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Analysis of wheeze sounds during tidal breathing according to severity levels in asthma patients

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ABSTRACT

Objective: This study aimed to statistically analyze the behavior of time-frequency features in digital recordings of wheeze sounds obtained from patients with various levels of asthma severity (mild, moderate, and severe), and this analysis was based on the auscultation location and/or breath phase. **Method:** Segmented and validated wheeze sounds were collected from the trachea and lower lung base (LLB) of 55 asthmatic patients during tidal breathing maneuvers and grouped into nine different datasets. The quartile frequencies F_{25} , F_{50} , F_{75} , F_{90} and F_{99} , mean frequency (MF) and average power (AP) were computed as features, and a univariate statistical analysis was then performed to analyze the behavior of the time-frequency features. **Results:** All features generally showed statistical significance in most of the datasets for all severity levels [$\chi^2 = 6.021\text{--}71.65$, $p < 0.05$, $\eta^2 = 0.01\text{--}0.52$]. Of the seven investigated features, only AP showed statistical significance in all the datasets. F_{25} , F_{75} , F_{90} and F_{99} exhibited statistical significance in at least six datasets [$\chi^2 = 4.852\text{--}65.63$, $p < 0.05$, $\eta^2 = 0.01\text{--}0.52$], and F_{25} , F_{50} and MF showed statistical significance with a large η^2 in all trachea-related datasets [$\chi^2 = 13.54\text{--}55.32$, $p < 0.05$, $\eta^2 = 0.13\text{--}0.33$]. **Conclusion:** The results obtained for the time-frequency features revealed that (1) the asthma severity levels of patients can be identified through a set of selected features with tidal breathing, (2) tracheal wheeze sounds are more sensitive and specific predictors of severity levels and (3) inspiratory and expiratory wheeze sounds are almost equally informative.

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KEYWORDS

Asthma; breath sounds; wheeze detection; airway obstruction; severity level

Introduction

Asthma is a chronic disease induced by different environmental factors, including atmospheric pollution, house dust mites, viral respiratory tract infection, and smoking. According to the World Health Organization (WHO), 235 million individuals are suffering from asthma in underdeveloped and developing countries. Asthmatic patients generally exhibit sound-related symptoms during breathing. Specifically, during the breathing process, the lungs produce acoustic signals due to turbulent flow-related oscillations at the bronchi walls, and these respiratory acoustic signals provide meaningful information regarding the conditions of a patient's lungs. Normal lungs produce normal breath sounds, whereas pathological disorders or airway obstructions yield abnormal sounds, and the airway obstructions observed in asthmatic patients result in the production of wheeze sounds.

A few previous studies analyzed the correlation between changes in lung function values and the spectra of respiratory sounds [1–3]. Some researchers [2] collected data from asthmatic patients during tidal breathing and found a correlation between lung function values and the ratio of wheeze duration to total recording time (T_w/T_{tot}). Other researchers [1] collected data from ten asthmatic (mild to severe) patients during forced breathing from the trachea and chest, and their analysis using three features, namely the quartile frequencies F_{50} and F_{75} and the average power (AP), revealed that only F_{50} recorded at the trachea was significantly correlated with the force expiratory volume in one second (FEV_1). Another research group [3] collected data from 12 patients with asthma (moderate to severe) during forced breathing from the trachea and investigated the acoustic characteristics of the wheezes produced by normal subjects and patients

with stable and nonstable asthma. The results revealed that the mean frequency (MF) of normal subjects was different from that of asthmatic patients. A few other studies also analyzed only the characteristics of wheeze and normal sounds [4–6]. However, these studies did not perform statistical analyses comparing various auscultation locations, breathing phases and severity levels. Nevertheless, they affirm that computerized wheeze sound analysis is an active field of research, and previous reviews on computerized wheeze sound analysis have reported that most of the researchers in the field of computerized wheeze sound analysis are working on the detection or classification of wheeze sounds (a complete review of computerized wheeze sound analysis has been published [7]).

Taken together, the results from previous studies provide several important insights. First, the available data provide sufficient indication that lung function values of asthma can be identified from wheeze sound spectra. Second, although previous studies have collected data from patients with different asthmatic lung function values and conducted various analyses [7], very few of these studies related their findings to asthma severity levels. This research gap needs to be addressed in order to improve health outcomes for those with asthma through proper diagnosis and improved self-monitoring with the use of computerized devices. Current statistics dictates some urgency. WHO reports 235 million individuals suffering from asthma and 383 thousand related deaths in 2015. Countries with reliable established statistics on asthma, for example the US, noted that in 2007 asthma prevalence was about 8.2% (24.6 million people) of the total population, where 36% of them had at least one emergency department (ED) visit and 14% had at least one hospitalization [8]. This widespread prevalence of asthma and the health outcomes of poorly managed asthma, especially in low-income urban areas and impoverished communities in developing countries, has encouraged researchers to develop computerized devices for the self-monitoring and self-management of asthma. To this effect, physician-assisted devices, including spirometers and peak flow meters, are currently being used, but these devices are predominantly utilized during supervised forced respiratory maneuvers, which could pose a problem when dealing with children, during the long-term manipulation and continuous observation of patients, when treating very severe asthmatic conditions and during unsupervised sessions. In addition, wheezing during forced exhalation is not always correlated to the degree of airway obstruction in asthmatic patients, which reveals that

spirometry-based FEV_1 values might not always correlate with the asthma severity level [9].

This study attempts to investigate the behavior of time-frequency features in asthmatic patients with three different severity levels (mild, moderate, and severe). This is important to determine medication and other treatments that should be administered to patients. The management and monitoring of asthma in patients are implemented according to the asthma severity conditions, and the distribution of medication is also based on the severity levels [10]. Our study was designed to address issues related to self-management and self-monitoring (unsupervised sessions), and thus we primarily focused on tidal breathing maneuvers. Time-frequency features were extracted from wheeze segments obtained from patients with mild, moderate and severe asthma during tidal breathing and were then analyzed to detect their behavior under different severity conditions. We further extended our analysis and observations according to the location [trachea and lower lung base (LLB)] phase [inspiratory (Inspir) and expiratory (Expir)] and their combination [trachea inspiratory (T-Inspir), trachea expiratory (T-Expir), LLB inspiratory (LLB-Inspir) and LLB expiratory (LLB-Expir)].

Methodology

Investigation sites

Pakistan, which is exhibiting increasing trends in urbanization and western lifestyle, is an economically developing country with the sixth highest population. The physician-reported and self-reported prevalence of asthma among adult subjects in the major cities of Pakistan are 5.5% and 9.5%, respectively [11,12], and Gujranwala and Wazirabad are two densely populated cities in Pakistan known for industrial production. A study reported that Pakistan shares similar asthmatic statistics like the US in terms of ED visits and hospitalization [13]. Large portions of the populations in both of these cities migrated from rural areas, and asthmatic prevalence has been found to be increasing among migrating individuals. Urbanization and living in industrial areas increase the exposure of individuals to allergen and pollutants, which elevates the risk for allergy-related diseases and asthma. A research group [14] in Pakistan previously investigated various parameters related to asthma and other allergy-related diseases and compared them with those in other countries, and the findings from Pakistan were similar to the observations obtained in other countries.

Protocol

The protocol used for respiratory sound data acquisition [15] was designed according to the Computerized Respiratory Sound Analysis (CORSAs) standard [16] and after a detailed study of the literature [7]. The CORSAs standard was defined in 2000 by a task force of the European Respiratory Society, which included researchers from seven European Countries (Belgium, Britain, Finland, France, Germany, Italy, and the Netherlands), and is the only available standard for the collection of computerized respiratory sound data.

Ethics statement

Data were collected from two hospitals – Al-Mustafa Chest Clinic at Wazirabad, Pakistan, and District Headquarters Teaching Hospital at Gujranwala, Pakistan. Ethical permission was separately obtained from the ethical committees of both hospitals, and the study was performed in accordance with the principles of the Declaration of Helsinki. The patients who visited these hospitals were subjected to standard administrative procedures, which included the recording of personal details, such as racial/ethnic groups, socioeconomic level and occupation, etc. In addition, all the patients were provided the standard education brochures on asthma and the conventional strategies (non-computer-based techniques) used for its management. No additional questionnaire related to asthmatic care was completed by the patients.

Inclusion and exclusion criteria

Case report forms were filled for all the subjects by the diagnosing physicians. The patients were diagnosed according to the available standards [17], and the asthma severity levels (mild, moderate and severe) were identified according to the National Asthma Education and Prevention Programme – Expert Panel Report 3 [10,17]. The diagnosis of asthma was based on shortness of breath, wheezing history (frequency of hospitalization or visits to the ED), and general condition of the patient. Such practices have also been observed in other studies [18–20]. Given these details, the subjects were recruited based on suggestions from senior medical officers at both hospitals. Children and geriatric patients were not considered in this study. The selected subjects were nonsmokers who were not addicted to drugs. In addition, the selected subjects were those diagnosed as asthmatic patients without any other lung, heart or bowel region disease, and none of the patients had taken any medication for a

few hours prior to data collection. The asthma severity level of the selected patients was verified by at least two physicians in both hospitals. If the physicians had conflicting opinions regarding a subject, he/she was excluded from the study. Prior to data collection, the subjects were given instructions regarding the procedures, and written informed consent was obtained from the subjects that agreed to participate in this study. Our records indicate that 65 patients were referred by the physicians, but only 55 ($\approx 85\%$) agreed to participate in this study.

Devices for data acquisition

In this study, a wireless digital stethoscope (WISE) [21] was used for data collection. WISE (Sunmeditec Co, Ltd.) is a commercially available device with dimensions of $144 \times 63 \times 73$ mm and a weight of 270 g that is manufactured in Korea. The frequency response of this stethoscope is in the range of 20–2000 Hz. The hardware of the device comprises an air-coupled microphone, a transmitter and a receiver. WISE converts mechanical vibrations into electric signals through an air-coupled condenser. All the data were collected using VPM3000W software, which accompanies WISE and is saved on the computer. This device has also been used in a few previous studies [22–25].

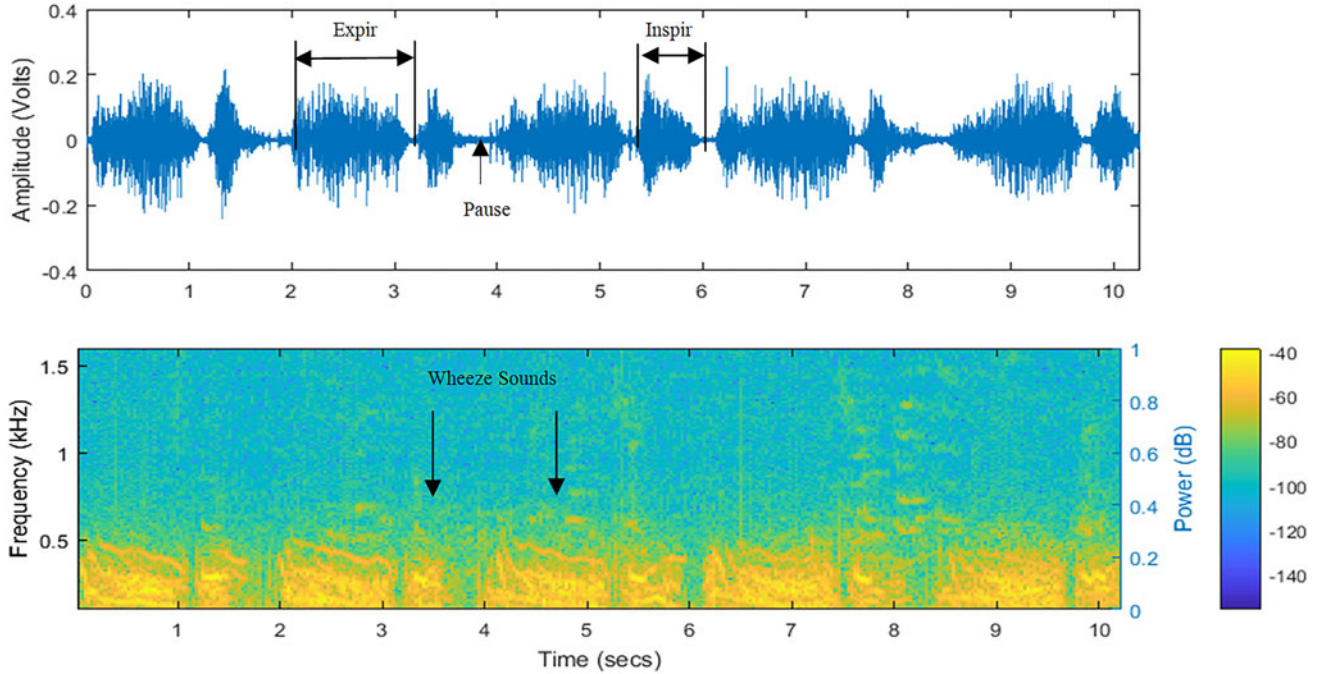
Auscultation location and procedure

Respiratory sound recordings were obtained using a single-channel WISE device. Specifically, data were collected from the trachea and the left and right LLBs [26]. The exact location in the LLB was selected through ordinary auscultation based on sounds with sufficient intensity [1] and according to a previous study [26]. In this study, the differences in breath sounds between the right and left LLBs [27] were considered negligible, and both locations were thus considered the LLB.

All the recordings were obtained from the subjects while in a sitting position with their hands on their lap. The subjects were asked to breathe through their mouth to exert effects on the upper airway and to keep quiet and avoid any movements during data recording. In addition, the subjects were asked to hold their breath for 10 s and then breathe normally without any targeted flow. To ensure the quality and reliability of the data, short-term recordings consisting of 60 to 90 s were conducted. The data were collected in a soundproof room, and the environmental conditions

Table 1. Summary of datasets used in this study.

	Total subjects	Male	Female	All	Trachea	LLB	Inspir	Expir	T-Inspir	T-Expir	LLB-Inspir	LLB-Expir
Mild	17	9	8	199	49	150	98	101	20	29	78	72
Moderate	18	12	6	254	85	169	127	127	32	53	95	74
Severe	20	13	7	322	123	199	158	164	54	69	104	95
Total	55	34	21	775	257	518	383	392	106	151	277	241

**Figure 1.** Recording of respiratory sound and spectrogram.

and subject's posture were identical in all cases; hence, the ambient noise did not show variations among the patients, as described previously [1].

Subject details

All the data were collected from subjects suffering from asthma. A total of 55 subjects (34 males and 21 females, age $\mu(\text{SD}) = 55(12.2)$ years) were included in the study. The details of the patient groups with different asthma severity levels were the following: (1) mild – 17 patients, male:female = 9:8, age $\mu(\text{SD}) = 50(12.1)$ years; (2) moderate – 18 patients, male:female = 12:6, age $\mu(\text{SD}) = 51.5(13.7)$ years; and (3) severe – 20 patients, male:female = 13:7, age $\mu(\text{SD}) = 50(11.5)$ years.

Data acquisition and preprocessing

Respiratory sound data were acquired at a sampling frequency of 8000 Hz. The respiratory sounds were filtered using a first-order high-pass Butterworth filter at 7.5 Hz to remove any DC offset, and an eighth-order low-pass Butterworth filter with a 2500 Hz frequency was subsequently applied to remove aliasing.

The dominant frequency of the lung sounds, which lies between 100 and 1600 Hz, was obtained using a fourth-order Butterworth filter, which would ensure that the noise in the recorded respiratory sounds (e.g. motion artifacts and heart sounds) was filtered out.

Segmentation

The wheeze sounds, together with the phases in the breath cycles (Inspir and Expir), were identified by two dedicated and independent physicians who were blinded to the severity of the asthma, and this identification was performed manually through an audio-visual inspection of the recordings and with the aid of spectrograms. The segments for which the physicians had conflicting opinions were excluded from the study. Similar protocols have been used in previous studies [28,29]. This process produced a database of wheezes labeled according to the asthma severity level, phase and location, and the details of all wheeze segments are provided in Table 1. The manifestation of wheeze sounds can be noted in Figure 1, which shows the respiratory sounds recorded from a 57-year-old man suffering from severe asthma.

Analysis

The wheeze segments were analyzed using a Fast Fourier Transform (FFT) approach [25,28,30–32] which transforms a digitized time domain signal into the frequency domain. In this study, the FFT of the segments was obtained with a 512-point Hamming window, which is a smooth window with acceptable leakage, and 50% overlap to obtain the power spectrum density within the range of 100–1600 Hz [25,31,33]. The amplitude of the power spectrum was interpreted as a probable distribution of frequencies (the sum of the absolute power spectrum values normalized to 1). The distributions of the frequencies of all the recordings obtained using this method were comparable, regardless of the loudness of the lung sounds [34,35] and the lung capacity. The quartile frequencies F_{25} , F_{50} , F_{75} , F_{90} and F_{99} were obtained from the characterized frequency spectra as the frequencies corresponding to 25%, 50%, 75%, 90% and 99% of the area in the normalized power spectrum, respectively. Furthermore, due to the nonlinear behavior of wheeze sounds [34], the MF [36] and normalized AP [37] were calculated. It has been demonstrated that quartile frequencies have the ability to provide the global frequency distribution of respiratory sounds, which is the primary interest of our study. These types of features have been used to analyze breath sounds from asthmatic subjects in some previously related clinical studies [1,3] as well as recent studies [19,35].

Statistical analyses were performed to compare different combinations of mild, moderate and severe samples based on the following considerations: (1) all wheeze samples regardless of the location and phase, (2) samples from different locations – trachea and LLB, (3) samples from different phases – Inspir and Expir; and (4) samples from different combinations of location and phase – T-Inspir, T-Expir, LLB-Inspir and LLB-Expir. In this statistical analysis, the normality of the data was tested, which revealed that the data were not normally distributed. Subsequently, a non-parametric test (Kruskal–Wallis) based on a univariate analysis was used to investigate the overall significance of the differences among the three severity levels. A *post hoc* test (Mann–Whitney test) was then applied to assess the significance of the differences between different pairs of severity levels, and in all the statistical analyses, a 95% confidence level was considered to indicate significance, i.e., selected datasets were considered significantly different if $p < 0.05$. The strength of the statistical analysis, depending on the test, was assessed using Cohen's effect size (η^2), as described in a previous study [38]. Eta squared (η^2)

was used to determine the effect size as follows: 0.01, small; 0.06, medium; and 0.138, large. All computations were performed using MATLAB, and the statistical analyses were performed using IBM SPSS.

3. Results

The μ and SD values of the features in all the datasets are shown in Figures 2–8. The results indicate that most of the μ and SD values for the lower-frequency quartiles (F_{25} and F_{50}) and AP obtained for the severe asthma group were higher compared with those found for the mild and moderate asthma groups. In contrast, most of the μ and SD values for the higher-frequency quartiles (F_{75} and F_{90}) and MF obtained for the moderate asthma group were higher compared with those found for the mild and severe asthma groups. In addition, both of these trends were observed for F_{99} , with a few exceptions.

Table 2 presents a summary of the statistical analysis among the three severity levels and the corresponding *post hoc* results for pairs *a* – mild & moderate, *b* – mild & severe and *c* – moderate & severe. Overall, most of the features exhibited an ability to discriminate the severity levels using all the tested datasets. The discrimination of the severity levels using all the wheeze samples showed that all the tested features were significant [$\chi^2 = 10.028$ –65.63, $p < 0.05$, $\eta^2 = 0.01$ –0.08].

We subsequently assessed whether the auscultation location was significantly related to the asthma severity level and found that all the tested features [$\chi^2 = 19.294$ –67.931, $p < 0.05$, $\eta^2 = 0.08$ –0.27] showed significant differences among the dataset of sounds that originated from the trachea. In contrast, in the dataset of sounds obtained from the LLB auscultation location, only F_{25} [$\chi^2 = 16.47$, $p < 0.05$, $\eta^2 = 0.03$], F_{99} [$\chi^2 = 9.729$, $p < 0.05$, $\eta^2 = 0.02$], and AP [$\chi^2 = 11.504$, $p < 0.05$, $\eta^2 = 0.02$] showed statistically significant differences.

The analyses based on the different respiratory phases showed that all the features exhibited statistical significance for the determination of the asthma severity level based on the Inspir dataset [$\chi^2 = 9.238$ –35.208, $p < 0.05$, $\eta^2 = 0.02$ –0.09]. However, the analysis of the Expir dataset revealed that all the features with the exception of F_{90} and F_{99} showed statistical significance [$\chi^2 = 11.395$ –34.24, $p < 0.05$, $\eta^2 = 0.03$ –0.09].

The results of the tests conducted with the combinations of location and phase revealed some interesting insights. First, all the features showed statistical

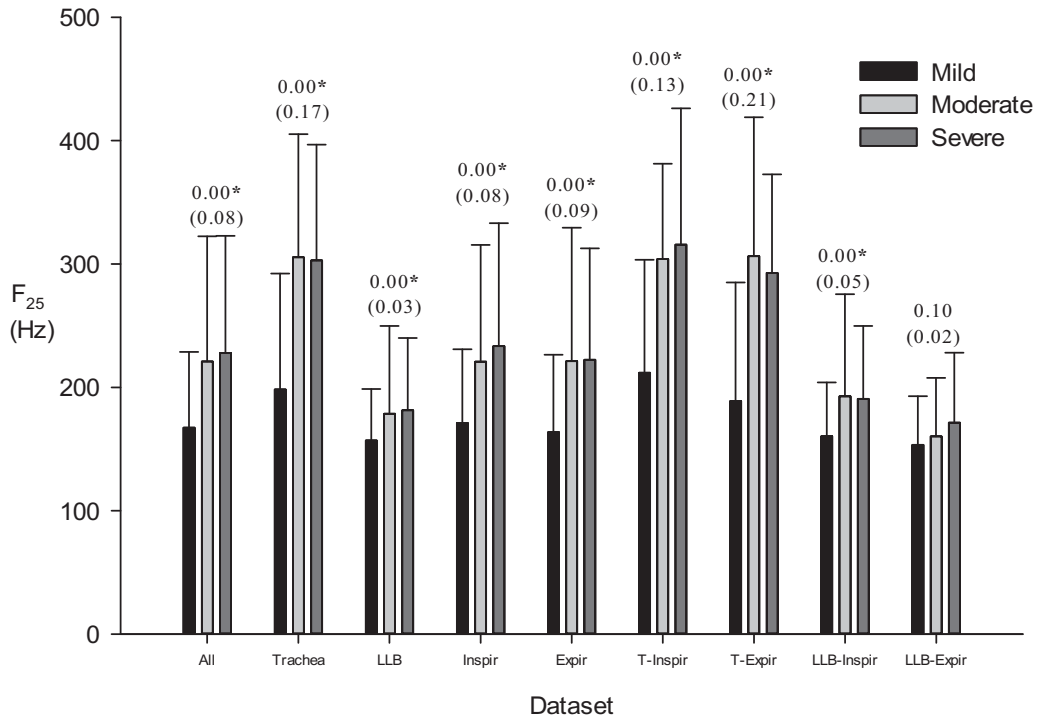


Figure 2. Results of the repeated-measures Kruskal–Wallis analysis for F_{25} (Hz) – μ , SD and p (η^2) values. (* indicates statistical significance, $p < 0.05$).

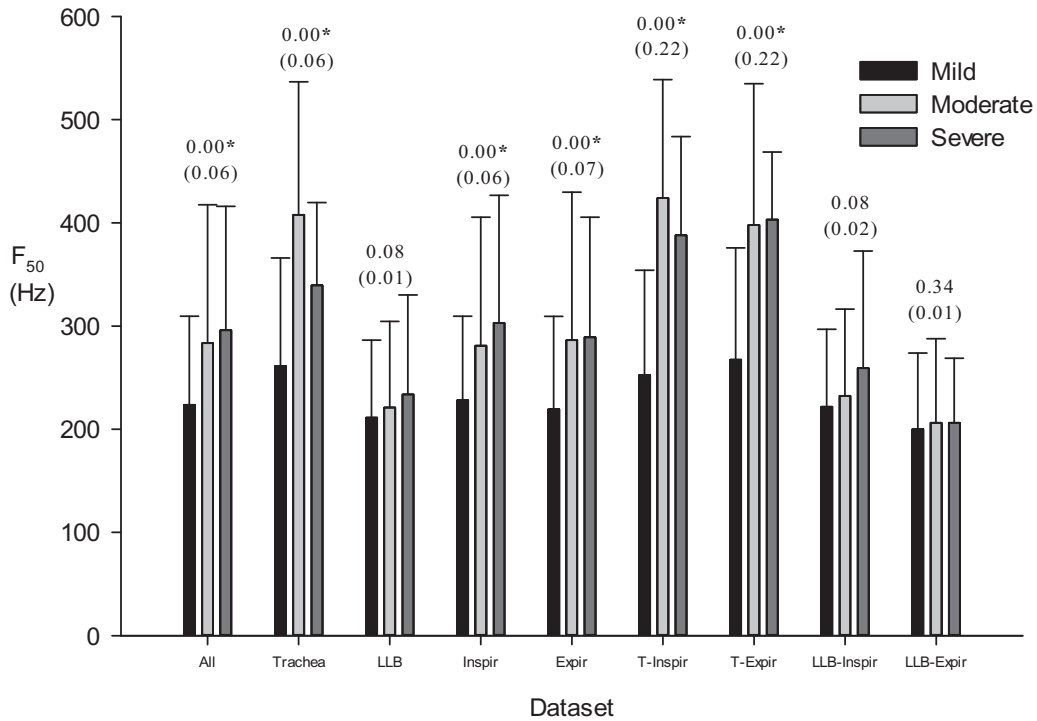


Figure 3. Results of the repeated-measures Kruskal–Wallis analysis for F_{50} (Hz) – μ , SD and p (η^2) values. (* indicates statistical significance, $p < 0.05$).

significance with a large effect size for the determination of the asthma severity level based on the T-Inspir dataset [$\chi^2 = 3.079\text{--}54.723$, $p < 0.05$, $\eta^2 = 0.07\text{--}0.52$]. The analyses based on the T-Expir dataset showed significant differences with a medium

to large effect size for most of the features [$\chi^2 = 7.271\text{--}34.364$, $p < 0.05$, $\eta^2 = 0.05\text{--}0.23$]. In contrast, the analyses using the LLB-Inspir dataset showed that all the features with the exception of F_{50} exhibited statistical significance [$\chi^2 = 6.02\text{--}14.369$, $p < 0.05$,

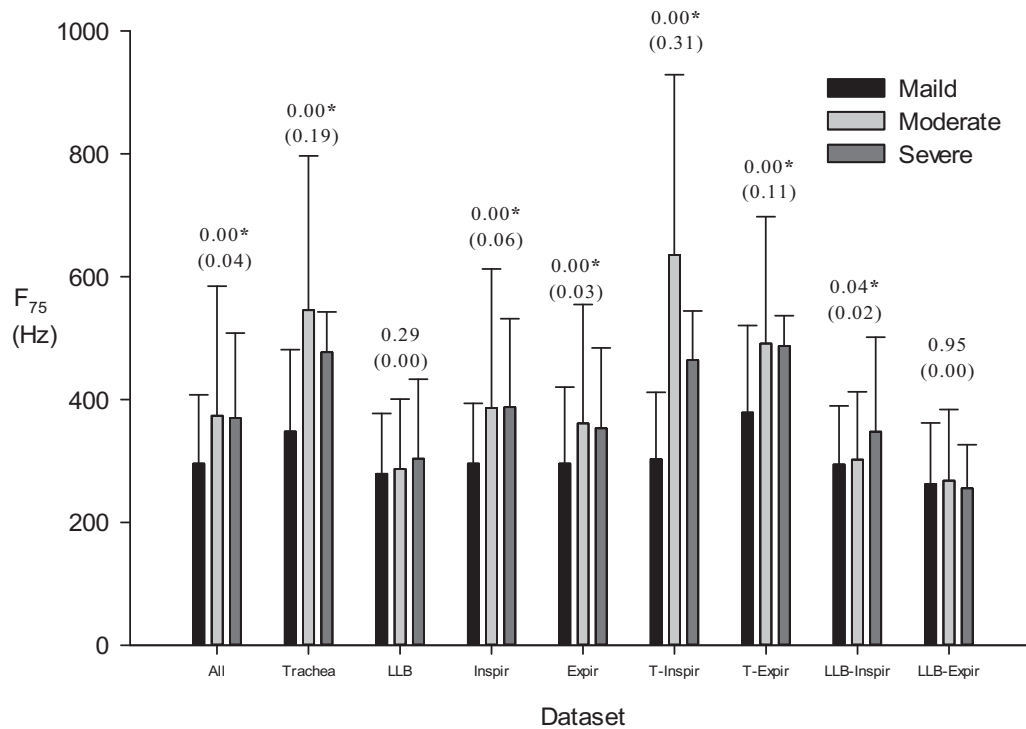


Figure 4. Results of the repeated-measures Kruskal–Wallis analysis for F_{75} (Hz) – μ , SD and p (η^2) values. (* indicates statistical significance, $p < 0.05$).

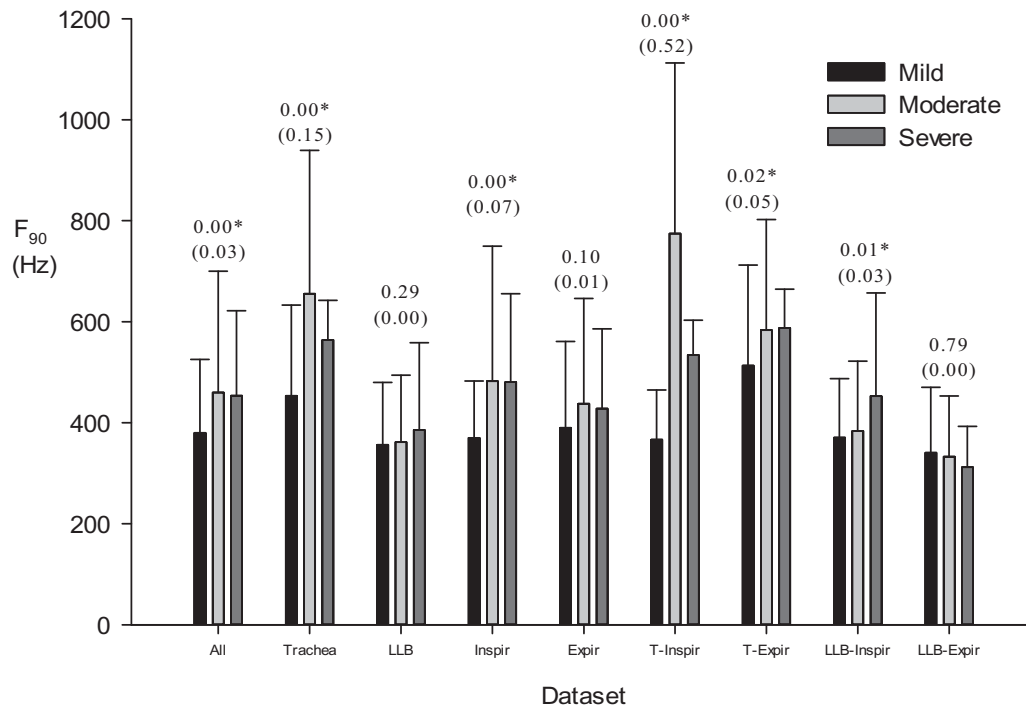


Figure 5. Results of the repeated-measures Kruskal–Wallis analysis for F_{90} (Hz) – μ , SD and p (η^2) values. (* indicates statistical significance, $p < 0.05$).

$\eta^2 = 0.02$ – 0.05], and the analyses of the LLB-Expir dataset revealed that all the features with the exception of AP were statistically significant [$\chi^2 = 6.155$, $p < 0.05$, $\eta^2 = 0.03$].

The *post hoc* test results are also presented in Table 2. The percentage of observations for the individual features that showed significant pairwise differences between severity levels were tallied. Specifically,

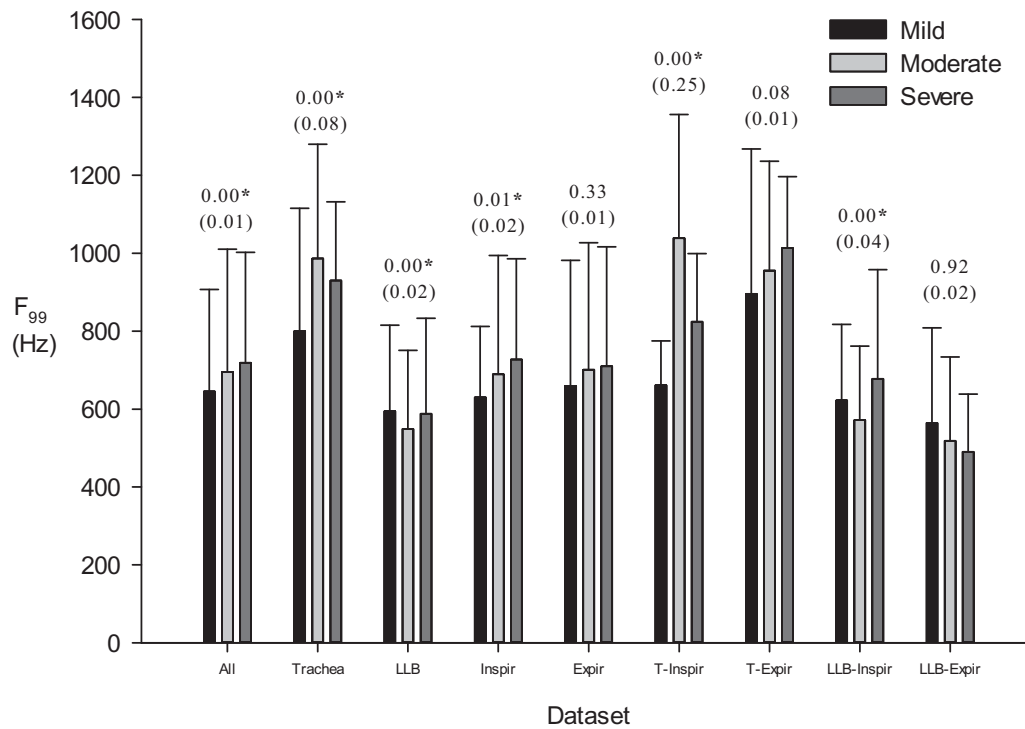


Figure 6. Results of the repeated-measures Kruskal–Wallis analysis for F_{99} (Hz) – μ , SD and p (η^2) values. (* indicates statistical significance, $p < 0.05$).

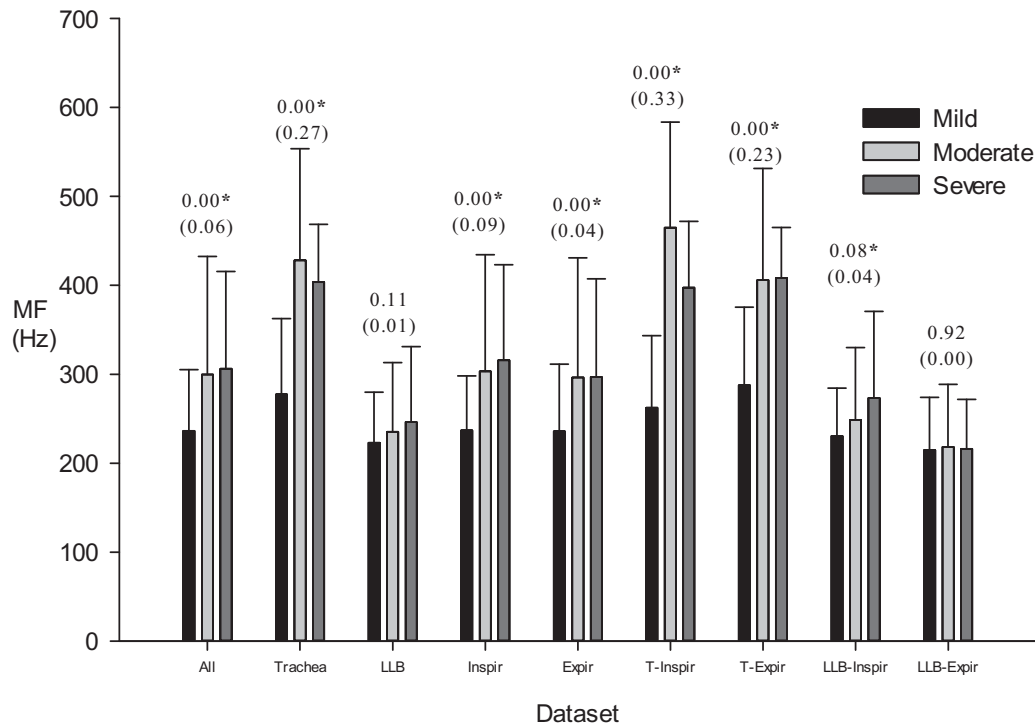


Figure 7. Results of the repeated-measures Kruskal–Wallis analysis for MF (Hz) – μ , SD and p (η^2) values. (* indicates statistical significance, $p < 0.05$).

the analysis of pair *a* revealed values of 100%, 86%, 67% and 78% for F_{25} and F_{50} , for F_{75} and MF, for F_{90} and F_{99} and for AP respectively. In contrast, the values for F_{25} , F_{50} , F_{75} , and F_{90} , for F_{99} , for MF and for AP obtained in the assessment of pair *b* were 100%,

67%, 86% and 89% respectively, and the assessment of pair *c* found values of 29%, 50%, 83%, 43% and 44% for F_{75} , F_{90} , F_{99} , MF and AP respectively. These findings suggest that the moderate and severe asthma levels can be better discriminated by the upper-frequency

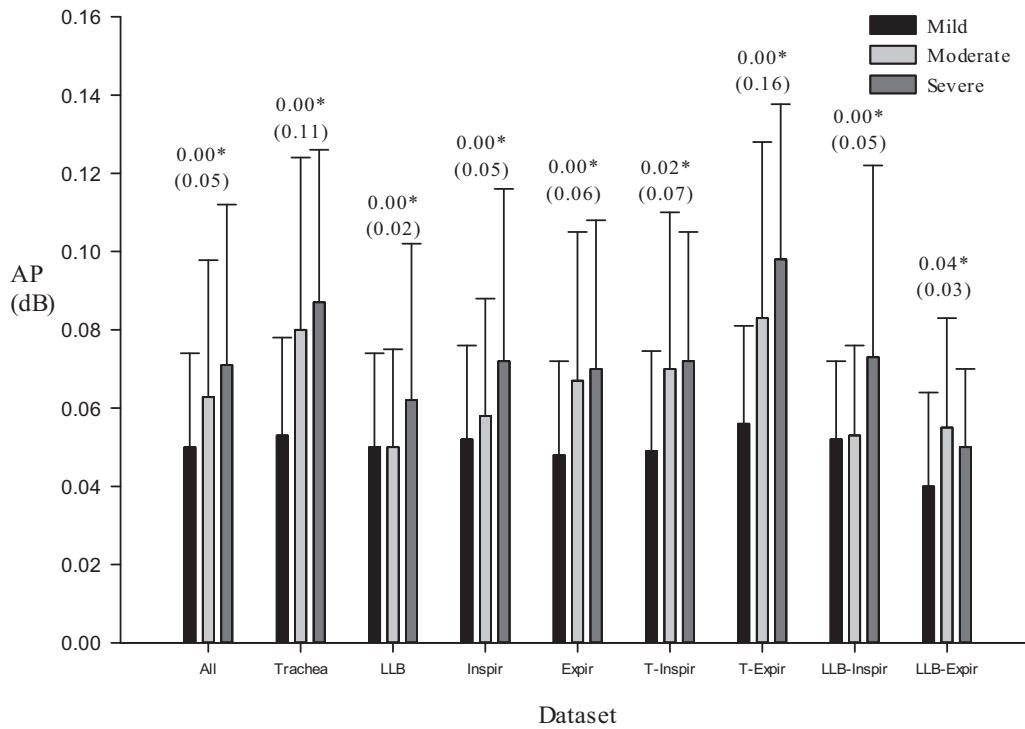


Figure 8. Results of the repeated-measures Kruskal–Wallis analysis for AP (dB) – μ , SD and p (η^2) values. (* indicates statistical significance, $p < 0.05$).

Table 2. Summary of the analysis of the significance of the features for the discrimination of the various datasets – p (η^2) values * and details of the *post hoc* test – a (mild and moderate), b (mild and severe), and c (moderate and severe).

Dataset	F_{25}	F_{50}	F_{75}	F_{90}	F_{99}	MF	AP
All	0.00 (0.08)^{a,b}	0.00 (0.06)^{a,b}	0.00 (0.04)^{a,b}	0.00 (0.03)^{a,b}	0.00 (0.01)^{b,c}	0.00 (0.06)^{a,b}	0.00 (0.05)^{a,b,c}
Trachea	0.00 (0.17)^{a,b}	0.00 (0.22)^{a,b}	0.00 (0.19)^{a,b}	0.00 (0.15)^{a,b,c}	0.00 (0.08)^{a,b}	0.00 (0.27)^{a,b}	0.00 (0.11)^{a,b}
LLB	0.00 (0.03)^{a,b}	0.08 (0.01)	0.29 (0.00)	0.29 (0.00)	0.00 (0.02)^{a,c}	0.11 (0.01)	0.00 (0.02)^{a,b}
Inspir	0.00 (0.08)^{a,b}	0.00 (0.06)^{a,b}	0.00 (0.06)^{a,b,c}	0.00 (0.07)^{a,b}	0.01 (0.02)^{b,c}	0.00 (0.09)^{a,c}	0.00 (0.05)^{b,c}
Expir	0.00 (0.09)^{a,b}	0.00 (0.07)^{a,b}	0.00 (0.03)^{a,b}	0.10 (0.01)	0.33 (0.01)	0.00 (0.04)^{a,b}	0.00 (0.06)^{a,b}
T-Inspir	0.00 (0.13)^{a,b}	0.00 (0.22)^{a,b}	0.00 (0.31)^{a,b,c}	0.00 (0.52)^{a,b,c}	0.00 (0.25)^{a,b,c}	0.00 (0.33)^{a,b,c}	0.02 (0.07)^{a,b}
T-Expir	0.00 (0.21)^{a,b}	0.00 (0.22)^{a,b}	0.00 (0.11)^{a,b}	0.02 (0.05)^b	0.08 (0.03)	0.00 (0.23)^{a,b}	0.00 (0.16)^{a,b,c}
LLB-Inspir	0.00 (0.05)^{a,b}	0.08 (0.02)	0.04 (0.02)^{b,c}	0.01 (0.03)^{b,c}	0.00 (0.04)^{a,c}	0.00 (0.04)^{b,c}	0.00 (0.05)^{b,c}
LLB-Expir	0.10 (0.02)	0.34 (0.01)	0.95 (0.00)	0.79 (0.00)	0.92 (0.02)	0.92 (0.00)	0.04 (0.03)^a

*The bold font indicates statistical significance, $p < 0.05$. a, b and c indicate statistical significance, as determined through the *post hoc* test.

quartiles. In addition, the results showed that the Inspir-related datasets could significantly discriminate between moderate and severe asthma, whereas the Expir-related datasets showed poor performance in discriminating between moderate and severe asthma.

4. Discussion

The management of an asthmatic patient requires prior knowledge of the patient's condition. Any medicine or treatment provided must suit the condition of the patient [10]. In general, three conditions are considered during the treatment of asthmatic patients: mild, moderate, and severe asthma. Using computerized techniques, researchers [1,3] have analyzed correlations of analytical

lung function values obtained using spirometers to spectral behavior obtained from breath sounds. Although lung function values provide an indication of the state of the lungs, they are not always related to airway obstruction in asthmatic patients. In addition, lung function values obtained from spirometers are not always capable of identifying changes in airway obstruction [9].

In this study, the discrimination of patients with mild, moderate, and severe asthma was first assessed using time frequency-based features – F_{25} , F_{50} , F_{75} , F_{90} , F_{99} , MF and AP. The results of our study show that this set of selected features show good performance with all the tested datasets, as shown in Figures 2–8 [$\chi^2 = 6.02$ – 67.93 , $p < 0.05$, $\eta^2 = 0.01$ – 0.52]. Our findings provide evidence of a correlation to physiology, similar to the findings obtained in a previous

study where, the airway thickness (wall area) was calculated and correlated to normal, mild, moderate, and severe asthma using computed tomography, and the researchers concluded that variations in wall thickness are related to the asthma severity [39]. Similarly, another study noted that high-pitch sounds are produced when the air caliber becomes narrow, which leads to the fluttering of airway walls and fluids [40] and thus the generation of wheeze sounds. These previous studies indicate that changes in lung airways inevitably cause changes in the frequency of breath sounds. In patients with severe asthma, this effect becomes particularly obvious, where wheezes are louder than the underlying breath sounds and can be clearly heard when the patient's mouth is open. The findings obtained in the present study agree with those of previous studies [2,39,40], revealing that an obstruction of the lung airway affects the frequencies of breath sounds from which wheezes manifest.

Some studies have used other or related features using a similar approach. Several previous studies have correlated lung function values with, the breath cycle power spectrum [35,41,42], the mean frequency of non-wheeze segments [1], the mean frequency of wheeze segments, the number of wheezes [3], and the ratio of wheezing duration to the total recording time (T_w/T_{tot}) [2]. However, the wheeze data used in these previous studies [3,35,41,42] was obtained during forced breathing maneuvers. According to some previous studies [9,43,44], wheezes can also be generated by normal subjects during forced breathing, and hence, such wheezes are not always related to the degree of airway obstruction in asthmatic patients [9]. On the other hand, asthma also has been induced in several previous studies [1,35,42] in selected subjects under medication. However, evidence shows that medication affects the changes in the frequencies of breath sounds [4] and that the induced wheeze sounds might also differ from spontaneous wheeze sounds [45]. Compared with these studies, our work demonstrates that the asthma severity levels of asthmatic patients can be differentiated based on spontaneous and non-induced wheeze sounds during tidal breathing.

This work also investigated the correlation of wheeze sounds obtained from two auscultation locations, the trachea and LLB, to the severity levels. Previous studies of airway obstruction [3,35,41,42] collected data from the trachea only. Another study [1] collected data from the trachea and LLB and found that only MF from the tracheal breath sounds is correlated to lung function values. Our analysis of MF yielded similar observations with a large effect size

for all trachea-related datasets [$\chi^2 = 34.364\text{--}67.931$, $p < 0.05$, $\eta^2 = 0.23\text{--}0.33$]. Furthermore, as revealed in Figures 2–8, all the features with the exception of AP were statistically insignificant for the discrimination of the LLB-Expir dataset based on the asthma severity level [$\chi^2 = 6.155$, $p < 0.05$, $\eta^2 = 0.03$], whereas all the features with the exception of F_{50} were statistically significant for the discrimination of the LLB-Inspir dataset [$\chi^2 = 6.02\text{--}14.396$, $p < 0.05$, $\eta^2 = 0.02\text{--}0.05$]. In contrast, the same features showed good performance in the discrimination of the trachea-related datasets with a large effect size [$\chi^2 = 4.852\text{--}54.723$, $p < 0.05$, $\eta^2 = 0.03\text{--}0.52$]. These findings revealed that the correlation of severity levels with selected features can be better observed in the trachea than in the LLB, which concurs with the results of a previous study [1]. Thus, these results indicate that tracheal wheeze sounds are more sensitive and specific predictors of airway obstruction, similarly to the findings of another study [46]. This difference could be due to the physiology of the LLB, which behaves as a stronger filter. Other studies [45,47] also found that the trachea appears to be superior for the recording of wheeze sounds, even though it does not allow the physical identification of the pathology location. The researchers of previous studies [27,45,48] also concluded that the respiratory sounds from various auscultation locations of the body show different behaviors. Taken together, these results provide evidence that sounds from the trachea and LLB have different characteristics.

The behavior of time-frequency features in patients with different severity levels was also investigated within breath phases. All the features were found to be statistically significant for the discrimination of majority of Inspir-related datasets [$\chi^2 = 6.012\text{--}54.723$, $p < 0.05$, $\eta^2 = 0.02\text{--}0.52$]. In contrast, F_{99} exhibited poor ability to discriminate the Expir-related datasets, while all the other features showed significant difference in at least one Expir-related dataset [$\chi^2 = 6.15\text{--}34.364$, $p < 0.05$, $\eta^2 = 0.03\text{--}0.22$]. Once again, our findings concur with the results from previous studies [5,6,48], which proves that sounds obtained during the Inspir and Expir phases exhibit different behavior. This finding could be due to the variations in the physiology of the airway passage (i.e., short and long airways) experienced by the airflow during the Inspir and Expir phases [45]. Nevertheless, it was observed that Inspir and Expir wheeze sounds are almost equally informative for characterizing the severity level of asthma patients, as observed in a previous study [46].

Overall, the results presented in Table 2 indicate the ability of the individual time-frequency features to discriminate between severity levels. In general, all the features showed statistical significance in the discrimination of the severity levels (mild, moderate, and severe) using all the datasets [$\chi^2 = 6.021\text{--}67.931$, $p < 0.05$, $\eta^2 = 0.01\text{--}0.52$]. Of the nine investigated datasets, only AP showed significance in discriminating all the datasets [$\chi^2 = 6.15\text{--}41.053$, $p < 0.05$, $\eta^2 = 0.02\text{--}0.16$]. Interestingly, F_{50} was statistically insignificant ($p > 0.05$) for the discrimination of all LLB-related datasets. This observation concurs with the findings obtained in a previous study [1]. We also noted that F_{25} , F_{90} and F_{99} have not been previously used in the literature. However, our findings indicate that these features show statistical significance in the discrimination of at least six datasets [$\chi^2 = 4.852\text{--}65.63$, $p < 0.05$, $\eta^2 = 0.01\text{--}0.52$]. We also observed some other trends. F_{75} was previously used [1] to characterize non-wheeze segments and was found to be statistically insignificant, whereas we found that this feature was statistically significant for the discrimination of wheeze sounds using at least seven wheeze datasets [$\chi^2 = 6.012\text{--}48.103$, $p < 0.05$, $\eta^2 = 0.02\text{--}0.19$]. The same previous study also investigated the significance of AP for the discrimination of non-wheeze segments and found that this feature was not statistically significant for the discrimination of asthma severity levels based on sounds from the trachea and LLB. In contrast, we found that AP was significant for the discrimination of asthma severity using all the datasets [$\chi^2 = 6.15\text{--}41.053$, $p < 0.05$, $\eta^2 = 0.02\text{--}0.16$]. MF was found to be statistically significant with a large effect size for the discrimination of asthma severity levels based on all trachea-related datasets [$\chi^2 = 34.364\text{--}34.952$, $p < 0.05$, $\eta^2 = 0.23\text{--}0.33$], and this finding could explain the results obtained with using this feature for the discrimination of asthma severity [1,3].

The μ and SD values of the tested features (Figures 2–8) did not indicate any specific trend with respect to the severity of the obstruction. However, significant differences were found for all the features in most of the datasets. These findings concur with the findings of a previous study [46], which indicated that wheeze sound spectra do not follow any specific pattern with respect to the severity level but can be used for the detection of airway obstruction.

This study has a few limitations. During the data collection process, we limited our investigation sites to only two, both of which are considered industrial cities. Furthermore, because asthma shows high prevalence worldwide, a larger sample size containing

balanced proportions of different genders and severity levels would provide better insights regarding the tested hypotheses. In addition, a more rigorous scientific and quantitative measure could be adopted for the labeling of asthma severity levels and breath phases, such as with the aid of a spirometer.

5. Implications for future research

In the future, this study can be extended to an analysis of the characteristics of wheezes in other diseases with similar symptoms, e.g. COPD and pneumonia, and their behavior in other related populations in which the monitoring and management of asthma is a priority, such as children and the elderly. Future studies should also focus on advanced signal processing methods for transforming and obtaining feature sets that would achieve a better representation of the spectral and phase responses of the signals. An accurate and low-computation-cost solution could indeed provide a strategy for the development of a much needed portable and affordable computerized decision support system (CDSS) for asthmatic patients. Such an application must be easily tailored to individual patients and should be aligned to the current practices of physicians and patient ergonomics.

6. Conclusion

The analysis of time-frequency features performed in this study demonstrated that the asthma severity level (mild, moderate, and severe) can be identified through a computerized analysis of wheeze sounds obtained during tidal breathing maneuvers. The behavior of the selected features indicated that the auscultation location and breath phase produce wheeze sounds with different characteristics. The findings of the study also indicated that all the tested features generally discriminated the severity level in most of the datasets. However, of the seven investigated features, only AP was able to discriminate the severity level in all nine datasets. Interestingly, F_{25} , F_{50} and MF showed statistical significance with a large effect size for the discrimination of severity levels using all trachea-related datasets. The *post hoc* results showed that most of the features presented significant differences in pairs *a* and *b*. However, the severity levels in pair *c* were discriminated by the MF and AP as well as by the upper-frequency quartiles F_{75} , F_{90} , and F_{99} . The analysis of the different phases indicated that Inspir and Expir wheeze sounds are almost equally informative for defining the asthma severity level, and the analysis

of different locations showed that tracheal wheeze sounds are more sensitive and specific predictors of airway obstruction. However, tracheal auscultation does not provide sufficient knowledge of the location of the pathology, which is one of the reasons why this method is not favoured in medical practice. Future analyses should attempt to improve the results obtained using the LLB as the auscultation location.

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Disclosure statement

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