,e], Marianna Morelli [c], Andreina Manfredi [d,e], Matteo D'Arienzo [c], Caterina Vacchi [e], Fulvio Savorani [c], Giovanni Vinci [c], Francesco Barsotti [c], Maria Teresa Mascia [d,e], Carlo Salvarani [d,e], Marco Sebastiani [d,e]

[a] University of Modena and Reggio Emilia, Department of Sciences and Methods for Engineering, via Amendola 2, 42122, Reggio Emilia, Italy
[b] University of Modena and Reggio Emilia, Artificial Intelligence Research and Innovation Center (AIRI), Via Pietro Vivarelli 10, 41125, Modena, Italy
[c] Emergency Room and Emergency Medicine, Azienda Policlinico di Modena, via del Pozzo 71, 42124, Modena, Italy
[d] University of Modena and Reggio Emilia, Department of Surgery, Medicine, Dentistry and Morphological Sciences with Transplant Surgery, Oncology and Regenerative Medicine Relevance, via del Pozzo 71, 42124, Modena, Italy
[e] Rheumatology Unit, Azienda Policlinico di Modena, via del Pozzo 71, 42124, Modena, Italy

A R T I C L E I N F O

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A B S T R A C T

The coronavirus disease 2019 (COVID-19) has severely stressed the sanitary systems of all countries in the world. One of the main issues that physicians are called to tackle is represented by the monitoring of pauci-symptomatic COVID-19 patients at home and, generally speaking, everyone the access to the hospital might or should be severely reduced. Indeed, the early detection of interstitial pneumonia is particularly relevant for the survival of these patients. Recent studies on rheumatoid arthritis and interstitial lung diseases have shown that pathological pulmonary sounds can be automatically detected by suitably developed algorithms. The scope of this preliminary work consists of proving that the pathological lung sounds evidenced in patients affected by COVID-19 pneumonia can be automatically detected as well by the same class of algorithms. In particular the software VECTOR, suitably devised for interstitial lung diseases, has been employed to process the lung sounds of 28 patient recorded in the emergency room at the university hospital of Modena (Italy) during December 2020. The performance of VECTOR has been compared with diagnostic techniques based on imaging, namely lung ultrasound, chest X-ray and high resolution computed tomography, which have been assumed as ground truth. The results have evidenced a surprising overall diagnostic accuracy of 75% even if the staff of the emergency room has not been suitably trained for lung auscultation and the parameters of the software have not been optimized to detect interstitial pneumonia. These results pave the way to a new approach for monitoring the pulmonary implication in pauci-symptomatic COVID-19 patients.

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an RNA virus that may lead to the coronavirus disease 2019 (COVID-19). Fever is the most commonly reported finding in 84%–87% of COVID-19 cases [1], however hyposmia, hypogeusia and diarrhea are other possible symptoms of the disease [2]. In the initial stages of the disease fever may be absent and patients may have only chills and respiratory symptoms. Although most of cases are clinically mild, many patients can present further pulmonary signs as, for instance, ground-glass opacity at lungs on chest X-ray [3]. On the other hand, at advanced stages of the disease, patients may suffer from severe pneumonia, acute respiratory distress syndrome (ARDS) and refractory hypoxaemia; in some cases patients may even develop respiratory failure with permanent organ

* Corresponding author. University of Modena and Reggio Emilia, Department of Sciences and Methods for Engineering, via Amendola 2, 42122, Reggio Emilia, Italy.

E-mail addresses: fabrizio.pancaldi@unimore.it (F. Pancaldi), pezzuto.giuseppe@aou.mo.it (G.S. Pezzuto), giulia.cassone@unimore.it (G. Cassone), morelli.marianna@aou.mo.it (M. Morelli), andreina.manfredi@unimore.it (A. Manfredi), darienzo.matteo@aou.mo.it (M. D'Arienzo), caterina.vacchi@unimore.i (C. Vacchi), savorani.fulvio@aou.mo.it (F. Savorani), vinci.giovanni@aou.mo.it (G. Vinci), francesco.barsotti@aou.mo.it (F. Barsotti), mariateresa.mascia@unimore.it (M.T. Mascia), carlo.salvarani@unimore.it (C. Salvarani), marco.sebastiani@unimore.it (M. Sebastiani).

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damage and dysfunction. When extra-pulmonary system dysfunctions appear, the risk of sepsis and septic shock is severe and this leads to a significant increase in the fatality rate. Recent findings showed that the disease is mild in the majority of patients (81%) and only a few of them develop severe pneumonia, pulmonary edema, ARDS, or different organ damages [4]. Chest x-ray is essential to evaluate for COVID-19 mimics such as pneumonia, pleural effusion, or pulmonary edema. Typical COVID-19 findings include hazy opacities that are often bilateral and peripheral [5]. Sensitivity of chest x-ray largely varies according to the different studies, but it is generally high, up to 100% accuracy in the early COVID-19 pandemic [4]. *High resolution computed tomography* (HRCT) remains the best diagnostic tool in combination with molecular tests and allows to reduce false-negative rates [6]. COVID-19 pandemic has determined a rapid impulse for the development of telemedicine applications, especially for monitoring both pauci-symptomatic COVID-19 patients and patients with other diseases, generally speaking for everyone the access to the hospital might be precluded or severely reduced [7]. Despite the introduction of telemedicine, at least two circumstances require the direct use of stethoscopes to detect lung implications and take decisions accordingly, firstly in intubated patients in intensive care unit and, secondly, in pauci-symptomatic at home patients [8]. In patients at home, monitoring is particularly relevant to early detect the occurrence of interstitial pneumonia, since a prompt diagnosis is necessary as well as the admission in hospital is oftenly required [2]. Recently, two studies have proved the relationship between the lung auscultatory characteristics and outcomes of patients with SARS-CoV-2 infection [9,10]. Wang et al. investigated several features of lung sounds with clinical relevance in COVID-19 patients [9], whereas Zhang et al. used an electronic stethoscope to perform auscultation while physicians are dressed in their personal protective equipment [10].

The automatic detection of adventitious lung sounds has attracted much interest in the last years. For instance, time-varying autoregressive modeling and thresholding is employed in Ref. [11], tsallis entropy and neural networks are exploited in Ref. [12], frequency analysis and thresholding is used in Ref. [13], some properties of nonlinear time series are combined with principal component analysis in Ref. [14], time-frequency analysis and cepstral analysis are embodied in deep learning machines in Refs. [15,16]. Most of these studies rely on “heterogeneous” datasets collected from multiple sources or datasets suitably assembled; only the works [11,13] stem from clinical studies and, in particular, only the work [13] is based on pulmonary sounds acquired from COVID-19 patients.

The embodiment of algorithm development and clinical study is of particular relevance for two main reasons, as confirmed by our previous studies and by the work [15], namely the availability of a common gold standard for the definition of the ground truth and the description of the scenario with an application-specific task. The last point is very important since a proper shaping of the target sets for classification can lead to a significant overestimation of the results [15].

In patients with rheumatoid arthritis and connective tissue diseases, we have already proved the usefulness of a software called VECTOR (VElcro Crackles detecTOR) in identifying pulmonary implications from the analysis of lung sounds [17,18]. Velcro crackle is a pulmonary sound oftenly defined as a fine, soft and short crackle, similar to the sound generated when gently separating the strips of velcro attached to the blood pressure cuff. Velcro crackle has been identified by many authors as an early marker of *interstitial lung disease* (ILD) or pulmonary fibrosis [18,19]. Since most patients with SARS-CoV-2 pneumonia evidence ground glass opacity or reticulation at the HRCT [20] similarly to patients with ILD or pulmonary fibrosis, the same tools developed for the detection of velcro crackles in patients affected by rheumatoid arthritis and connective tissue diseases can be synergistically exploited even to screen patients with COVID-19 pneumonia. The scope of this exploratory study consists of evaluating the diagnostic accuracy of VECTOR in the identification of interstitial pneumonia secondary to SARS-CoV-2 infection. The technical contribution of this work is twofold. Firstly, we can confirm that lung sounds represent a reliable marker of interstitial pneumonia even when the pathogenesis is related to SARS-CoV-2 infection. Then, this pioneering work could form the basis for a new approach to the management of patients denoting symptoms coherent to COVID-19. In particular, a new tool based on an electronic stethoscope could provide a diagnostic accuracy similar to, or even better than, that of expert physicians, still keeping the medical personnel in very safe conditions. Secondly, the algorithm developed to detect ILDs and employed in Ref. [17] is described in detail for the first time in the technical literature.

The remaining of the work is described as follows. The method adopted in this study is introduced in Section 2, whereas the algorithm implemented in the version of the employed software VECTOR is shown Section 3. The results are described in Section 4 and discussed in Section 5.

2. Method

The population of this study is composed by all the patients referred to the Emergency Room at the University Hospital of Modena (Italy) during the month of December 2020, for symptoms or signs suggestive for SARS-CoV-2 infection; the symptoms may include any combination of fever, cough, dyspnoea, ageusia and/or anosmia. The study was approved by the Ethical Committee of the University Hospital of Modena. All patients involved in the study signed an informed consent. Twenty-eight consecutive patients has been enrolled, 11 females (39.3%) and 17 males (60.7%), with a median age of 50.5 years in the range 18–77 years. Sixteen patients were affected by comorbidities, namely 7 patients by 1 comorbidity, 3 patients by 2 comorbidities and 6 patients by 3 or more comorbidities. Among the various recorded comorbidities, it is worth mentioning diabetes, cardiovascular diseases, autoimmune diseases and *chronic obstructive pulmonary diseases* (COPD). Demographic data and comorbidities of the population involved in the study are summarized in Table 1. It is worth pointing out that the working conditions in the emergency room did not allow a prolonged exposure to COVID-19 patients, then this preliminary study takes into consideration only a limited cohort of patients and a limited number of clinical data have been collected. However, since the results are encouraging (see Sections 4 and 5), the study will be extended to a larger population.

The electronic stethoscope Littmann 3200 has been employed to record the lung sounds of each patient at $N_a = 8$ auscultation points, namely paravertebral lower lobes, axillary lower lobes, paravertebral middle lobes and paravertebral upper lobes. The auscultation spots are illustrated in Fig. 1. In principle, the longer is the auscultation, the larger is the number of inspiration/expiration cycles and the better is the performance of the VECTOR algorithm. Despite hyperventilation can be easily handled in outpatient visits, this additional temporary inconvenience should be definitely avoided in an emergency room hosting patients with symptoms compatible with COVID-19. In our setup, the auscultation time is mostly between 5 s and 10 s per spot, corresponding

Table 1
Demographic data and comorbidities of the patients enrolled in the study.

Number of patients	28
Sex [Females/Males]	11/17 (39.3%/60.7%)
Median age [years], range [years]	50.5, 18-77
Comorbidities [number of patients]	16 (57.1%)
1 comorbidity [number of patients]	7 (25%)
2 comorbidities [number of patients]	3 (10.7%)
3 or more comorbidities [number of patients]	6 (21.4%)
Diabetes [number of patients]	3 (10.7%)
Cardiovascular diseases [number of patients]	11 (39.3%)
Autoimmune diseases [number of patients]	3 (10.7%)
COPD [number of patients]	3 (10.7%)

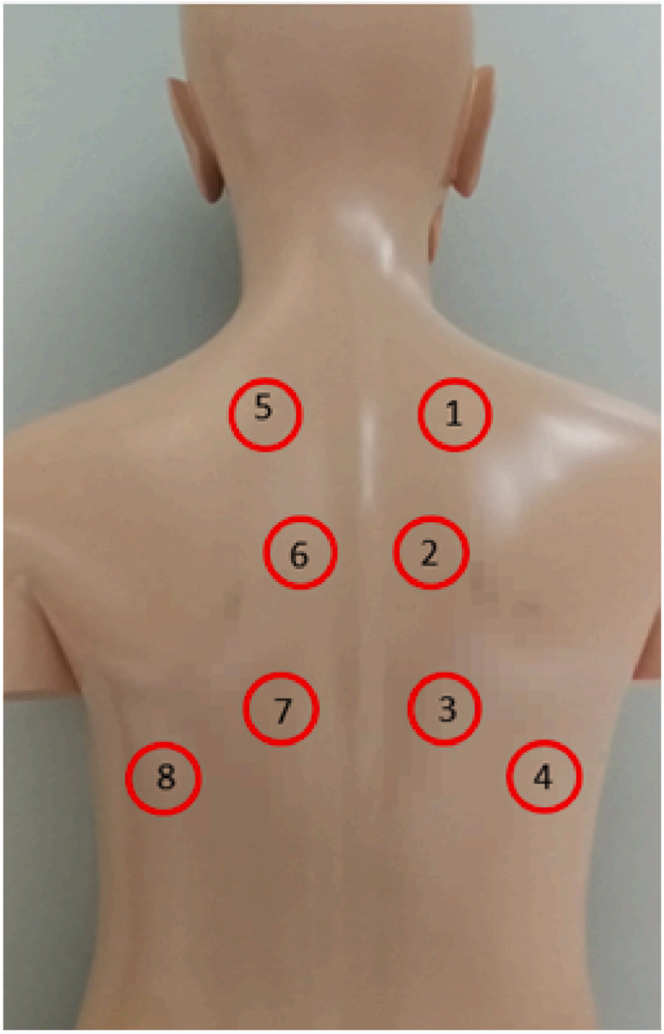

Fig. 1. Auscultation points.

roughly to 2–5 inspiration/expiration cycles, even if some auscultations as long as 15–30 s have been collected. Shorter auscultations would not carry on enough inspiration-expiration cycles to be processed by the algorithm. Longer auscultations are not feasible in practice in the considered scenario.

Each auscultation is digitized and saved as a WAV file over the memory onboard the stethoscope. Then the set of N_a audio files acquired for each patient are transferred to a personal computer through a Bluetooth link. The employed electronic stethoscope is characterized by a sampling frequency $f_s = 4$ kHz. Then the audio files are analyzed through the software VECTOR running on a commercial low-end personal computer [17,18,21]. The algorithm performs a binary classification (positive or negative to interstitial pneumonia). Very minimal training has been provided to the physicians involved in the study during a remote video call.

The presence of interstitial pneumonia has been assessed through either *lung ultrasound* (LUS) or chest X-Ray. In doubtful cases an HRCT has been required. LUS evaluation was performed by three experienced physicians. Patients was in a sitting position and LUS data were captured in both hemithorax areas (left and right), namely intercostal spaces of the upper and lower parts of the anterior, lateral and posterior chest. In the evaluation of pathological LUS data, the following findings have been searched for: (a) B-lines > 2 (hyperechoic vertical artifacts arising from the pleural line, extending to the bottom of the screen without fading and vacillating with lung movement, which occurs when the lung loses normal aeration but is not completely consolidated for imbibition, but also for inflammatory infiltrates or increase in fibrous tissue); (b) coalescent B-lines (coalescence of many vertical artifacts to form more extended echogenic patterns corresponding to severe lung aeration loss); (c) subpleural consolidations (hypoechoic areas that appear as the subpleural density approaches the density of solid tissue, suggesting subpleural fluid-filled alveoli).

Lung sounds have been acquired in the emergency room before the LUS, chest X-Ray and rhino-pharyngeal swab for SARS-CoV-2. Patients with a negative swab have been excluded from the study. Indeed, lung auscultation was blind with respect to the swab result, as well as the analysis of lung sounds through the software VECTOR was blind with respect to all the other investigations.

Finally, the performance of VECTOR has been compared with that of imaging techniques in terms of predictive value for the detection of COVID-19 pneumonia. The spectrogram of the lung sounds acquired at the right axillary lower lobe of a patient affected by interstitial pneumonia (diagnosed through the HRCT) is shown in Fig. 2. The yellow/green lines around the 5th and 9th second of the auscultation can be *qualitatively* classified by physicians as “velcro crackles”.

3. VECTOR

The flow chart illustrating the behavior of the software VECTOR in the suitable form to detectILDs is shown in Fig. 3. The approach adopted to process the auscultations referring to a given patient is described hereafter. Firstly, the N samples of the N_a audio signals $s_i[n]$, with $i = 1, 2, \ldots, N_a$ and $n = 0, 1, \ldots, N-1$, are divided into frames of dimension $w = f_s t_r$ samples, where t_r represents the “time resolution”. As a consequence, each audio signal is composed by a sequence of $N_w = \lfloor N/w \rfloor$ frames, where $\lfloor . \rfloor$ denotes the floor function. Then the audio frames of the ith signal undergo a *linear predictive coding* (LPC) of order L to extract the coefficients $a_i[l, m]$, where $l = 0, 1, \ldots, L$ and $m = 0, 1, \ldots, N_w - 1$. The reader interested in LPC can refer to the milestone papers [22,23]. Hard thresholding is performed to identify the inspiration periods; in particular the frames carrying a power P_w lower than $P_{th} = \overline{P}_w C_{th}$ are discarded, where $\overline{P}_w$ represents the mean power of the frames and C_{th} denotes a “threshold parameter” to be set for performance optimization. It is worth pointing out that, in patients affected by interstitial diseases, velcro crackles appear mainly in inspiration periods, i.e. when the air flow can involve even the parts of the lung affected by pulmonary disorders. To this aim, the patient is required to deeply breath during auscultation. However, for the same reason, no crackle can be detected in patients that are not capable to deeply breath because of respiratory failure, even if the radiological pattern is compatible with an interstitial lung disease. The spectrogram of the inspiration periods resulting from the analysis of the same lung sounds of Fig. 2 is shown in Fig. 4 as an example. Note that the sounds classified by physicians as “velcro crackles” are evidenced around the 5th and 9th second. However, other sounds are also highlighted, as for instance between the 7th and 8th second, that can be classified as “noise”.

The LPC coefficients $a_i[l, m]$ are averaged over the frame (i.e. time) index m leading to

$$\overline{a}_i[l] = \frac{1}{N_w} \sum_{m=0}^{N_w - 1} a_i[l, m]. \tag{1}$$

Various statistical features are extracted from the “mean coefficients” $\overline{a}_i[l]$ as a function of the LPC order index l, thus leading to the quantities

$$\mu_i = \frac{1}{L} \sum_{l=0}^{L} \overline{a}_i[l], \tag{2}$$

$$\sigma_i^2 = \frac{1}{L-1} \sum_{l=0}^{L} \left(\overline{a}_i[l] - \mu_i\right)^2, \tag{3}$$

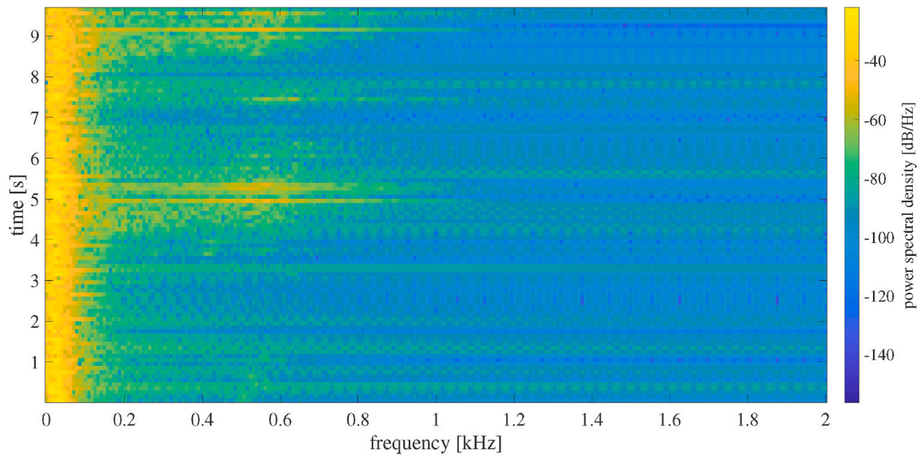

Fig. 2. Spectrogram of the lung sounds acquired at the right axillary lower lobe of a patient affected by interstitial pneumonia (diagnosed through the HRCT).

$$\varsigma_i = \frac{\frac{1}{L}\sum_{l=0}^{L}(\overline{a}_i[l] - \mu_i)^3}{\sigma_i^3}, \tag{4}$$

$$k_i = \frac{\frac{1}{L}\sum_{l=0}^{L}(\overline{a}_i[l] - \mu_i)^4}{\sigma_i^4}, \tag{5}$$

$$m5_i = \frac{1}{L}\sum_{l=0}^{L}(\overline{a}_i[l] - \mu_i)^5 \tag{6}$$

and

$$m6_i = \frac{1}{L}\sum_{l=0}^{L}(\overline{a}_i[l] - \mu_i)^6. \tag{7}$$

Mathematically, μ_i, σ_i^2, ς_i, k_i, $m5_i$ and $m6_i$ represent mean, variance, skewness, kurtosis, central moment of the 5th order and central moment of the 6th order, respectively, of the "mean coefficients" $\overline{a}_i[l]$ with respect to the LPC order index l. Then, the mean values of the quantities computed in equations (2)–(7) are extracted as

$$\overline{\mu} = \frac{1}{N_a}\sum_{i=1}^{N_a}\mu_i, \tag{8}$$

$$\overline{\sigma}^2 = \frac{1}{N_a}\sum_{i=1}^{N_a}\sigma_i^2, \tag{9}$$

$$\overline{\varsigma} = \frac{1}{N_a}\sum_{i=1}^{N_a}\varsigma_i, \tag{10}$$

$$\overline{k} = \frac{1}{N_a}\sum_{i=1}^{N_a}k_i, \tag{11}$$

$$\overline{m5} = \frac{1}{N_a}\sum_{i=1}^{N_a}m5_i \tag{12}$$

and

$$\overline{m6} = \frac{1}{N_a}\sum_{i=1}^{N_a}m6_i. \tag{13}$$

The rationale behind this approach consists of considering velcro crackle as an unvoiced sound. Since it is well known that (a) LPC coefficients are related to the power spectrum of the signal and (b) velcro crackle has an identifiable power spectrum "signature" [21], the presence of pathological lung sounds can be inferred from the analysis of the quantities devised in equations (8)-(13).

Principal component analysis (PCA) is then applied to the features (8)–(13), i.e. to the first 6 statistical moments. We believe that this represents the most intuitive approach to "combine" the devised LPC coefficients, but we cannot exclude that other techniques could yield some benefits. Finally, hard thresholding is performed for a binary classification b between positive and negative patients with respect to interstitial pneumonia secondary to COVID-19. It is worth stressing that the parameters of the algorithms have not been optimized to detect pulmonary implications of COVID-19, in fact the parameters devised in Ref. [17] have been also employed in this study to setup the software VECTOR. For instance, in our previous study [17] we tested several prefiltering techniques based on low-pass, high-pass and band-pass filters, but we achieved no performance improvement. However from this preliminary study we cannot exclude that some types of prefiltering can be beneficial.

4. Results

The parameters of the algorithm behind VECTOR have been set according to the version suitable to detect ILDs as devised in the study [17]. These parameters are described as follows: $t_r = 0.1$ s, $w = 400$, $C_{th} = 1$ (consequently $P_{th} = \overline{P}_w$, i.e. the frames having a power lower than the mean power of the audio signal are discarded) and $L = 10$; in particular, in the work [17] we found that increasing the order of the LPC analysis beyond $L = 10$ entailed no performance improvement. For instance, if the duration of the auscultation is $d = 10$ s, the corresponding number of frames is $N_w = N/w = df_s/t_r f_s = d/t_r = 100$. The inspiration period usually lasts 0.5–1 s. Since the time resolution $t_r = 0.1$ s, each inspiration is composed by 5–10 frames. In our experience this leads to a good compromise between time and frequency resolution, in particular for the time selection of the inspiration period. The number of principal components considered for hard thresholding and the binary classification of the patient is 4. The mean vector, coefficient matrix and thresholds of the principal components are not reported in detail for space limitation. These numerical details can be provided to the interested researchers after a written request, e.g. an email, to the corresponding author.

Twenty-eight consecutive patients were enrolled in the study, 11 females (39.3%) and 17 males (60.7%), with a median age of 50.5 years (range 18–77). Interstitial pneumonia was recorded in 17 patients (57.1%). The results achieved by the software VECTOR are summarized in the confusion plot shown in Fig. 5, where "negative" and "positive" refer to interstitial pneumonia, respectively. The ground truth is represented by diagnostic tools based on imaging, i.e. LUS, chest x-ray and HRCT. Our algorithm correctly identified 21/28 patients, resulting in an overall diagnostic accuracy of 75%. 12 patients had interstitial pneumonia and 9 were negative. 5 patients with pneumonia were not detected by VECTOR, while in 2 patients VECTOR reported a false positive result. VECTOR showed a positive predictive value of 85.7% and a negative predictive value of 64.3%, sensitivity and specificity were

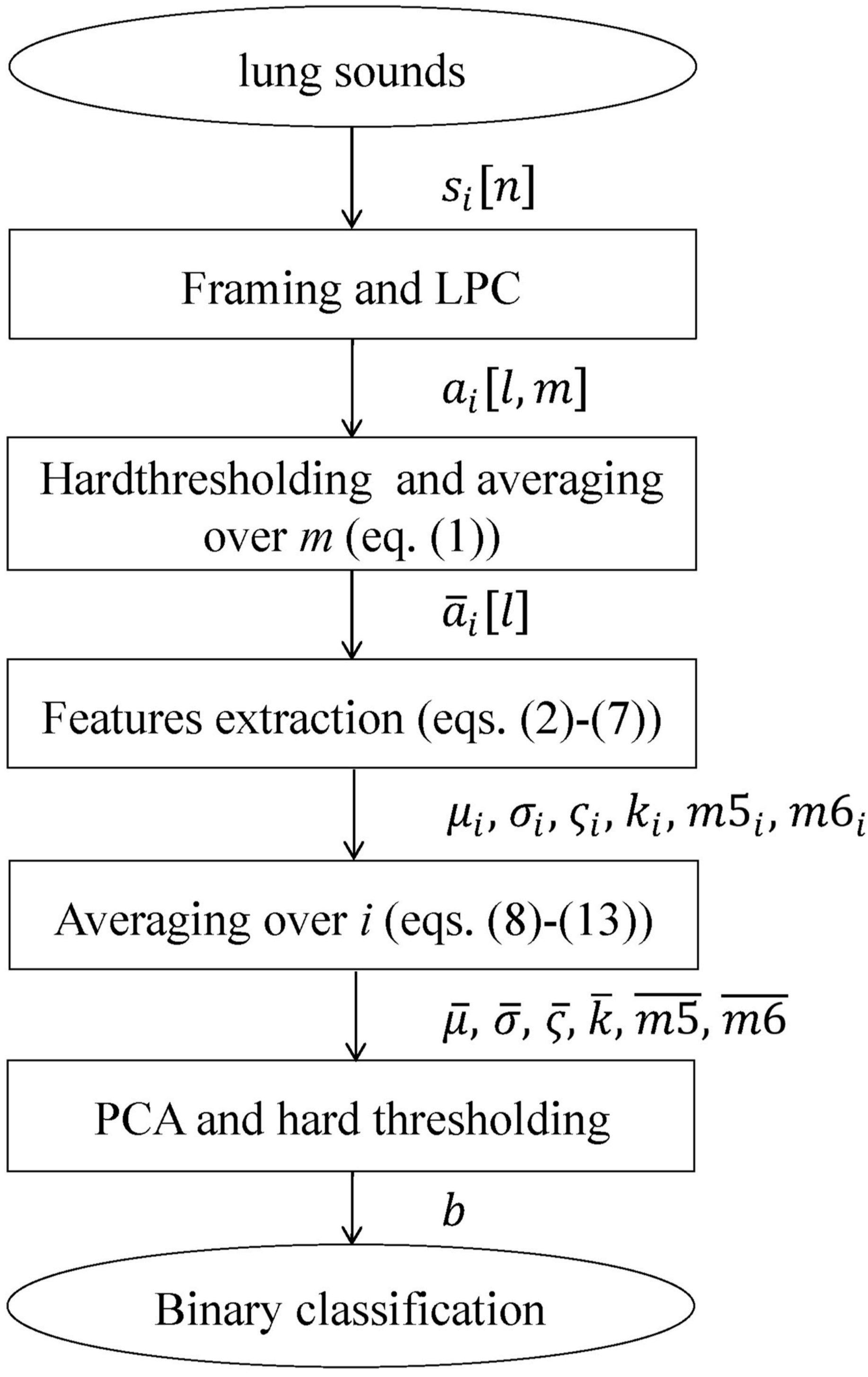

Fig. 3. Flow chart of the algorithm behind VECTOR software in the suitable form to detect ILDs.

70.6% and 81.8%, respectively. In 4 (over 5) false negative patients, clinical conditions were severe, with desaturation in 2 cases. To the best of our experience, this can negatively influence the performance of VECTOR, since patient should be able to deeply breath for obtaining a meaningful result. Fortunately, these cases are not critical for the correct evaluation of patient's clinical status, since the measurement of the saturation through a simple pulse oximeter can easily provide the information required to take a decision about hospitalization. The *qualitative* evaluation of the auscultations of the 5 false negatives confirms the last deduction based on our experience. In fact, in 2 cases velcro crackles are very weak, short and available only in few auscultations, whereas in the remaining 3 cases velcro crackles are not identifiable. The 2 false positives have different genesis. Wet crackles, probably entailed by cardiac insufficiency, are unproperly detected by the algorithm in one case, whereas almost all the auscultations are affected by artifacts in the other case.

The detection regions in the PCA space are shown in Fig. 6. Considering the COVID-19 dataset and the thresholds devised in Ref. [17] to detect connective tissue diseases, only the first and third PCA components affect the results (i.e. the second and fourth PCA components do not raise a pathological suspicion with respect to the considered thresholds). For this reason the detection regions can be

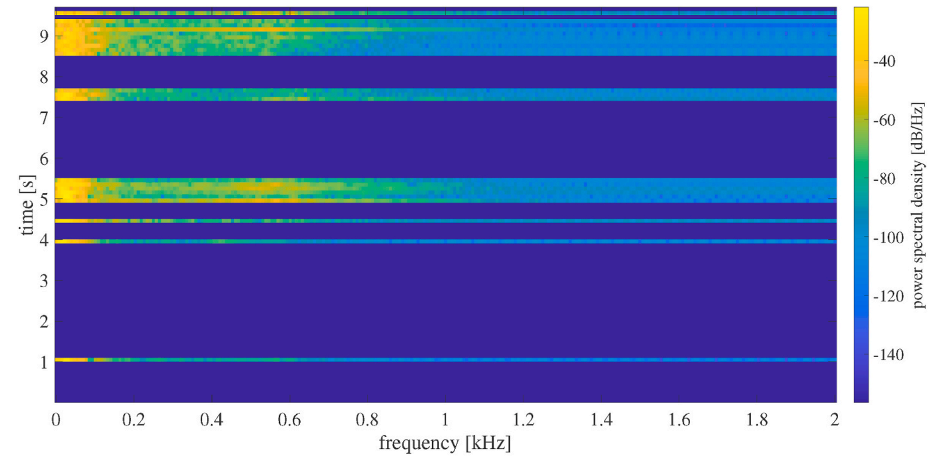

Fig. 4. Spectrogram of the inspiration periods resulting from the analysis of the same lung sounds of Fig. 2.

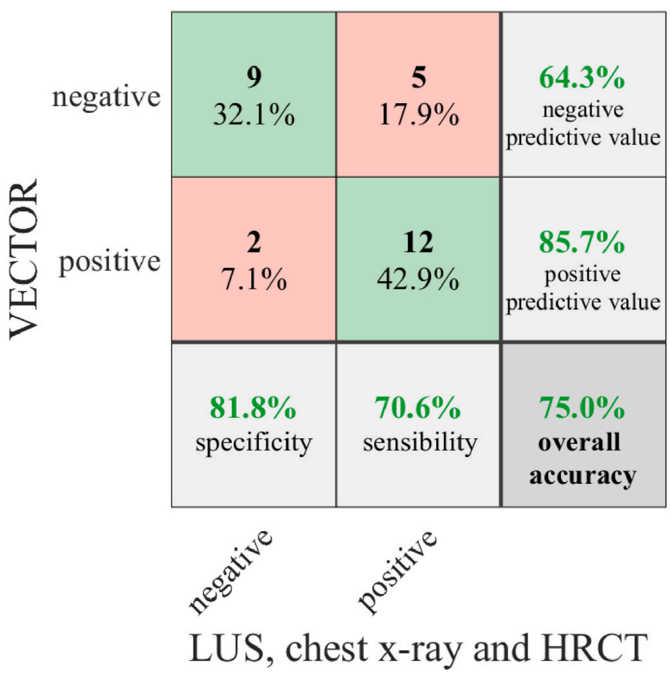

Fig. 5. Confusion plot of VECTOR output with respect to the ground truth represented by LUS, chest x-ray and HRCT.

represented on a bidimensional space, i.e. on a plane. The rectangle depicted in light green includes the patient classified by our software VECTOR as negatives, whereas the remaining of the white plane includes the patients classified as positives. The markers denote the ground truth obtained by imaging techniques, in particular green circles and red asterisks represent true negatives and true positives, respectively. As a consequence, the 5 red asterisks in the green rectangle are the false negatives, whereas the 2 green circles on the white plane are the false positives. Indeed, more refined classifiers could be employed to improve the performance of the tool in future studies.

The robustness of VECTOR algorithm has been assessed through subjective annotations provided by physicians. The 8 auscultations of each patient have been qualitatively ranked in terms of clinical relevance. Best auscultations mainly include the lung sounds, either physiological or pathological, suitable to raise a diagnostic suspicion; on the contrary, worst auscultations mainly collect room noise, voices, cough and artifacts. Then the performance of VECTOR are assessed progressively discarding the worst auscultations. The performance of the algorithm does not change discarding 1 or 2 auscultations, i.e. exploiting 7 or 6 auscultations per patients, respectively, instead of 8. This means that negligible information is available in the worst auscultations. Further discarding 3 and 4 auscultations, i.e. processing 5 and 4 auscultations for each patient, improves the sensibility but not the specificity. The performance of VECTOR exploiting 4 auscultations for each patient is summarized in Fig. 7. The sensibility increases to 82.4% and the negative predictive value increases to 75%, whereas specificity and positive predictive value are unchanged at 81.8% and 85.7%, respectively. The number of false negatives decreases from 5 to 3. The 2 patients evidencing weak and short velcro crackles can be properly detected if the worst auscultations are discarded, but 3 false negatives remains since crackles are not identifiable. 2 false positives are still present for the above mentioned reasons. The overall accuracy achieves 82.1%, which is very similar to our previous studies [17,21]; this further confirms the suitability of VECTOR as support for the diagnosis of interstitial pneumonia secondary to COVID-19.

To the best of our knowledge, the only work that is fairly comparable with this investigation is [13]. In that work, the lung sounds of 9 patients affected by COVID-19 and 4 healthy volunteers have been acquired through a smartphone placed in front of the mouth. The diagnostic criterion for COVID-19 infection is based on the frequency analysis of lung sounds. The achieved diagnostic accuracy is about 85%, with 1 false negative and 1 false positive over the population of 13 people. As a consequence, specificity and sensibility are 75% and 89%, respectively, whereas the negative and positive predictive values are (again) 75% and 89%. For the sake of fairness, it is worth noting that [13] is a preprint and has not been peer-reviewed, i.e. it reports new medical research that has yet to be evaluated and so should not be used to guide clinical practice.

5. Discussion

On March 11th, 2020, the World Health Organization declared the COVID-19 outbreak as a pandemic. The response strategy included early diagnosis, patient isolation, symptomatic monitoring of contacts, as well as suspected and confirmed cases, and a public health quarantine. In this context, telemedicine, in particular video or phone consultations, has been promoted to reduce the risk of virus transmission [24]. The need of a home health care service has become particularly relevant for patients with non- or pauci-symptomatic infection by SARS-CoV-2. In fact, health monitoring of at home patients is crucial to early detect the possible rapid decay of lung function entailed by COVID-19 pneumonia [25]. Furthermore, the contact between clinicians and hospitalized patients should be minimized to reduce the risk of infection, e.g. doctors should be able to assess the clinical status of patients still being dressed in their

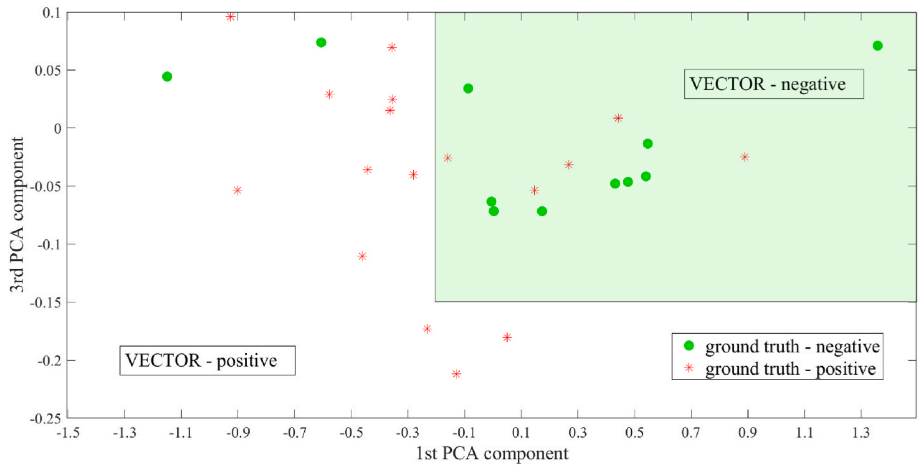

Fig. 6. Detection regions in the PCA space. The rectangle in light green includes the patient classified by VECTOR as negatives, whereas the remaining of the white plane includes the patients classified as positives. Green circles and red asterisks represent true negatives and true positives, respectively.

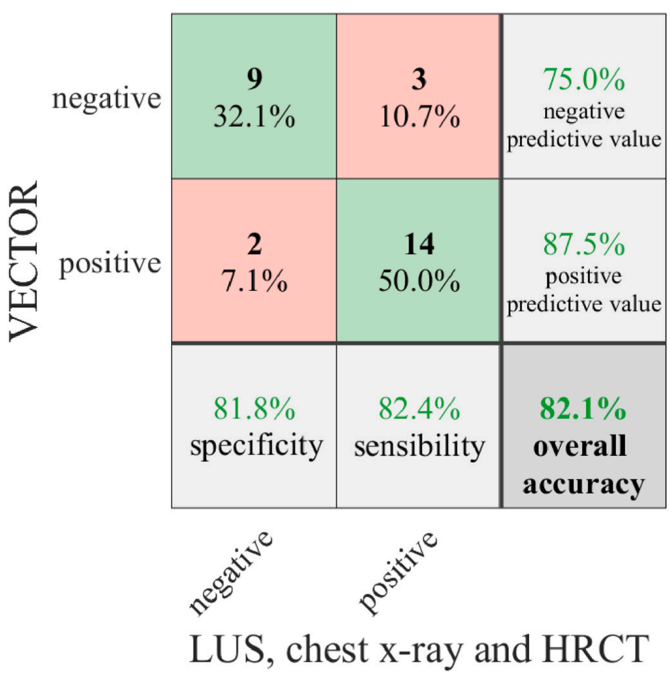

Fig. 7. Confusion plot of VECTOR output with respect to the ground truth represented by LUS, chest x-ray and HRCT. The best 4 auscultations are considered (over the available 8).

personal protective equipment. In both scenarios, the adoption of new instruments and tools endowed with a remote control is fundamental.

Recent works proved that velcro crackles can be early detected in patients with idiopathic pulmonary fibrosis, interstitial lung diseases and other forms of interstitial pneumonia [18,19]. Then the lung sounds can be acquired with an electronic stethoscope and processed through suitably developed algorithms to detect pulmonary implications. For instance, the software VECTOR have shown high sensitivity and specificity, regardless of the radiological pattern, in patients affected by rheumatoid arthritis and connective tissue diseases [17,18]. These results have motivated the proposed preliminary study, in fact the availability of algorithms and software suitable to the detection of COVID-19 pneumonia would allow the management of complicated situations even by non-experienced physicians. It is worth pointing out that in the last years we noticed two types of "randomness" in the acquisition of lung sounds, one is operator-dependent and the other is patient-dependent. The former type of randomness is related to the maneuver of the doctor and depends on a number of factors as, for instance, positioning and pression on the phonendoscope, tipping fingers on the head of the phonendoscope, rubbing the phonendoscope on the skin and so on. The latter type of randomness is related to the behavior of the patient as, for instance, deeply or lightly breathing, coughing, talking and so on. In a "normal" outpatient visit room, a trained rheumatologist can keep under control the above mentioned sources of noise and can achieve a good repeatability of measurement. On the contrary, the chaotic condition of the emergency room in the pandemic period might have influenced the quality of auscultations. It is worth stressing that in December 2020 the medical staff was not vaccinated yet and the clinical procedures were under development; these factors have certainly limited the confidence on the medical staff in "handling" patients with possible symptoms of COVID-19. Environmental noise and speaking voices have reduced the possibility to acquire a clean recording, as well as a very minimal training have been provided to the physicians involved in the study. Above all, we have employed an algorithm developed previously of the pandemic for patients affected by connective tissue diseases. In other word, the parameters of the algorithm have not been optimized for the pathological lung sounds of COVID-19 pneumonia. Nonetheless, very important indications have been collected. Firstly, at least 4 over the 5 false negative cases had severe pulmonary implications. This prevents the possibility for the patient to deeply breath and to stimulate the portions of the lungs responsible of velcro crackles. Moreover, 4 or 5 deep breaths are necessary for each auscultation in order to devise reliable results, however a pulmonary deficit can appreciably shorten the duration of audio recordings. Discarding the worst 4 auscultations (over 8) for each patient allows to improve the performance of the algorithm; in fact, even weak and short velcro crackles can be detected and false negatives decreases from 5 to 3. However, in 3 patients velcro crackles are not identifiable at all, probably because of severe pulmonary implications; luckily, these patients are not critical in the clinical practice, since other simple diagnostic tools are effective, like for instance pulse oximeters. Despite this, patients with mild or light lung involvement are of great clinical importance for early diagnosis and could be properly detected by VECTOR. The 2 false positives can be explained by the presence of comorbidities in one case and by the presence of strong artifacts in almost all the auscultations of the other case.

Considering the exploratory nature of this study, the performance of the VECTOR algorithm is surprising even in the detection of COVID-19 pneumonia. The number of false positive results is very limited and acceptable. However, the number of false negative cases should be reduced, even if the severe pulmonary deficit can be identified with other simple tools like a pulse oximeter. Indeed, after this blind investigation about VECTOR performance in a COVID-19 scenario, we are working on a new algorithm properly focused to the detection of interstitial pneumonia. We are aware that the weakness point of our research is represented by the limited number of patients enrolled in the emergency room. We believe that a study involving more patients and exploiting a suitably developed tool, in terms of both acquisition hardware and processing algorithm, can disclose the potential of the proposed solution. The confidence earned by the medical staff from vaccination and one year of experience can certainly play a positive role as well. Nonetheless, the current results are already encouraging and the application perspectives are very interesting. In fact a remote auscultation, even a self-auscultation of the patient, followed by an algorithm running on a commercial computer would completely prevent the contact with the sanitary personnel. Moreover, non-expert physicians could handle almost all the patient management, demanding to expert physicians only the diagnosis. It is worth noting that most of the zoonoses appeared in the last 20 years affect the respiratory system, so that deepening the knowledge in this field can be important even to be ready against possible new infections.

CRediT authorship contribution statement

Fabrizio Pancaldi: Conceptualization, Methodology, Software, Writing – original draft, Writing – review & editing, Visualization, Supervision. **Giuseppe Stefano Pezzuto:** Investigation. **Giulia Cassone:** Validation, Visualization. **Marianna Morelli:** Investigation. **Andreina Manfredi:** Validation. **Matteo D'Arienzo:** Investigation. **Caterina Vacchi:** Validation. **Fulvio Savorani:** Investigation. **Giovanni Vinci:** Investigation. **Francesco Barsotti:** Investigation. **Maria Teresa Mascia:** Validation. **Carlo Salvarani:** Validation. **Marco Sebastiani:** Conceptualization, Methodology, Validation, Formal analysis, Writing – original draft, Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.compbiomed.2022.105220.

References

[1] C.R. Carpenter, P.A. Mudd, C.P. West, E. Wilber, S.T. Wilber, Diagnosing COVID-19 in the emergency department: a scoping review of clinical examinations, laboratory tests, imaging accuracy, and biases, Acad. Emerg. Med. 27 (8) (2020) 653–670, https://doi.org/10.1111/acem.14048.
[2] Y. Cao, X. Liu, L. Xiong, K. Cai, Imaging and clinical features of patients with 2019 novel coronavirus SARS-CoV-2: a systematic review and meta-analysis, J. Med. Virol. 92 (9) (2020) 1449–1459, https://doi.org/10.1002/jmv.25822.
[3] E.S. Hosseini, N.R. Kashani, H. Nikzad, J. Azadbakht, H.H. Bafrani, H.H. Kashani, The novel coronavirus disease-2019 (COVID-19): mechanism of action, detection and recent therapeutic strategies, Virology 551 (2020) 1–9, https://doi.org/10.1016/j.virol.2020.08.011.
[4] N. Chen, M. Zhou, X. Dong, J. Qu, F. Gong, Y. Han, Y. Qiu, J. Wang, Y. Liu, Y. Wei, J. Xia, T. Yu, X. Zhang, L. Zhang, Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in wuhan, China: a descriptive study, Lancet 395 (10223) (2020) 507–513, https://doi.org/10.1016/s0140-6736(20)30211-7.
[5] S. Guneyli, Z. Atceken, H. Dogan, E. Altinmakas, K.C. Atasoy, Radiological approach to COVID-19 pneumonia with an emphasis on chest CT, Diagn. Interventional Radiol. 26 (4) (2020) 323–332, https://doi.org/10.5152/dir.2020.20260.
[6] C.A. Raptis, M.M. Hammer, R.G. Short, A. Shah, S. Bhalla, A.J. Bierhals, P.D. Filev, M.D. Hope, J. Jeudy, S.J. Kligerman, T.S. Henry, Chest CT and coronavirus disease (COVID-19): a critical review of the literature to date, Am. J. Roentgenol. 215 (4) (2020) 839–842, https://doi.org/10.2214/ajr.20.23202.
[7] L. A. Valentino, M. W. Skinner, S. W. Pipe, The role of telemedicine in the delivery of health care in the COVID-19 pandemic, Haemophilia 26 (5). doi:10.1111/hae.14044.
[8] T. Fukumitsu, Y. Obase, Y. Ishimatsu, S. Nakashima, H. Ishimoto, N. Sakamoto, K. Nishitsuji, S. Shiwa, T. Sakai, S. Miyahara, K. Ashizawa, H. Mukae, R. Kozu, The acoustic characteristics of fine crackles predict honeycombing on high-resolution computed tomography, BMC Pulm. Med. 19 (1). doi:10.1186/s12890-019-0916-5.
[9] B. Wang, Y. Liu, Y. Wang, W. Yin, T. Liu, D. Liu, D. Li, M. Feng, Y. Zhang, Z. Liang, Z. Fu, S. Fu, W. Li, N. Xiong, G. Wang, F. Luo, Characteristics of pulmonary auscultation in patients with 2019 novel coronavirus in China, Respiration 99 (9) (2020) 755–763, https://doi.org/10.1159/000509610.
[10] P. Zhang, B. Wang, Y. Liu, M. Fan, Y. Ji, H. Xu, M. Xu, S. Chen, Q. Li, Z. Zhang, Lung auscultation of hospitalized patients with SARS-CoV-2 pneumonia via a wireless stethoscope, Int. J. Med. Sci. 18 (6) (2021) 1415–1422, https://doi.org/10.7150/ijms.54987.
[11] B. Reyes, N. Olvera-Montes, S. Charleston-Villalobos, R. González-Camarena, M. Mejía-Ávila, T. Aljama-Corrales, A smartphone-based system for automated bedside detection of crackle sounds in diffuse interstitial pneumonia patients, Sensors 18 (11) (2018) 3813, https://doi.org/10.3390/s18113813.
[12] A. Rizal, R. Hidayat, H.A. Nugroho, Multiscale tsallis entropy for pulmonary crackle detection, Int. J. Adv. Intell. Inf. 4 (3) (2018) 192, https://doi.org/10.26555/ijain.v4i3.273.
[13] E. Furman, A. Charushin, E. Eirikh, G. Furman, V. Sokolovsky, S. Malinin, V. Sheludko, The remote analysis of breath sound in COVID-19 patients: A series of clinical cases. doi:10.1101/2020.09.16.20195289.
[14] V. Raj, A. Renjini, M. Swapna, S. Sreejyothi, S. Sankararaman, Nonlinear time series and principal component analyses: potential diagnostic tools for COVID-19 auscultation, Chaos, Solitons Fractals 140 (2020) 110246, https://doi.org/10.1016/j.chaos.2020.110246.
[15] B.M. Rocha, D. Pessoa, A. Marques, P. Carvalho, R.P. Paiva, Automatic classification of adventitious respiratory sounds: a (un)solved problem? Sensors 21 (1) (2020) 57, https://doi.org/10.3390/s21010057.
[16] F.-S. Hsu, S.-R. Huang, C.-W. Huang, C.-J. Huang, Y.-R. Cheng, C.-C. Chen, J. Hsiao, C.-W. Chen, L.-C. Chen, Y.-C. Lai, B.-F. Hsu, N.-J. Lin, W.-L. Tsai, Y.-L. Wu, T.-L. Tseng, C.-T. Tseng, Y.-T. Chen, F. Lai, Benchmarking of eight recurrent neural network variants for breath phase and adventitious sound detection on a self-developed open-access lung sound database—HF_lung_v1, PLoS One 16 (7) (2021), e0254134, https://doi.org/10.1371/journal.pone.0254134.
[17] A. Manfredi, , G. Cassone, S. Cerri, V. Venerito, A. L. Fedele, M. Trevisani, F. Furini, O. Addimanda, F. Pancaldi, G. D. Casa, R. D'Amico, R. Vicini, G. Sandri, P. Torricelli, I. Celentano, A. Bortoluzzi, N. Malavolta, R. Meliconi, F. Iannone, E. Gremese, F. Luppi, C. Salvarani, M. Sebastiani, Diagnostic accuracy of a velcro sound detector (VECTOR) for interstitial lung disease in rheumatoid arthritis patients: the InSPIRAtE validation study (INterStitial pneumonia in rheumatoid ArThritis with an electronic device), BMC Pulm. Med. 19 (1). doi:10.1186/s12890-019-0875-x.
[18] A. Manfredi, G. Cassone, C. Vacchi, F. Pancaldi, G. D. Casa, S. Cerri, L. D. Pasquale, F. Luppi, C. Salvarani, M. Sebastiani, Usefulness of digital velcro crackles detection in identification of interstitial lung disease in patients with connective tissue diseases, Archiv. Rheumatol.:10.46497/archrheumatol.2021.7975.
[19] G. Sgalla, S. L. F. Walsh, N. Sverzellati, S. Fletcher, S. Cerri, B. Dimitrov, D. Nikolic, A. Barney, F. Pancaldi, L. Larcher, F. Luppi, M. G. Jones, D. Davies, L. Richeldi, "velcro-type" crackles predict specific radiologic features of fibrotic interstitial lung disease, BMC Pulm. Med. 18 (1). doi:10.1186/s12890-018-0670-0.
[20] W. Zhao, Z. Zhong, X. Xie, Q. Yu, J. Liu, Relation between chest CT findings and clinical conditions of coronavirus disease (COVID-19) pneumonia: a multicenter study, Am. J. Roentgenol. 214 (5) (2020) 1072–1077, https://doi.org/10.2214/ajr.20.22976.
[21] F. Pancaldi, M. Sebastiani, G. Cassone, F. Luppi, S. Cerri, G.D. Casa, A. Manfredi, Analysis of pulmonary sounds for the diagnosis of interstitial lung diseases secondary to rheumatoid arthritis, Comput. Biol. Med. 96 (2018) 91–97, https://doi.org/10.1016/j.compbiomed.2018.03.006.
[22] J. Makhoul, Linear prediction: a tutorial review, Proc. IEEE 63 (4) (1975) 561–580, https://doi.org/10.1109/proc.1975.9792.

[23] D. O'Shaughnessy, Linear predictive coding, IEEE Potentials 7 (1) (1988) 29–32, https://doi.org/10.1109/45.1890.
[24] T. Greenhalgh, J. Wherton, S. Shaw, C. Morrison, Video consultations for covid-19, BMJ (2020) m998, https://doi.org/10.1136/bmj.m998.
[25] M. Thomas, O. J. Price, J. H. Hull, Pulmonary function and COVID-19, Curr. Opin. Physiol.doi:10.1016/j.cophys.2021.03.005.