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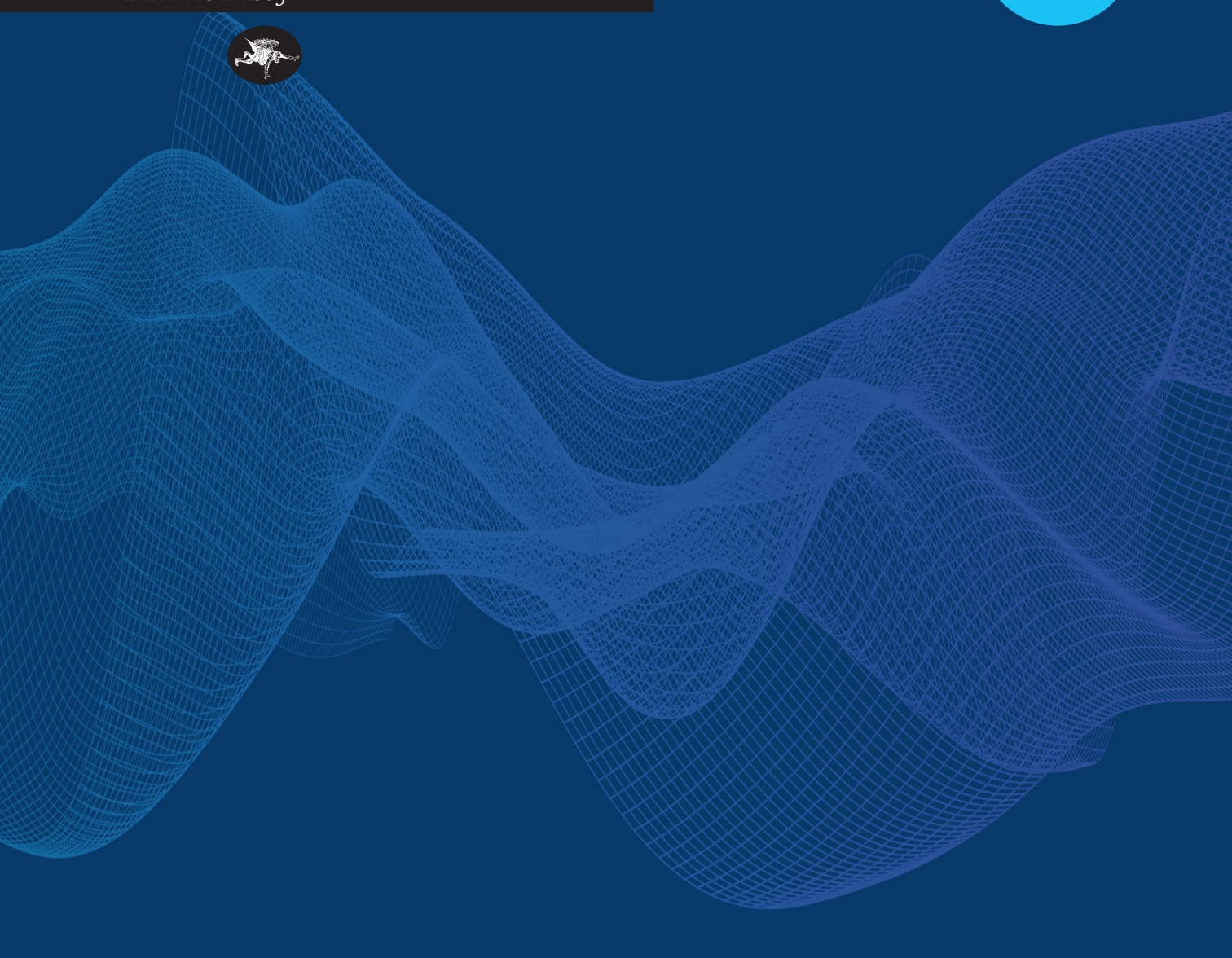

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Sense of loneliness and meaning in life in chronic obstructive pulmonary disease patients. Preliminary studies

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ABSTRACT

Background: Chronic obstructive pulmonary disease (COPD) interferes with everyday functioning but its impact on the loneliness and the meaning in life of the patients is unclear. Objectives: to determine whether the COPD severity levels correlate with the sense of loneliness and dimensions of the sense of meaning in life.

Methods: 144 patients with COPD during a period of absence of an infectious exacerbation were examined. The number of infectious exacerbations over the past year, the Modified Medical Research Council (mMRC) dyspnea score, the COPD Assessment Test (CAT) score were determined as well as the feelings of loneliness using the De Jong Gierveld Loneliness Scale (DJGLS) and the sense of meaning in life using the Life Attitude Profile-Revised (LAP-R) questionnaire.

Results: The age, the mMRC and CAT scores, the number of pack/years, as well as the number of infectious exacerbations during the year correlated positively with the feeling of loneliness. These variables (except for age) correlated negatively with the LAP-R scales apart from Existential Vacuum, which correlated positively. The subjects from the COPD severity group D (the most seriously ill people) had the highest level of loneliness, while it was the lowest in the subjects from group A (the least ill people). No statistical difference was observed between groups B and C.

Conclusions: With the increase in the values of the selected parameters determining the severity of COPD the sense of meaning in life decreases and loneliness intensifies.

Key words: COPD, loneliness, life style, Psychiatric status Rating Scales

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Availability of data and material: The data used to support the findings of this study are available from the corresponding author upon request: Marcin Kosmalski, marcin.kosmalski@umed.lodz.pl

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Background

In Poland, approximately 10% of the population suffers from COPD, which is also the fourth most common cause of death after cardiovascular diseases, malignant tumors, accidents, injuries, and poisonings [1, 2]. In Poland, more men than women suffer from COPD, and the average age of onset is between 55 and 60 years [3]. COPD is associated with extremely severe impairment of quality of life [4, 5].

Dynamic pulmonary distention accompanying the disease is the cause of chronic dyspnea both at rest and on exertion [6]. Chronic respiratory failure [7] and secondary pulmonary hypertension complicated by right ventricular heart failure [8-10] may develop as complications of COPD, all of which significantly impair the social functioning of patients [11]. This is associated with the possible loss of a job, the reduction of the social support network, loneliness, loss of life goals leading to a lack of meaning in life, and secondary anxiety and depressive disorders. The mental state of patients with COPD is additionally aggravated by high comorbidity including, for example, lung cancer, pancreatic tumors, type II diabetes, ischemic heart disease, and many others [12-16]. The levels of COPD severity are determined by the Cartesian product of the number of infectious exacerbations per year and the daily symptoms in the form of dyspnea measured by the modified Medical Research Council (mMRC) scale or the COPD Assessment Test (CAT) scale. Severity grade A means the mildest course of the disease, and risk grade D is the most severe. The question then arises as to whether the COPD severity grades correlate with feelings of loneliness and a sense of meaning in life. This question is important because, on the one hand, chronic shortness of breath, recurrent infections, as well as anxiety and depression may be unfavorable prognostic factors, and on the other hand, a high sense of meaning in life can protect against the psychological effects of COPD and provide motivation, for example, for moderate physical activity. Regular physical activity reduces shortness of breath in COPD and improves the prognosis along with the quality of life [17, 18]. Loneliness is the subjective feeling of the absence of a network of social support for the subject. Its most cohesive definition was presented by Cacioppo et al - loneliness results from the discrepancy between the desired and actually achieved a level of social ties, which is the cause of discomfort for the subject [19]. Factors that determine the feeling of loneliness include people and global random events such as the COVID-19 pandemic [20, 21]. Loneliness is one of the correlates of the meaning in life [22]. The construct of meaning in life was introduced to psychology and medicine by Viktor Frankl [23], and further developed by Salvatore R. Maddi [24, 25]. This construct was developed in various theoretical approaches and led to the emergence of such well-known concepts as the sense of coherence in the sense of Aaron Antonovsky [26, 27], or the concept of the meaning in life by Gary T. Reker [28].

The aim of this study is to determine whether the degrees of COPD severity and the dimensions determining the qualification for individual grade of COPD severity (such as the number of infectious exacerbations, mMRC score and the CAT score) correlate with the sense of loneliness and dimensions of the sense of meaning in life. In connection with the stated research goal, the following research questions were formulated:

1. Do the dimensions of life meaning and loneliness correlate with:
   - the results of the mMRC dyspnea scale;
   - the results of the CAT scale;
   - the number of pack/years;
   - the number of infectious exacerbations per year;
   - the patients' age?
2. Do the COPD severity grades, i.e. A, B, C, D, differ in the intensity of feeling of loneliness and the dimensions of the Life Attitude Profile-Revised (LAP-R) scale?
3. Is there a correlation between the LAP-R dimensions and the feeling of loneliness in the group of patients with COPD?

Material and Methods

Subjects

The survey was conducted over a period of 6 months from 06.2022 to 12.2022. The criteria for

inclusion in the study were a diagnosis of COPD and at least one-year follow up of the patient in an outpatient clinic of lung diseases. All patients included in the study had previously been diagnosed with COPD based on spirometry with forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) values. The inclusion criteria for the study were a diagnosis of COPD and informed consent of the patient to participate in the study. A group of 144 patients who were patients of the Medical University of Lodz Norbert Barlicki University Clinical Hospital No. 1 Outpatient Clinic of Lung Diseases was included in the study. That group was selected from among 186 patients with COPD. Ten out of these patients did not give their consent to the questionnaire study, 11 subjects returned incomplete questionnaires, 15 were excluded from the study because of cancer, stroke or heart attack, or a surgical procedure undergone in the past year and 6 were unable to complete the questionnaires due to dementia or other cognitive impairment, and the worsening of heart failure in III and IV class of The New York Heart Association functional classification (NYHA). Other severe systemic diseases were not a contraindication to participation in the study, as COPD is accompanied by high comorbidity. The patients were studied between infectious exacerbations. All were assessed by the number of infectious exacerbations over the past year, the mMRC dyspnea score, the CAT score, the feelings of loneliness using the DJGLS, and the sense of meaning in life using the LAP-R questionnaire.

Scales

De Jong Gierveld Loneliness Scale (DJGLS)

The feeling of loneliness was assessed according to the De Jong Gierveld Loneliness Scale (DJGLS) adapted in Polish by Paweł Grygiel et al. (2013), with the consent of the author of the tool (Cronbach's alpha 0.89) [29-31]. Detailed psychometric characteristics of the DJGLS can be found in the works of De Jong Gierveld and Grygiel [29, 30]. The tool has eleven questions and each item has a five-point answer scale [29]. A more profound sense of loneliness is reflected by a rise in the total DJGLS score [29]. The demographic data was collected in the form of a questionnaire, containing questions concerning the patients' age, gender, the number of pack/years, as well as the number of infectious exacerbations during the last year.

Life Attitude Profile – Revised (LAP-R)

The sense of meaning in life was measured using the Polish adaptation of the Life Attitude Profile – Revised (LAP-R) questionnaire, originally developed by Gary T. Reker, published by the Psychological Test Laboratory of the Polish Psychological Association (Cronbach's alpha between 0.70 and 0.80) [32, 33]. The questionnaire includes 8 scales (6 simple and 2 complex ones). The simple scales include Purpose (life goals and a sense of direction), Coherence (understanding of oneself and the environment), Choice/Responsibleness (a view on the ability to make life choices), Death acceptance (lack of fear of death, and accepting death as normal), Existential vacuum (absence of meaning in life, goals and direction), Goal seeking (desire for new experiences). Each item is rated from 1 (strongly disagree) to 7 (strongly agree) and each subscale has 8 items. The Existential vacuum scale is scored negatively, all the other scales positively. The two complex scales are calculated from the simple scales. They include The Personal Meaning Index (life goals, sense of direction, understanding of themselves and environment), a sum of coherence and purpose, and Existential Transcendence (a general measure of life attitudes), a sum of purpose, coherence, choice/responsibleness, death acceptance with subtraction of existential vacuum and goal seeking.

mMRC and COPD Assessment Test (CAT)

The mMRC and COPD Assessment Test (CAT) scales of dyspnea were taken from the commonly available COPD diagnostic and treatment standard referred to by the GOLD acronym (https://goldcopd.org/; 04.05.2021). The study was approved by the Bioethics Committee of the Medical University of Lodz (consent no. RNN/137/22/KE).

Each patient participating in the study received information for the patient with a detailed description of the study and an informed consent form. The patients were informed of the fully anonymous and voluntary nature of the study.

Statistical analysis

In the study, the internal consistency of the LAP-R scale was assessed with the use of Cronbach's Alpha along with the study of the inter-correlation between the dimensions of the scale. The numbers with percentages were used to describe nominal variables, and the median with 25 and 75% quartiles (Q1-Q3) was used to describe continuous variables with a distribution other than normal and ordinal. The distribution of continuous variables was tested using the Shapiro-Wilk W test. The Mann-Whitney U test was used to assess the differences between the two groups, while for groups > 2, the non-parametric ANOVA equivalent - the Kruskal Wallis test - was used. After obtaining statistical significance for the p global analysis of variance, the *post-hoc* test - Dunn's test was performed. The relationship between the variables was investigated using Spearman's rank correlation. Statistical significance was assumed at the level of $p < 0.05$. Statistical analyses were performed using the statistical program STATISTICA, version 13.3 (TIBCO 2022, Poland).

Results

The study included 144 patients diagnosed with COPD, the largest group of whom (over 79%) were male patients, and only 20.83% were females. The median age of the patients was 59 years (Q1-Q3 = 54.00-63.00). Among the subjects, the largest group were patients with mMRC = 2 (38.89%), with a severity level of COPD - D (29.86%). Patient demographics information is presented in Table 1.

The total internal consistency for all dimensions on the LAP-R scale was satisfactory and Cronbach's alpha was 0.78 (Table 2). In the study of intercorrelation between the simple dimensions, very strong positive correlations (r^2=0.946, $p < 0.001$) were shown between the goal (PU) and choice/responsibleness (CR), PU and goal-seeking (GS) ($r^2 = 0.933$, $p < 0.001$) and CR and GS ($r^2 = 0.922$, $p < 0.001$). On the other hand, a strong negative correlation was observed between PU and existential vacuum (EV) ($r^2 = -0.840$, $p < 0.001$) (Table 3).

Table 1. Demographic data of the study population.

Factor		N (%) / Median (Q1-Q3)
Age [Years]		59.00 (54.00-63.00)
Gender	Male	114 (79.17%)
	Female	30 (20.83%)
mMRC	1	11 (7.64%)
	2	56 (38.89%)
	3	37 (25.69%)
	4	40 (27.78%)
Degree of risk of COPD	A	30 (20.83%)
	B	34 (23.61%)
	C	37 (25.69%)
	D	43 (29.86%)
CAT		13.00 (7.00-32.50)
Number of pack/years		50.00 (40.00-60.00)
Number of infectious exacerbations	0	15 (10.42%)
	1	49 (34.03%)
	2	32 (22.22%)
	3	31 (21.53%)
	4	14 (9.72%)
	5	2 (1.39%)
	6	1 (0.69%)

CAT, the COPD Assessment Test; COPD, chronic obstructive pulmonary disease; mMRC, the Modified Medical Research Council. Data is expressed as a number of patients (included %) and median (Quartile 1; Quartile 3) for age, CAT and number of pack/years.

The study showed statistically significant correlations between the dimensions of the LAP-R scale and the sense of loneliness according to the DJGLS scale, and factors such as mMRC, the obtained CAT result, the number of pack/years as well as the number of infectious exacerbations among COPD patients.

Significant but weak correlations were found between the LAP-R dimensions PU ($R^2 = -0.269$, $p < 0.001$), CR ($R^2 = -0.286$, $p < 0.001$), EV ($R^2 = 0.258$, $p < 0.001$), GS ($R^2 = -0.239$, $p < 0.001$), TMPI ($R^2 = 0.250$, $p < 0.001$), ET ($R^2 = -0.238$, $p < 0.001$) and the age of patients; however, no correlation was observed between age and coherence (CO) and acceptance of death (DA). Similarly weak, positive

Table 2. Analysis of the reliability of the LAP-R scale dimensions.

LAP-R	Mean±SD	Median (Q1-Q3)	Cronbach's alpha	Correlations
Purpose (PU)	26.31±7.87	28.00 (23.00-31.50)	0.70	0.95
Coherence (CO)	35.65±6.85	39.00 (31.50-40.00)	0.72	0.90
Choice/Responsibleness (CR)	29.47±7.60	30.50 (27.00-35.00)	0.71	0.94
Death Acceptance (DA)	30.39±3.81	30.00 (29.00-31.00)	0.80	-0.03
Existenial Vacuum (EV)	36.19±8.78	33.00 (31.00-40.50)	0.90	-0.87
Goal Seeking (GS)	26.92±7.34	29.00 (27.00-30.00)	0.72	0.91
The Personal Meaning Index (TPMI)	61.97±14.09	67.00 (56.00-71.00)	0.65	0.98
Existential Transcendence (ET)	58.71±22.39	66.50 (47.50-74.50)	0.68	0.93
Total	-	-	0.78	-

LAP-R, the Life Attitude Profile-Revised. Data are expressed as mean value ± standard deviation (SD) as well as median (Quartile 1; Quartile 3).

Table 3. Intercorrelations between the simple and complex dimensions of the LAP-R scale.

	PU	CO	CR	DA	EV	GS	TPMI	ET
PU	1.000							
CO	**0.832***	1.000						
CR	**0.946***	**0.840***	1.000					
DA	-0.092	-0.101	-0.100	1.000				
EV	**-0.840***	**-0.749***	**-0.776***	0.019	1.000			
GS	**0.933***	**0.814***	**0.922***	-0.039	**-0.798***	1.000		
TPMI	**0.963***	**0.951***	**0.937***	-0.101	**-0.833***	**0.917***	1.000	
ET	**0.935***	**0.894***	**0.914***	0.078	**-0.915***	**0.869***	**0.957***	1.000

CO, coherence; CR, choice/responsibleness; DA, death acceptance; ET, existential transcendence; EV, existential vacuum; GS, goal seeking; PU, purpose; TPMI, the personal meaning index. *p assessed using the Spearman's rank correlation. The bolded results indicate statistically significant differences (*p<0.001*).

correlations were obtained between the DJGLS scale (R^2 = 0.222, p = 0.007) and age.

In the case of the LAP-R scale dimensions, negative (moderate to strong) correlations were obtained between the studied factors and the dimensions of PU, CR, GS, TMPI, ET (Table 4). Positive correlations were observed for the EV dimension of the LAP-R scale with mMRC R^2 = 0.624, CAT R^2 = 0.682, the number of pack/years R^2 = 0.776, the number of infectious exacerbations R^2 = 0.722 (p <0.001) and the DJGLS scale with mMRC (R^2 = 0.855), CAT (R^2 = 0.674), the number of pack/years (R^2 = 0.780), the number of infectious exacerbations (R^2 = 0.832) (all correlation p<0.001). The analysis of differences in the intensity of the feeling of loneliness according to the DJGLS scale and the COPD severity levels showed statistically significant differences in the results obtained in the DJGLS scale between groups A vs B (p <0.001), A vs C (p <0.001), A vs D (p <0.001), B vs C (p <0.001) and C vs D (p <0.001) (Figure 1). There were no statistically significant differences between people at severity of COPD B vs C (median = 34.00, Q1-Q3 = 32.00-37.00 vs median = 38.00, Q1-Q3 = 37.00-40.00; p = 0.457). The largest differences were observed between people at risk A (median = 20.00, Q1-Q3 = 14.00-27.00) and patients at risk D (median = 51.00, Q1-Q3 = 35.00-54.00).

The analysis of differences in the results obtained in the dimensions of the LAP-R scale with the COPD severity grades also showed no differences between the subjects belonging to the B vs C severity groups, for all 8 dimensions of the LAP-R scale. There were also no

Table 4. Correlation of demographic factors with the dimensions of the LAP-r scale and the DJGLS scale of the sense of loneliness.

	LAP-R scale								
Factors	**PU**	**CO**	**CR**	**DA**	**EV**	**GS**	**TMPI**	**ET**	**DJGLS scale**
Age [Years]	**-0.269***	-0.148	**-0.286***	0.011	**0.258***	**-0.239***	**-0.250***	**-0.238***	**0.222****
mMRC	**-0.635***	**-0.631***	**-0.620***	**-0.286***	**0.624***	**-0.619***	**-0.649***	**-0.646***	**0.855***
CAT	**-0.715***	**-0.719***	**-0.685***	**-0.334***	**0.682***	**-0.681***	**-0.731***	**-0.712***	**0.674***
Number of pack/years	**-0.856***	**-0.723***	**-0.831***	**-0.336***	**0.776***	**-0.831***	**-0.849***	**-0.810***	**0.780***
Number of infectious exacerbations	**-0.842***	**-0.716***	**-0.824***	**-0.264***	**0.722***	**-0.816***	**-0.844***	**-0.803***	**0.832***

CAT, the COPD Assessment Test; CO, coherence; CR, choice/responsibleness; DA, death acceptance; DJGLS, the De Jong Gierveld Loneliness Scale; ET, existential transcendence; EV, existential vacuum; GS, goal seeking; LAP-R, the Life Attitude Profile-Revised; mMRC, the Modified Medical Research Council; PU, purpose; TPMI, the personal meaning index. p assessed using the Spearman's rank correlation. The bolded results indicate statistically significant differences (*$p<0.001$; **$p<0.05$).

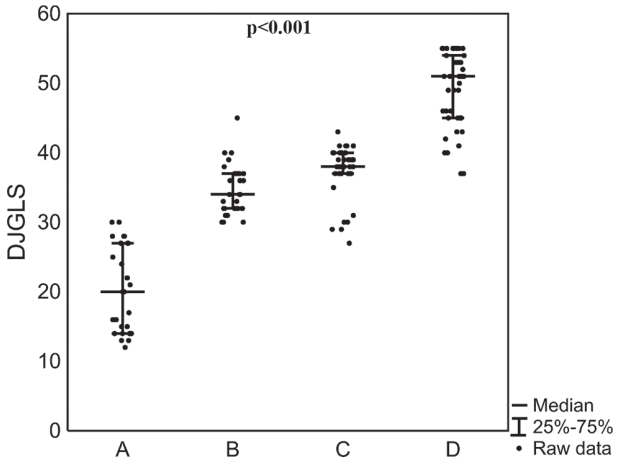

Figure 1. Statistically significant differences (p global <0.001) in the intensity of loneliness on the DJGLS scale based on the COPD risk grade (A, B, C, D). The chart shows the most important difference between the paired patients from the A vs D risk group.

differences between groups B vs D and C vs D for the death acceptance dimension. However, a statistically significant, although slightly higher result obtained in the acceptance of death dimension was noticed in persons belonging to the severity group A in comparison with patients from groups B, C, and D.

For dimensions such as life goal (median = 15.00, Q1-Q3 = 10.00-23.00), choice/responsibleness (median = 25.00, Q1-Q3 = 13.00), coherence (median = 29.00, Q1-Q3 = 28.00-31.00), goal-seeking (median = 22.00, Q1-Q3 = 10.00-27.00), the personal meaning index (median = 45, Q1-Q3 = 38.00-54.00) and the existential transcendence (median = 30.00. Q1-Q3 = 19.00-45.00), it was noticed that patients belonging to the COPD-D severity grade obtained statistically significantly lower results than other patients (Figure 1S and Table 1S - Supplement). However, in the case of experiencing an existential vacuum, as in the case of the feeling of loneliness on the DJGLS scale, patients with severity grade D obtained significantly higher EV scores (median = 45.00, Q1-Q3 = 19.00-45.00) than patients with other severity grades (A, B or C).

In the study of the relationship between the sense of loneliness on the DJGLS scale and all LAP-R dimensions, strong negative correlations were shown between the results obtained on the DJGLS scale and dimensions such as goal, coherence, choice/responsibleness, goal-seeking, personal meaning index and existential transcendence (Table 5). A negative, but weak, correlation was also shown between DJGLS and death acceptance (R2 = -0.368, p <0.001), while a positive relationship was found between the feeling of loneliness and existential vacuum.

Discussion

We demonstrated in our study that age, mMRC, and CAT scores, the number of pack/years, and the number of infectious exacerbations during the year correlated positively with feelings of loneliness. There

Table 5. Correlation between the DJGLS scale and the LAP-R scale.

	PU	CO	CR	DA	EV	GS	TMPI	ET
DJGLS scale	**-0.937***	**-0.835***	**-0.909***	**-0.368***	**0.863***	**-0.904***	**-0.943***	**-0.916***

CO, coherence; CR, choice/responsibleness; DA, death acceptance; DJGLS, the De Jong Gierveld Loneliness Scale; ET, existential transcendence; EV, existential vacuum; GS, goal seeking; LAP-R, the Life Attitude Profile-Revised; mMRC, the Modified Medical Research Council; PU, purpose; TPMI, the the personal meaning index. p assessed using the Spearman's rank correlation. The bolded results indicate statistically significant differences (*$p<0.001$).

are no analogous correlation studies in the literature between the aforementioned variables in patients with COPD, except for age [34]. The same variables correlated positively with the intensity of the existential vacuum. Also, these variables, except for age, correlated negatively with the following scales: Purpose, Coherence, Choice/Responsibleness, Death Acceptance, Goal Seeking, The Personal Meaning Index, and Existential Transcendence. In the case of age, correlations with the Coherence scale and Death Acceptance did not reach statistical significance. The reliability of the tools used has been positively verified by us, which is presented in Tables 2 and 3. Based on the obtained results, it can be concluded that the sense of meaning in life decreases and loneliness intensifies with the increase in the selected parameters determining the severity of COPD (mMRC, CAT, number of pack/years, number of infectious exacerbations per year). Increased loneliness and lack of meaning in life translate into poor quality of life in COPD and increased depression, which has often been studied in the population of patients with COPD [15, 33]. The highest level of loneliness (Figure 1) was observed in severity group D (the patients most seriously ill), and the lowest in group A (the least ill ones). On the other hand, the lack of statistical significance in the severity of loneliness between people from risk groups B and C is noteworthy. Both group B and group C are people with moderate severity of COPD symptoms, but they differ clinically, because severity grade B means low dyspnea with frequent infectious exacerbations, whereas severity grade C means a high severity of symptoms with a low risk of infectious exacerbations [36]. It is noteworthy that most of the statistically significant correlations we obtained had an absolute value exceeding 0.6. It means that the correlations between the clinical variables and the LAP-R scale dimensions and the severity of loneliness (DJGLS) are very strong. Table 5 shows that loneliness strongly correlates with the dimensions of the LAP-R scale, and the absolute value of most correlations is greater than 0.8. Possibly, both the sense of loneliness and the sense of meaning in life are dependent on one statistical factor. This factor probably determines the quality of life, although measuring the quality of life of COPD patients was not the goal of our study [35].

Paige et al. demonstrated that loneliness was an independent factor in the arrival of COPD patients at the hospital emergency departments [12]. In turn, Bu et al. showed that the feeling of loneliness did not correlate with the risk of hospitalization of patients with COPD, while poor social network correlated with hospitalizations in this group of people [34]. In 2004, interesting results of a population study of 15,010 participants were published. COPD was diagnosed in 307 men (4.3%) and 396 women (5.6%). It turned out that depression was diagnosed twice as often in the group of patients with COPD (16.2%) compared to healthy people (7.5%). Risk factors for depression in COPD patients were found to be loneliness, low levels of social support, social phobia, and type D of behavior [37]. Behavior type D is also defined as a stress-prone personality. People with type D personalities tend to feel negative emotions, e.g. anxiety, show a pessimistic approach to life, and feel constant tension and insecurity. They are withdrawn in social relations due to fear of rejection. The concept of type D personality was formulated by Johann Denollet as a risk factor for coronary heart disease, similar to the previously defined type A personality [38]. Our own research has demonstrated that type D is also associated with the risk of asthma and the severity of its course [39]. It should be noted that both asthma and COPD are associated with pulmonary obstruction and there are many clinical similarities between the two diseases, and differential diagnosis between them is quite difficult [40, 41].

In some patients, asthma co-occurs with COPD, which is referred to as asthma-chronic obstructive pulmonary disease overlap syndrome (ACOS) [42].

It has also been demonstrated that during the respiratory rehabilitation of patients with COPD, a greater sense of loneliness correlated positively with low exercise capacity, and worsening of depression and anxiety. Surprisingly, however, a greater sense of loneliness correlated with a greater improvement in the functioning of respiratory capacity in the process of respiratory rehabilitation [43]. Numerous studies indicate that the COVID-19 pandemic has significantly increased social distancing and feelings of loneliness in COPD patients [44, 45]. Therefore, it can be assumed that the percentage of diagnosed cases of depression in people with COPD will increase in the coming years. Moreover, research conducted by Reijnders et al. (2018) showed that the subjectively felt loneliness of COPD patients worsens their prognosis [43].

Limitations of the study

Our research was performed and statistically developed before the publication of the GOLD standards of 2023 (https://goldcopd.org/2023-gold-report-2/; 02.12.2023). In this standard, COPD is divided into three risk levels: A, B, E. Risk level E is approximately the risk level C plus D included in the previous GOLD standards. In our study, the results of the examined variables of levels C and D differ, which raises some doubts whether the creation of category E is justified.

The disproportion between the number of women and the number of men in the studied sample was an important limitation of our study. The selection of patients was not random, although the predominance of men with COPD over women with COPD reflects the epidemiological trend. The current COPD epidemic reflects the prevalence of nicotine addiction syndrome about 20 years ago when men smoked much more often than women. The study also did not take into account the flow-volume parameters such as forced vital capacity of the lungs (FEV_1), forced vital capacity of the lungs (VC), the Tiffeneau index, peak maximum flow (PEF), and small airway flows (MEF25, MEF50, MEF75) in the clinical characterization of patients. These parameters were taken into account when diagnosing COPD. However, their values were not analyzed. On the other hand, the classification of COPD severity according to spirometry criteria is currently being abandoned in favor of variables such as the severity of symptoms, the shortness of breath scale (mMRC), or the number of infectious exacerbations per year. Other recognized negative prognostic factors in COPD include low exercise capacity, low BMI, reduced carbon diffusion (DLCO in pedice), the presence of gasometric abnormalities, the volume of resting pulmonary hyperinflation, the presence of pulmonary hypertension, and high CRP concentration. Therefore, the values of parameters readable from the flow-volume loop are not the most important prognostic factors in the course of COPD. It would be good to determine in future studies whether the factors listed above are predictors of loneliness in patients with COPD [46].

Conclusion

The age, the mMRC, and CAT scores, the number of pack/years, as well as the number of infectious exacerbations during the year correlated positively with the feeling of loneliness and positively with the severity of the existential vacuum. These variables (except for age) correlated negatively with the scales: Purpose, Coherence, Choice/Responsibleness, Death Acceptance, Goal Seeking, The Personal Meaning Index, and Existential Transcendence. Statistical significance for the age variable was not obtained with respect to correlations with the Coherence and Death Acceptance scales, and the other scales correlated with that variable negatively. In view of the above, it can be concluded that with the increase in the values of the selected parameters determining the severity of COPD (mMRC, CAT, number of pack/years, number of infectious exacerbations per year), the sense of meaning in life decreases and loneliness intensifies. The subjects from the COPD severity group D (the most seriously ill people) had the highest level of loneliness, while it was the lowest in the subjects from group A (the least ill people). In contrast, there was no statistical significance between groups B and C.

Promoting health behaviors such as smoking cessation, physical activity, weight loss, and social

integration of COPD patients can improve not only the patient's somatic condition, but also have a positive effect on their mental state. Treating mental disorders in COPD patients can positively affect their mental state [37].

In the continuation of this study, it would also be necessary to find out whether cognitive impairment accompanying COPD has a prognostic significance in COPD [47].

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Appendix

Supplementary Materials

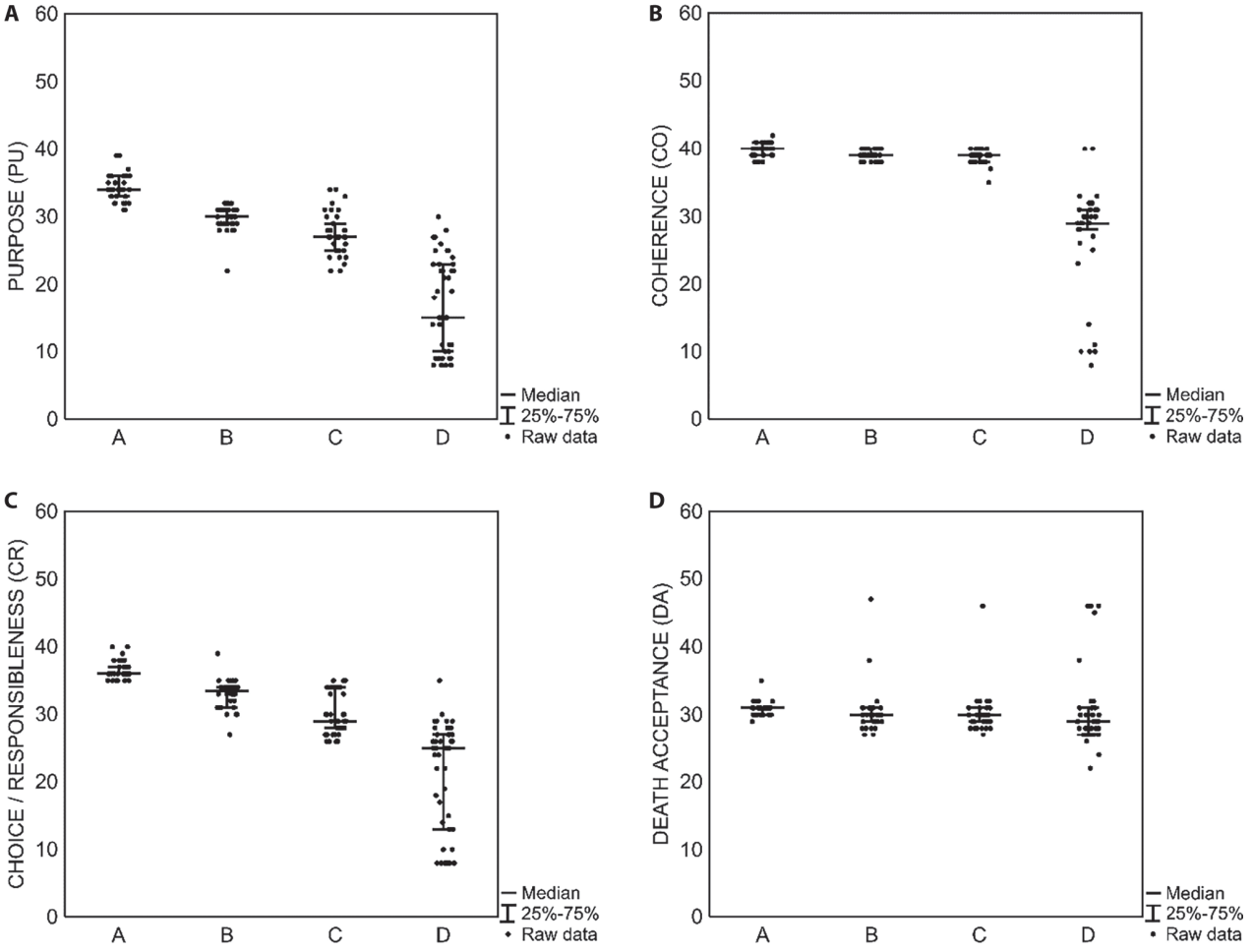

Figure 1S. Statistically significant differences (p global <0.001) in the intensity of individual dimensions of the LAP-R scale, based on the risk of COPD (A, B, C, D); A) Purpose (PU) in risk groups A, B, C, D; B) Coherence (CO) in risk groups A, B, C, D; C) Choice / Responsibleness (CR) for risk groups A, B, C, D; D) Death Acceptance (DA) in risk groups A, B, C, D; E) Existential Vacuum (EV) in risk groups A, B, C, D; F) Goal seeking (GS) in risk groups A, B, C, D; G) The personal meaning index (TPMI) in risk groups A, B, C, D; H) Existential transcendence (ET) in risk groups A, B, C, D.

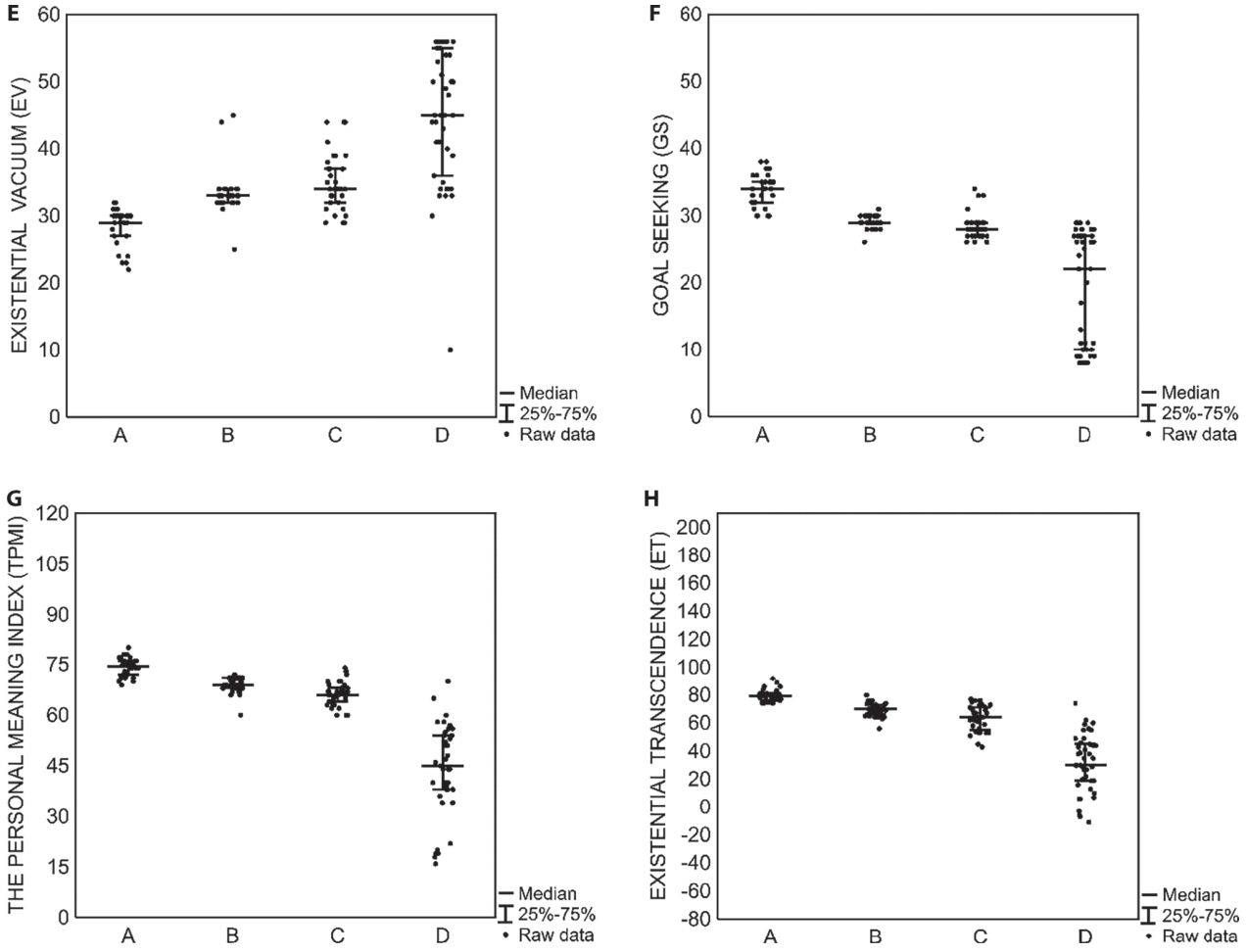

Figure 1S. (*continued*)

Table 1S. Differences between the COPD risk groups (A, B, C, D) for all dimensions of the LAP-R scale.

	LAP-R scale							
Risk of COPD groups	**PU**	**CO**	**CR**	**DA**	**EV**	**GS**	**TPMI**	**ET**
A vs B	**0,002**	**0,320**	**0,001**	**0,009**	**<0,001**	**<0,001**	**0,004**	**<0,001**
A vs C	**<0,001**	**0,033**	**<0,001**	**0,032**	**<0,001**	**<0,001**	**<0,001**	**<0,001**
A vs D	**<0,001**	**<0,001**	**<0,001**	**<0,001**	**<0,001**	**<0,001**	**<0,001**	**<0,001**
B vs C	0,157	1,000	0,105	1,000	1,000	0,185	0,188	0,609
B vs D	**<0,001**	**<0,001**	**<0,001**	1,000	**<0,001**	**<0,001**	**<0,001**	**<0,001**
C vs D	**<0,001**	**<0,001**	**<0,001**	0,672	**<0,001**	**0,002**	**<0,001**	**<0,001**

CO, coherence; CR, choice/responsibleness; DA, death acceptance; ET, existential transcendence; EV, existential vacuum; GS, goal seeking; LAP-R, the Life Attitude Profile-Revised; PU, purpose; TPMI, the personal meaning index. * p-value assessed using the Spearman's rank correlation.

The bolded results indicate statistically significant differences (*p<0.001*).

Original Research Article

OPEN ACCESS

An Italian Delphi Consensus on the Triple inhalation Therapy in Chronic Obstructive Pulmonary Disease

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ABSTRACT

Background: The management of chronic obstructive pulmonary disease (COPD) lacks standardization due to the diverse clinical presentation, comorbidities, and limited acceptance of recommended approaches by physicians. To address this, a multicenter study was conducted among Italian respiratory physicians to assess consensus on COPD management and pharmacological treatment.

Methods: The study employed the Delphi process using the Estimate-Talk-Estimate method, involving a scientific board and expert panel. During a 6-month period, the scientific board conducted the first Delphi round and identified 11 broad areas of COPD management to be evaluated while the second Delphi round translated all 11 items into statements. The statements were subsequently presented to the expert panel for independent rating on a nine-point scale. Consensus was considered achieved if the median score was 7 or higher. Consistently high levels of consensus were observed in the first rating, allowing the scientific board to finalize the statements without requiring further rounds.

Results: Topics generating substantial discussion included the pre-COPD phase, patient-reported outcomes, direct escalation from a single bronchodilator to triple therapy, and the role of adverse events, particularly pneumonia, in guiding triple therapy prescriptions. Notably, these topics exhibited higher standard deviations, indicating greater variation in expert opinions.

Conclusions: The study emphasized the significance that Italian pulmonologists attribute to managing mortality, tailoring treatments, and addressing cardiovascular comorbidities in COPD patients. While unanimous consensus was not achieved for all statements, the results provide valuable insights to inform clinical decision-making among physicians and contribute to a better understanding of COPD management practices in Italy.

Key words: Chronic Obstructive Pulmonary Disease (COPD); Delphi process; triple combination therapy; long-acting beta2-agonist; long-acting muscarinic receptor antagonist, and inhaled corticosteroid

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Ethics approval and consent to participate: Ethical approval of his work was not required as no human or animal subjects were involved.

Availability of data and material: The data underlying this article are available in this article.

Conflict of interest: PS received personal fees from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Chiesi Farmaceutici Spa, Laboratori Guidotti Spa, Neopharmed Gentili spa, Novartis, Menarini Industrie Farmaceutiche Riunite Srl, ABC farmaceutici and Biotest Italia srl, outside the submitted work. CM received fees as a speaker in national and international congress from GSK, Novartis, Sanofi, AstraZeneca, Chiesi, Menarini, Boehringher, Berlin Chemie, Guidotti, Chesi, Zambon. AP reports grants from

Chiesi, AstraZeneca, GSK, BI, TEVA, Sanofi, and consulting fees, honoraria for lectures or advisory boards from Chiesi, AstraZeneca, GSK, Novartis, Sanofi, IQVIA, Avillon, Elpen Pharmaceuticals, Zambon, and Mundipharma. The other authors have no conflicts of interest to declare.

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Introduction

Chronic obstructive pulmonary disease (COPD) is a condition characterized by persistent and progressive airflow limitations along with respiratory symptoms, such as dyspnea, sputum production and cough [1]. It is associated with an abnormal inflammatory response of the lungs to harmful particles or gases [1] and with various risk factors, including cigarette smoking, respiratory infections, occupational exposures, air pollution, passive smoke and diet [1]. Globally, COPD is a significant cause of morbidity and mortality, resulting in a growing economic and social burden. According to the World Health Organization (WHO) report in 2021, COPD was responsible for 3.23 million deaths in 2019, making it the third leading cause of death globally [2].

The prevalence of COPD is projected to rise due to environmental factors and an aging population [3]. In Italy, COPD is responsible for a high proportion of respiratory disease-related deaths, accounting for 55% of such mortality [4-7].

Exacerbations are critical events in the course of COPD, having substantial short- and long-term impacts on patients and health care systems [1,8]. Frequent exacerbations are linked to reduced physical activity [9], poorer quality of life, increased mortality risk [10], and cardiovascular events [11,12]. Preventing exacerbations is a key objective in COPD management [13-15].

Early identification of the disease is a topic of discussion within the respiratory scientific community. As outlined in the current GOLD document, individuals of any age who exhibit respiratory symptoms and/or structural and/or functional abnormalities, but do not yet have airflow limitation (forced expiratory volume in the 1st second ([FEV_1]/ forced vital capacity [FVC] ≥ 0.7 post-bronchodilation) and have normal spirometry, are classified as pre-COPD patients [1]. These individuals are at an increased risk of developing airflow limitation in the future [1]. Currently, there is no established correlation between the timing of disease onset, the manifestation of symptoms, and the diagnosis of COPD. This is due to the fact that symptoms can indicate significant functional damage without providing a clear indication of when the disease initially started.

Triple therapy with inhaled corticosteroid/long-acting muscarinic antagonist/long-acting β2-agonist (ICS/LAMA/LABA) is recommended for patients with significant symptoms and frequent exacerbations [1]. Based on the available evidence, triple therapy shows potential for offering clinical benefits and reducing mortality in patients with symptomatic COPD who are at risk of exacerbations even when they are already receiving LAMA/LABA therapy [1,16-23]. Recognizing the unanswered issues and lack of conclusive evidence in COPD management, an Italian expert panel conducted a consensus process, using a modified Delphi method. Their aim was to assess agreement among Italian pulmonologists regarding crucial steps in COPD management and decision-making process to guide clinical decisions in real-life conditions. The process involved a scientific board of six experts in the field and aimed to expand global discussions on early inhaled therapy approaches for eligible COPD patients.

This consensus document presents the procedures and results of the structured approach, providing insights from Italian respiratory physicians to increase

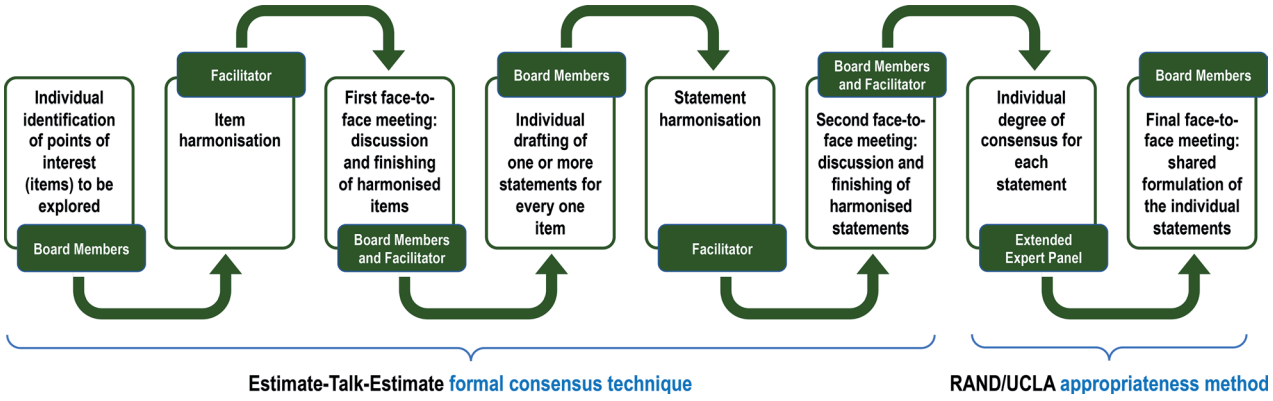

Figure 1. Workflow of the consensus process.

awareness and aid clinicians in making informed decisions, even in the early stages of the disease.

Methods

Figure 1 shows the workflow of the consensus process, which started using the Estimate-Talk-Estimate (ETE) method [24,25]. ETE (a formal means of reaching consensus that was developed to overcome some of the negative aspects of group dynamics) facilitates group decision making [26,27] by combining assembling of expert opinions on an anonymous basis during surveys with open exchange during workshops by a facilitator.

Identification of the statements

Firstly, five Italian experts in COPD management (SP, DF, MC, PG, PA, referred to as scientific board) were invited to individually identify points of interest (referred to as items) requiring further clarification or review. These were then harmonised and grouped by a senior clinical epidemiologist (GP) trained in developing group consensus (the facilitator) into 11 items that were proposed to the board members at a face-to-face meeting. The harmonised items were discussed to reach agreement between the facilitator's work and board members' opinions, after which the board members were invited to individually drew up one or more statements concerning each of agreed items. This led to the proposal of 11 statements, which were again subsequently harmonised by the facilitator. At a second face-to-face meeting, the board members and the facilitator reviewed and further discussed the harmonised statements until agreement was reached on their formulation.

Agreement rating of statements by the expert panel

The statements generated in this way were then presented via an on-line scoring platform to 104 experts chosen from specialized COPD management centers to represent the clinical practice in Italy for this field. The survey was conducted online through a secure survey website using a dedicated online platform (www.consensusdelphi-bpco.it). Experts expressed their degree of consensus by means of a RAND 9-point numerical rating scale ranging from 1 = totally disagree to 9 = totally agree, and consensus was reached that a statement had to be considered appropriate if the median score was ≥ 7 without disagreement, according to the RAND/UCLA Appropriateness Method User's Manual [28].

Collection and analysis of the results

After the completion of the individual and anonymous online survey, the scientific board thoroughly analyzed and discussed the gathered results and formulated comprehensive comments and indications regarding the optimal management of COPD patients in real-world clinical practice.

Results

Following the completion of the first Delphi round, the scientific board identified the following

broad areas of COPD management (referred to as items) that were deemed necessary to undergo evaluation within the context of Italian clinical practice (Table 1):

1. Identification and definition of the pre-COPD phase
2. Importance of patient-reported outcomes (PROs) in the management of COPD
3. Prevention of moderate to severe exacerbations
4. Reduction in the mortality rate as an efficacy outcome
5. Role of phenotypes and biomarkers in the definition of a therapeutic strategy
6. Role of the assessment of respiratory function in the management of COPD
7. Impact of comorbidities in the definition of the therapeutic strategy in COPD
8. Direct escalation from a single bronchodilator to triple therapy
9. Clinical and functional indices as drivers for first-line triple therapy
10. Possible occurrence of adverse events and their role as drivers in the prescription of triple therapy
11. Selection criteria for candidates for triple therapy

During the second Delphi round, the 11 items identified by the scientific board were translated into statements that were approved and then submitted to the experts for independent rating (Table 1).

A total of 73 out of 104 independent experts (70.2%) provided their rating on these statements expressing their agreement or disagreement. The names of the 73 experts who participated in the rating process can be found in the Appendix, listed alphabetically. The ratings provided by the experts were analyzed to determine the median rating and the percentages of experts who consented, were uncertain, or dissented for each statement, as presented in Table 1.

Consistently, the level of agreement among the experts was high, with median ratings ranging from 7 to 9 on the RAND nine-point scale. In the first round of voting, a median score of ≥ 7 was reached for all statements, indicating a consensus among the experts. As a result, no further rounds of rating were deemed necessary, and the scientific board proceeded to discuss and finalize the statements based on the obtained ratings.

Among the statements, numbers 1, 2, 8 and 10 were found to be the most controversial, as indicated by higher standards deviations ranging from 1.8 to 2.4. These statements generated more diverse opinions among the experts, reflecting greater variation in their individual ratings.

Discussion

The Italian experts involved in the field of COPD management reached a consensus on 11 statements, demonstrating their agreement as follows:

1. Identification and definition of the pre-COPD phase

Statement: All those situations characterized by the absence of $FEV_1/FVC < 0.7$ and highlighting a risk of developing COPD, such as cough and sputum persistence, increased residual volume, FEV_1 near to lowest normal limit, altered DL_{CO}, airways radiologic abnormalities, and emphysema in subjects exposed to cigarette smoke and/or other noxious inhaled agents, must be defined as pre-COPD.

The early identification of individuals who may eventually develop airflow obstruction consistent with a diagnosis of COPD can potentially allow for therapeutic interventions that can modify the course of the disease. In 2001, the GOLD (Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease) report introduced the concept of an "at risk" stage (GOLD stage 0) [29]. This stage was based on the presence of risk factors such as smoking and symptoms like chronic cough and sputum production, in the absence of spirometry abnormalities [29]. The pre-COPD population, defined by symptomatic individuals with structural or functional lung changes but without spirometric evidence of COPD, represents an at-risk group that shares many symptomatic and structural features with the established COPD population. However, they are distinct in terms of being predominantly female, older, having

Table 1. Statements approved by the scientific board and rated by the expert panel.

Item	Statement	Expert panel ranking
1. Identification and definition of the pre-COPD phase	All those situations characterized by the absence of $FEV_1/FVC < 0.7$ and highlighting a risk of developing COPD, such as cough and sputum persistence, increased residual volume, FEV_1 near to lowest normal limit, altered DLco, airways radiologic abnormalities, and emphysema; in subjects exposed to cigarette smoke and/or other noxious inhaled agents, have to be defined as pre-COPD	Median: 7 Consent: 68% Uncertain: 18% Dissent: 14%
2. Importance of patient-reported outcomes (PROs) in the management of COPD	Patient-reported outcomes (PROs) should be considered in the therapeutic management as well as the risk of exacerbation. The most commonly used questionnaires and scales are mMRC, CAT, TDI, and SGRQ	Median: 7 Consent: 70% Uncertain: 23% Dissent: 7%
3. Prevention of moderate to severe exacerbations	Available treatments (single or double bronchodilation, ICS/LABA, triple therapy and rehabilitation) are all able to reduce exacerbation risk after diagnosis	Median: 8 Consent: 87% Uncertain: 12% Dissent: 1%
4. Mortality rate reduction as efficacy outcome	Mortality is a mandatory outcome of therapy efficacy; as in other chronic diseases. Clinical trials and therapies should consider the reduction of mortality rate as a study endpoint	Median: 8 Consent: 83% Uncertain: 14% Dissent: 2%
5. Role of phenotypes and biomarkers in the definition of the therapeutical strategy	The presence of eosinophilia, identification of the emphysema as prevalent phenotype concomitant with the presence of bronchiectasis may or may not direct to the use of ICS as an add on to bronchodilator therapy	Median: 8 Consent: 86% Uncertain: 11% Dissent: 3%
6. Role of respiratory function in the management of COPD	Spirometry is required to make the diagnosis of COPD and it has also to be considered as a useful tool for disease management. Residual volume and DLco assessment can complement information provided by spirometry, and they are recommended after first COPD diagnosis. These second level respiratory functional assessments become mandatory when therapeutic goals are not reached	Median: 9 Consent: 93% Uncertain: 6% Dissent: 1%
7. Impact of comorbidities in the definition of the therapeutic strategy in COPD	The identification of comorbidities, due to their impact on symptoms, exacerbations, PROs, and mortality (particularly cardiovascular ones), is mandatory for a correct therapeutic management of COPD	Median: 8 Consent: 89% Uncertain: 10% Dissent: 1%
8. Direct escalation from single bronchodilator to triple therapy	In COPD management, direct escalation from single bronchodilator to triple therapy can be considered when therapeutic goals (exacerbations, PROs) are not reached	Median: 8 Consent: 74% Uncertain: 22% Dissent: 4%
9. Clinical and functional indices as drivers for a first-intention triple therapy	*Ab initio* triple therapy could be an option for patients recently discharged from hospital, or when dyspnea and exacerbations are both present in patients with reduced respiratory function	Median: 7 Consent: 69% Uncertain: 28% Dissent: 3%
10. Possible occurrence of adverse events and their role as drivers in the prescription of triple therapy	Controlled trials were not able to identify an increase of adverse events in patients on triple therapy compared with those on double therapy. Nevertheless, pneumonia risk and the type of therapy need to be evaluated before starting ICS therapy	Median: 7 Consent:68% Uncertain: 22% Dissent: 10%
11. Selection criteria for patients who are candidates for triple therapy	Failure to achieve therapeutic goals (presence of exacerbations in patients treated with double bronchodilators, persistence of respiratory symptoms after ICS/LABA) in patients adherent to therapy is an eligibility criterion for triple therapy	Median: 9 Consent:93% Uncertain: 6% Dissent: 11%

less smoking exposure, and fewer comorbidities. This highlights the importance of early identification and potential intervention in the pre-COPD stage to prevent progression to full-blown COPD [30].

Symptomatic individuals with "normal" spirometry results represent a heterogeneous group with various abnormalities, including cough, sputum production, dyspnea, exacerbation-like events, and radiographic features that may resemble the clinical and radiographic presentation of patients with spirometry-confirmed COPD. These individuals also experience a decreased health-related quality of life and are more likely to miss social and work activities.

The SPIROMICS study (Subpopulations and Intermediate Outcomes in COPD Study), a multicenter observational study of COPD aimed at guiding the development of future therapies for the disease [31], revealed that 42% of symptomatic smokers without spirometry-defined obstruction were prescribed bronchodilators, and 23% were prescribed inhaled corticosteroids, indicating that physicians recognized the need for treatment in these cases.

The category of GOLD stage 0 was eventually abandoned because not all individuals in this stage progressed to COPD [32]. However, reconsidering this decision, it may have been a missed opportunity. Many other therapeutic areas have embraced the concept of "predisease" (e.g., prediabetes, prehypertension, precancer, or preeclampsia) where not all patients will necessarily develop the disease, but identifying an at-risk population allows for stricter follow up and risk management.

A recent perspective by Martinez and colleagues [33] emphasized the urgency of identifying such individuals, particularly in the context of developing disease-modifying therapies. The COPD-Gene research group, in a recent publication, proposed combining symptoms, lung function, and computed tomography assessments to stage individuals with respect to their risk for developing COPD, suggesting a new disease classification scheme [34].

By going beyond the concept of GOLD stage 0, which solely identified at-risk individuals based on symptoms, we can identify a larger proportion of individuals who are likely to develop COPD. However, this statement sparked significant debate in our survey, with 68% of the panelists in agreement with it and 14% of the panelists who rated this statement with a score lower than 4, indicating their disagreement. They argued that the conditions proposed in the statement possibly qualify as overt COPD. These comments highlight the existence of a substantial grey area in the early identification of individuals who require close monitoring to initiate appropriate treatment promptly when their health condition worsens.

Slow Vital Capacity (SVC) can be different from FVC, and if FEV_1 is measured against FVC only, airway flow-limitation can be underestimated or missed. Brusasco et al. and Berton and Neder highlighted that SVC, which represents the total volume of air exhaled slowly, can often be greater than the FVC measured during a forced exhalation. This discrepancy can lead to an underestimation of airflow limitation if only the FEV_1/FVC ratio is used, thereby missing cases of mild to moderate obstruction [35,36].

Additionally, a thorough analysis of the flow-volume loop and assessment of flow limitation at lower pulmonary volumes is crucial. Pedersen and Butler emphasized that the shape and contour of the flow-volume loop can provide valuable insights into airway dynamics. Flow limitation at lower lung volumes can indicate small airway dysfunction, which may not be apparent in standard spirometric measurements. Recognizing these subtle abnormalities is essential for identifying individuals at risk for COPD who might benefit from early intervention. Integrating these comprehensive diagnostic approaches can significantly enhance the accuracy of COPD risk assessment and ensure timely and appropriate management [37].

2. *Importance of patient-reported outcomes in the management of COPD*

Statement: Patient-reported outcomes (PROs) should be considered in the therapeutic management as well as the risk of exacerbation. The most commonly used questionnaires and scales are modified Medical Research Council dyspnea scale (mMRC), COPD Assessment Test (CAT), Transition Dyspnea Index (TDI), and St George's Respiratory Questionnaire (SGRQ).

Patients with COPD experience impaired health-related quality of life (HRQoL) regardless of

disease severity [38,39]. Various key characteristics of COPD, such as chest symptoms, dyspnea, cough, sputum production, and exacerbations contribute to the negative impact on HRQoL. Other aspects like sleep disturbances, fatigue, emotional well-being, social functioning, and coping abilities can also be affected. PROs play a crucial role in assessing symptoms, their impact on daily activities, and treatment response [40,41]. In clinical trials, it is essential to incorporate PROs alongside clinical endpoints, to ensure a patient-centered approach in drug development.

In routine clinical practice, there is growing interest in this area, as evidenced by the 70% agreement with the formulation of this statement (7% disagreement). The presence of comorbidities (such as cardiovascular diseases, obesity, dumping syndrome, and obstructive sleep apnea syndrome) commonly observed in elderly patients with COPD can contribute to the subjective perception of HRQoL [42].

Some experts interviewed suggested that PRO data obtained from COPD patients without comorbidities which could potentially affect the overall assessment of HRQoL, are more reliable when collected using currently approved questionnaires. These considerations highlight the need for further research and literature focusing on the measurement of PROs in respiratory diseases. This would help address challenges associated with assessing these outcomes outside the context of clinical trials, which can be time consuming and subject to individual interpretation.

3. Prevention of moderate to severe exacerbations

Statement: Available treatments (single or double bronchodilation, ICS/LABA, triple therapy and rehabilitation) are all able to reduce exacerbation risk after diagnosis.

Preventing exacerbations is a crucial goal in the management of COPD [1] Prevention of exacerbations is based not only on bronchodilators (and antimicrobial therapy) [43] and rehabilitation but also on modification of risk factors, vaccinations and treatment of comorbid conditions [13,44,45]. The choice of medications within each class depends on achieving a favorable clinical response while considering factors such as adverse effects, availability, and cost. It is important to individualize treatment regimens because the relationship between symptom severity, airflow limitation, and exacerbation severity can vary among patients.

The expert panel achieved a significant consensus on this statement with only 1% disagreement (87% agreement). In the experts' comments, triple therapy was highlighted as a particularly effective approach in achieving the goal of preventing exacerbations. However, it is important to note that triple therapy is recommended as initial therapy in patients with ≥ 2 moderate exacerbations or ≥ 1 leading to hospitalization and eosinophilia ≥ 300 cells/µl, while in other cases it should be considered as a follow up strategy [1]. Therefore, bronchodilators as single agents or in combination therapy, along with appropriate pulmonary rehabilitation programs, should always be considered as first-line treatments.

4. Reduction in the mortality rate as an efficacy outcome

Statement: Mortality is a mandatory outcome of therapy efficacy, as in other chronic diseases. Clinical trials and therapies should consider the reduction of mortality rate as a study endpoint.

COPD should be recognized as a systemic disease that significantly contributes to both all-cause and disease-related mortality [41]. It is associated with various cardiac and non-cardiac comorbidities that contribute to the risk of mortality. For instance, heart failure affects around 20-30% of COPD patients [46,47] and significantly increases the risk of mortality [48,49]. Additionally COPD-related pulmonary hypertension (PH) is a significant respiratory comorbidity with a prevalence of 39.2% in the COPD population [50] and it is associated with reduced survival, particularly in advanced stages of COPD [51].

Furthermore, it is important to note that the frequency and severity of exacerbations in COPD have a detrimental impact on mortality [52]: hospitalizations related to acute exacerbations have been identified as predictors of mortality rates, particularly in relation to cardiovascular disease (CVD) within the subsequent 90 days, with an escalated risk of mortality corresponding to an increase in the number of exacerbation events [53]. Moreover, an elevated number and greater

severity of exacerbations are associated with an augmented risk of future exacerbations, all-cause mortality and mortality specifically related to COPD [52,54].

However, measuring mortality as a primary outcome in COPD randomized controlled trials (RCTs) has been infrequent. Several factors may account for this, including improved COPD management leading to reduced mortality rates, variation in death rates based on baseline lung function (FEV_1), placebo controlled trials showing treatment effects more prominently, differing intervention timings and follow up durations, exclusion of severe cases in studies using licensed therapies and potential withdrawal of patients in less effective treatment arms in longer studies [55].

Nevertheless, there are a few exceptions where mortality was included as a primary outcome in COPD studies, such as the TORCH (Toward a Revolution in COPD Health) [56], TIOSPIR (Tiotropium Safety and Performance in Respimat) [57], SUMMIT [58] and the NETT [59] studies, two long-term oxygen therapy trials [60,61], and, more recently, the ETHOS trial and a secondary analysis of the IMPACT trials [21,22]. Notably, the IMPACT and ETHOS trials demonstrated a reduction in all-cause mortality rates among patients receiving triple therapy [21,22]. In particular, the risk of all-cause mortality with triple therapy relative to dual therapy was 0.72 (95% confidence interval (CI), 0.53–0.99, P = 0.042), equivalent to a number needed to treat (NNT) of 121, and 0.51 (95% CI, 0.33–0.80; P = 0.0035), equivalent to a NNT of 80 in the IMPACT and ETHOS trials, respectively [21,22].

A recent meta-analysis by Chen et al. [62] showed that inhaled therapy containing ICSs, especially triple therapy, reduced all-cause mortality, likely due to the anti-inflammatory effect that limits inflammation driven injury, small airway narrowing and lung parenchyma destruction. Interestingly, budesonide was associated with a lower risk of all-cause mortality compared to other corticosteroids [53], probably due to its decreased risk of pneumonia [63-65].

Overall, studies investigating the impact of pharmacotherapy on mortality in patients with more severe COPD have shown reduced mortality rates, improved lung function and decreased risk of exacerbations [57].

In terms of triple therapy administration, a real-world retrospective observational study comparing single-inhaler triple therapy (SITT) and multiple inhaler triple therapy (MITT) demonstrated a reduction of 12-month all-cause mortality rate in patients using SITT [66].

This finding is intriguing because utilization of SITT offers the advantage of simplifying intricate inhaler regimens [67] and enhancing adherence and persistence, as opposed to MITT [68,69].

The expert panel largely agreed (83% agreement, 2% disagreement) with the importance of considering patient heterogeneity and the high prevalence of comorbid conditions in COPD when designing studies. Ideally, study designs should stratify patients based on their disease stage and the presence of specific comorbidities. Additionally, the panelists agreed that mortality is a pivotal outcome to be considered in study designs, given that COPD patients are subject to exacerbations events and are affected by comorbidities, that both pose a risk of death.

5. *Role of phenotypes and biomarkers in the definition of the therapeutic strategy*

Statement: The presence of eosinophilia, identification of the emphysema as prevalent phenotype concomitant with the presence of bronchiectasis may or may not direct to the use of ICS as an add on to bronchodilator therapy.

Literature data indicate the clinical significance of biomarkers in evaluating patients with COPD [70]. The availability of a blood-based biomarker would be highly valuable in both clinical practice and the optimization of patient selection for clinical trials, given the convenience of blood sampling. The role of blood eosinophil levels in the clinical manifestation of COPD has been a topic of intense debate.

Since the 2019 GOLD release [71], eosinophilia has been proposed and maintained in subsequent versions as a factor influencing treatment choices in COPD, particularly in support of ICS-based regimens. Two meta-analyses conducted in 2021 suggested that a cut-off value of 300 cells/μL may indicate the use of ICS-containing therapies [22,70]. Conversely, patients with a blood eosinophil count < 100 cells/μL are less likely to benefit from ICS treatment [22,70]. Furthermore, the aforementioned meta-analysis by Chen et al. identified an eosinophil count ≥ 200/μL as a predictor

for the reduction of all-cause mortality in COPD patients treated with inhaled therapy containing ICSs [62]. Bafadhel et al. conducted a *post-hoc* analysis of data form the ETHOS trial and demonstrated clear evidence of treatment benefits with ICS-containing triple therapy in terms of symptoms, disease-related QoL and lung function for patients with EOS counts greater than 100/μL [72]. These findings are consistent with results from the KRONOS study, which observed a reduction in exacerbation rate and improvement in lung function in patients with EOS counts ≥ 100/ μL and ≥ 150/ μL, respectively, when treated with triple therapy compared to dual therapy [73].

Similarly, the IMPACT study showed superiority in treatment benefits with ICS-containing triple therapy over LABA-LAMA therapy for patients with an EOS count ≥ 100/μL. The degree of benefits generally increased with higher baseline EOS counts [72,73], with an EOS count of 300/μL identified as the threshold for the greatest likelihood of treatment benefits with ICS [1]. Therefore, blood eosinophil levels serve as important predictors of triple therapy efficacy and should be assessed in patients with COPD, considering that patients with EOS counts ≥ 100/μL can also benefit from ICS-containing triple therapy, in line with the GOLD guidelines [1].

Interestingly the study by Chen et al. identified additional predictors for the reduction in all-cause mortality with inhaled therapy containing ICSs, including a history of ≥ 2 previous moderate or severe exacerbations in the previous year, GOLD stages III or IV disease, treatment duration > 6 months, age younger than 65 years and BMI ≥ 25 kg/m^2 [62]. The emphysema-predominant phenotype, regardless of the severity of FEV_1 impairment, has been identified as a predictor of poor response to ICS/LABA therapies [74]. It has been reported that one-third of patients with a predominant emphysema may also have a significant component of overlapping chronic bronchitis and bronchiectasis, which is more commonly found in the lower lobes [75]. Given the association of bronchiectasis with bacterial colonization, caution should be exercised when administering ICS in such cases [1].

The expert panel reached a substantial consensus (86% agreement, 3% disagreement) regarding the potential to determine the inclusion of an ICS in the treatment approach based on the presence of eosinophilia and the identification of emphysema as the predominant phenotype accompanied by bronchiectasis.

6. *Role of the assessment of respiratory function in the management of COPD*

Statement: Spirometry is required to make the diagnosis of COPD and it has also to be considered as a useful tool for disease management. Residual volume and DL_{CO} assessment can complement information provided by spirometry, and they are recommended after first COPD diagnosis. These second level respiratory functional assessments become mandatory when therapeutic goals are not reached.

According to the GOLD document [1], persistent airflow obstruction is the cornerstone of COPD diagnosis. To confirm the diagnosis, parameters such as FEV_1, FVC, and FEV_1/FVC ratio obtained from spirometry are important predictors at the population-level, although they may not always accurately reflect the severity of COPD outcomes [70]. In particular, FEV_1 alone does not fully capture the impairment in the small airways, lung hyperinflation, and emphysema [70]. The abnormalities in the small airways play a crucial role in the pathogenesis of COPD and can precede the development of airflow obstruction and emphysema [76,77]. The severity of COPD in terms of airflow obstruction, quality of life, and prognosis directly relates to the degree of inflammation, narrowing, and thickening of the small airways [78].

Some studies have indicated that the diffusing capacity for carbon monoxide (DL_{CO}) may be an equally good or even better prognostic marker than FEV_1 in severe acute exacerbations of COPD [79,80]. DL_{CO} also provides an assessment of emphysema levels and reflects the patient's performance status [81,82]. These findings suggest that DL_{CO} could serve as a reliable predictor of early pulmonary dysfunction and prognosis. Classification based on DL_{CO} can be valuable in determining the treatment strategy for patients with severe COPD.

The expert panel reached a very high rate of agreement (93% agreement, 1% disagreement) on the role of spirometry for the initial diagnosis and the assessment

of residual volume and DL_{CO} to supplement the information, particularly when the therapeutic goals are not achieved.

7. *Impact of comorbidities in the definition of the therapeutic strategy in COPD*

Statements: The identification of comorbidities, due to their impact on symptoms, exacerbations, PROs, and mortality (particularly cardiovascular ones), is mandatory for a correct therapeutic management of COPD.

Comorbidity is common among patients with COPD and early identification of comorbidities is crucial for implementing comprehensive management strategies that improve outcomes and reduce the burden of the disease [83]. The presence of COPD along with other diseases increases the likelihood of hospital admissions [84,85], healthcare costs [86], and reduces quality of life and exercise tolerance [87]. Furthermore, comorbidity is associated with increased mortality [88]. Compared to the general population patients with COPD have a higher prevalence of comorbidities, with cardiovascular diseases, osteoporosis, hypertension, and gastroesophageal disease being among the most prevalent [46,89-97].

Cardiovascular diseases are particularly important comorbidities in predicting all-cause mortality in patients with COPD. Old age, smoking history, and increased systemic inflammation are common risk factors shared between COPD and cardiovascular diseases [98]. However, some studies have shown that patients with COPD have an increased susceptibility to cardiovascular diseases independent of these risk factors [99-101].

Processes associated with COPD, such as lung hyperinflation, hypoxemia and systemic inflammation contribute to the increased risk of CVD [102]. In particular the coexistence of heart failure and COPD further increases the risk for hospitalization and mortality in patients [103-105].

It is worth noting that concomitant chronic diseases are often misdiagnosed or undiagnosed, and therefore untreated, in patients with COPD.

This is especially true for individuals with preserved ratio impaired spirometry (PRISm) findings where the FEV_1 to FVC ratio is normal, but FEV_1 is reduced. Despite having an increased risk of hospitalization [106,107] and mortality [108], individuals with PRISm findings are often overlooked as a category. A recent study revealed that patients with COPD GOLD stage ≥ 2 and PRISm findings were twice as likely to develop CVD, compared to patients with normal spirometry values, independent of common risk factors and even in the absence of a documented history of previous CVD [109].

The expert panel largely agreed (89% agreement, 1% disagreement) on the importance of identifying comorbidities in COPD patients for an appropriate management of the disease.

8. *Direct escalation from single bronchodilator to triple therapy*

Statement: In COPD management, direct escalation from single bronchodilator to triple therapy can be considered when therapeutic goals (exacerbations, PROs) are not reached.

The clinical spectrum of COPD is diverse, and appropriate adjustments in therapy are necessary as the disease progresses. Since 2020, the GOLD recommendations have suggested treatment escalation or de-escalation based on the worsening or improvement of symptoms and the persistence of exacerbations. Specifically, the GOLD 2023 document recommends to take into account the possibility of escalating treatment to triple therapy in cases where patients experience exacerbations and dyspnea while on monotherapy with a long-acting bronchodilator and have an eosinophil blood count of ≥ 300 cells/μl [1,16]. Notably, de-escalations should be done under close medical supervision [1,71].

The panel agreed (74% agreement, 4% disagreement) with the step-by-step approach proposed in the GOLD recommendations for COPD management but acknowledges the existing gap in everyday clinical practice.

This is particularly evident in cases where the diagnosis is made late, with noticeable signs of functional decline and radiographic damage, as well as in individuals who experience rapid disease progression. In such cases, a more aggressive therapeutic approach may be beneficial for better symptom and exacerbation

management as well as for reducing mortality rates. As mentioned previously, the panelists once again emphasize the importance of conducting a thorough patient profile assessment to determine the predominant phenotype and the most appropriate therapy.

9. Clinical and functional indices as drivers for a first-intention triple therapy

Statement: Ab initio triple therapy could be an option for patients recently discharged from hospital, or when dyspnea and exacerbations are both present in patients with reduced respiratory function.

The role of triple therapy in COPD has been discussed in various reviews and editorials [19,110-114]. However, only a few of them address the issues associated with its use outside of strict indications or when triple therapy should not be considered even if recommended. The KRONOS study demonstrated the efficacy and tolerability of triple therapy, suggesting that it may be a more suitable treatment option than corresponding dual therapies for symptomatic patients with moderate to very severe COPD, regardless of their exacerbation history [73]. Two recent papers [115,116] based on data from COPD patients in the United States and Spain analyzed the clinical characteristics and factors associated with the initiation of triple therapy in newly diagnosed patients. Variables such as lower FEV_1, higher exacerbation frequency, male sex, increased age, smoking, concomitant asthma, previous ICS-containing regimen associated with initiation of triple therapy, previous pneumonia, and history of lung cancer, were found to be associated with the initiation of triple therapy. Vanfleteren et al. [117] suggested that triple therapy should be considered as the first choice rather than a step-up approach in at least two situations:

- in patients discharged from the hospital after an acute COPD exacerbation where the diagnosis of COPD was made as a consequence of that severe exacerbation. These patients often receive inhaled bronchodilators (mostly continuous short-acting β_2-agonists and short-acting muscarinic antagonists as nebulized therapy), systemic steroids, and antibiotics during their hospitalization and are at a high risk of re-hospitalization, particularly during the first month [52,118].
- in newly diagnosed patients with severe airway obstruction (FEV_1 <50%), who are symptomatic, have a history of frequent moderate (≥ 2) or severe exacerbations (resulting in ≥1 hospitalization) in the previous year, and exhibit peripheral eosinophilia (> 300 cells/μL). These patients are at a high risk of recurrent exacerbations and/or hospitalization [52,76,77,118-120].

A recently published retrospective study [121] has shown that the prompt initiation of single-inhaler fluticasone furoate/umeclidinium/vilanterol after a moderate to severe COPD exacerbation is associated with significant reductions in exacerbations and healthcare costs compared to delayed initiation.

Approximately two-thirds of the panellists (69% agreement, 3% disagreement) agreed to consider initial triple therapy among the options for patients recently discharged from hospital, or with concomitant dyspnea, exacerbations and reduced respiratory function.

10. Possible occurrence of adverse events and their role as drivers in the prescription of triple therapy

Statement: Controlled trials were not able to identify an increase of adverse events in patients on triple therapy compared with those on double therapy. Nevertheless, pneumonia risk and the type of therapy need to be evaluated before starting ICS therapy.

A recent systematic review and meta-analysis of randomized controlled trials [122] examined the safety outcomes of one-year of triple therapy, which includes LABAs, LAMAs, and ICSs, compared to dual therapies in patients with COPD. The findings indicated that there was no significant difference in the risk of adverse events, serious adverse events, cardiovascular events, and respiratory tract infections between the ICS/LABA/LAMA group and the dual-therapy groups [122]. However, the analysis revealed that the risk of pneumonia was higher in the ICS/LABA/LAMA group than in the LABA/LAMA group (risk ratio, 1.43; 95% confidence interval, 1.21–1.68; $P < 0.001$) [122]. As a result, the balance between the

potential benefits of reducing exacerbations and the increased risk of infective events should be carefully evaluated at an individual level in order to achieve the best personalized outcomes.

Approximately 10% of the panellists (68% agreement, 10% disagreement) showed disagreement with the need to carefully evaluate pneumonia risk and the choice of therapy before starting inhaled corticosteroids.

11. Selection criteria for candidates for triple therapy

Statement: Failure to achieve therapeutic goals (presence of exacerbations in patients treated with double bronchodilators, persistence of respiratory symptoms after ICS/LABA) in patients adherent to therapy is an eligibility criterion for triple therapy.

This statement further expands on point 9 by highlighting the recommended step-up approach from double to triple therapy in cases where exacerbations and symptoms persist during follow up, after ensuring therapy compliance and the continuation of healthy habits such as smoking cessation and an active lifestyle. It is important to note that this recommendation is applicable in the absence of comorbidities, particularly cardiovascular conditions, and is supported by the literature and international guidelines [1].

The expert panel largely agreed (93% agreement, 11% disagreement) on the appropriateness of escalating treatment to ICS-containing triple therapy when therapeutic goals are not achieved in patients adherent to dual therapy (i.e. presence of exacerbations in patients treated with double bronchodilators, persistence of respiratory symptoms after ICS/LABA).

Conclusions

The analysis of the current management of COPD patients in Italy has identified 11 items and corresponding statements. However, the evaluation of these statements by 73 physician experts in COPD management did not exceed 90% agreement, indicating the need for further work. The following areas were highlighted for future improvement:

- Increasing awareness in the Italian scientific community about the mortality risk associated with COPD, aiming for a consensus that surpasses 90% agreement;
- Emphasizing the importance of early diagnosis to prevent disease progression;
- Recognizing that early therapeutic intervention can lead to a better disease control and prevent exacerbations that may contribute to mortality over time;
- Strengthening the evidence base, particularly regarding the selection of biomarkers, pulmonary function indices, and characterization of phenotypes, to guide decision-making in selecting appropriate therapeutic approaches;
- Identify tools such as PROs and questionnaires that can be useful in managing COPD patients.

Moreover, there was unanimous agreement among the survey participants on the importance of implementing strategies that enhance patient profiling and enable tailored management approaches for individuals with COPD.

Abbreviations

CAT: COPD Assessment Test
COPD: chronic obstructive pulmonary disease
DLco: diffusion capacity in the lungs for carbon monoxide
FEV_1: forced expiratory volume in the 1st second
FVC: forced vital capacity
ICS: inhaled corticosteroids
LABA: long-acting β_2-receptor agonists
mMRC: modified Medical Research Council dyspnea scale
PRO: patient-reported outcome
SGRQ: St George's Respiratory Questionnaire
TDI: Transition Dyspnea Index.

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APPENDIX

Expert Panel

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Original research article

Clinical utility of bedside Contrast-Enhanced Ultrasound (CEUS) in the diagnosis of pneumonia in elderly patients: Comparison with clinical, radiological and ultrasound diagnosis

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ABSTRACT

Aims: to measure the clinical impact of contrast-enhanced ultrasound (CEUS) in the diagnosis of community-acquired pneumonia (CAP), compared to clinical, radiological and ultrasound diagnosis.

Methods: 84 patients (47/37 males/females, mean age:78,57±11,7 Y) with clinical suspicion of pneumonia and with ultrasound findings of peripheral lung lesions, were investigated with CEUS for a better characterization. Final diagnosis of 65 cap was obtained with complete disappearance of symptoms and pulmonary nodule(s); 19 neoplasms: 16 patients performed histologically with bronchoscopy; 3 refused (non-invasive diagnosis with basal CT-scan and positron emission tomography (PET) with fluorodeoxyglucose (FDG)). Sensitivity, specificity, overall diagnostic accuracy (ODA) (and corresponding AUROC) of clinical-data (CD), chest X-ray(CXR), Lung-ultrasound(LUS), CEUS were calculated with SPSS 26.0 software.

Results: Final diagnosis: 65 CAP, and 19 chest cancers. 9/65 (13%) patients died, of these 7/9 with older age and heart disease as comorbidity. CD: True-Positive (TP):23, True-negative (TN): 17; False-Positive (FP):2; False-negative (FN):42 (sens:35,4% spec:89,5% ODA10%: PPV:92%, NPV:28,8%) (AUROC±SEauc:0,46±0,076); CXR: TP: 36, TN:14; FP:5, FN:29; (sens: 55,4%; spec: 73,7%; ODA: 32%; PPV:87,5%, NPV:32,66%) (AUROC±SEauc:0,645±0,068). US: TP:59; TN: 14; FP:5, FN:6 (sens: 90,8%, spec: 73,7%, ODA: 84,9%, PPV:92,2%, NPV:70%) (AUROC±SEauc:0,9417±0,024); CEUS: TP: 63; TN: 19; FP:0; FN:2 (sens: 96,9%; spec: 100% ODA: 97,5%; PPV: 100%, NPV:90,5%) (AUROC±SEauc:0,98±0,01).

Conclusions: Clinical-data and chest X-RAYS are insufficient to obtain a correct diagnosis of CAP in elderly population; US demonstrated a good accuracy to establish CAP, but with a relatively low specificity; in these cases, CEUS is able to give a correct characterization, allowing you to save the need for a chest contrast-enhanced-CT (CECT).

Key words: Contrast-Enhanced Ultrasound, Pneumonia, Lung ultrasound, Chest X-ray, diagnostic accuracy, elderly people, bedside contrast-enhanced ultrasound

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Introduction

Community-acquired pneumonia (CAP) refers to the infectious inflammation of lung parenchyma (including alveolar wall, ie, pulmonary interstitium in general meaning) acquired outside of hospitals, including pneumonia caused by pathogens with proven latency, the onset of disease is during the latency after the patient is admitted into hospital [1]

CAP is a major cause of morbidity and mortality both in the USA and globally: CAP had an incidence of 24.8 episodes per 10,000 adults, with the highest incidence in those aged 65 to 79 years (63 cases per 10,000 adults) and 80 years and older (164.3 cases per 10,000 adults) [2]. As the burden of CAP continues to increase due to several factors, the advances in its diagnosis, prevention, and treatment have taken on even greater interest and importance [3].

The clinical symptoms and signs of CAP include cough (with or without sputum production), fever, chills, tachypnoea, tachycardia, pleuritic chest pain, dyspnoea, altered mental status, dehydration, and hemoptysis; clinical findings will include a temperature greater than 37.8°C, heart rate over 100/min, respiratory rate greater than 25/min, oxygen saturations in room air < 90%, rhonchi or focal rales on auscultation of the lungs, decreased breath sounds, and bronchophony [4].

Patient history, physical examination and laboratory tests (Clinical Diagnosis -CD-) are important when diagnosing CAP [5]. However, because clinical manifestations can be nonspecific, a definitive diagnosis of pneumonia requires the presence of new infiltrates on chest x-ray (CXR), together with respiratory symptoms consistent with a lower respiratory infection.

Although it may seem self-evident, an essential question in the management of patients with CAP is whether the diagnosis is in fact correct. CAP can present in variable ways, some of which are similar to other conditions such as acute bronchitis, viral respiratory tract infections and cardiac failure. Older Patients with several comorbidities (Chronic Heart failure, dementia, COPD etc.) who are more likely to develop CAP, may not be able to give a reliable description of symptoms. Patients may present with two or more conditions at once, confusing the diagnostic process [6]. This may occur as a coincidence or alternatively be due to a cause–effect relationship between them. Examples of the latter include that a chest infection can precipitate either an exacerbation of cardiac failure or an acute coronary syndrome [7]. Actually CXR is universally considered "the gold standard" imaging for diagnosis of CAP [5]. Over recent years, studies have reported that there is misdiagnosis of pneumonia because of difficulty interpreting CXR in patients with multiple comorbidities, especially cardiac and pulmonary comorbidities. Misdiagnosis may lead to delayed antimicrobial treatment or overuse of antibiotics [5]. A multicenter study demonstrated that only 43.5% of patients with opacities on CECT had opacities noted on CXR. The sensitivity, specificity, and positive predictive values for chest radiograph were 43.5%, 93.0%, and 26.9%, respectively, indicating that CXR had poor sensitivity and positive predictive values for detecting pulmonary opacities [8]. The role of lung ultrasound (LUS) in the diagnosis of pneumonia is becoming more and more important; two different metanalyses demonstrated high values of sensitivity for detection of pneumonia but a relatively low specificity (from 72 to 86%) [9, 10]. Recently, In a multicenter study, LUS was demonstrated a powerful tool to improve CAP diagnosis in the ED, reducing diagnostic uncertainty from 73% to 14% [11]. In Italian study [12], LUS performed at hospital admission was proven to be useful for ruling in the diagnosis and bacterial etiology of CAP and for ruling out mortality in patients with CAP

Newly, contrast-enhanced US (CEUS) was used (and debated) for diagnosis of pulmonary nodules [13] and also for pneumonia [14, 15]. Actual WFSUMB guidelines [13] refer use of CEUS in patients with a history of pneumonia only if the course is complicated or if CEUS might help to differentiate between potential differential diagnoses.

We prospectively investigated the role of clinics, CXR, ultrasound and CEUS in the diagnosis of CAP in the elderly population(>60 Y [16]) in which clinical presentation of CAP pneumonia is variable and often not typical (in comparison younger people affected by CAP pneumonia) [17] and spiral CT is difficult to perform. Secondary aim was the clinical impact of ceus in characterizing peripheral nodules highlighted by lung ultrasound.

Table 1. Subdivision of pneumonia based on dimensions (row), sex and number (columns)

	Pneumonia							
	Males			Males	Females		Females	Total
Dimensions (Mm)	**1**	**2**	**Multiple**		**1**	**2**		
10-20	4	1		5	2		2	7
20-30	2			2	2		2	4
30-40	10	3	2	15	10	1	11	26
40-50	5	2		7	6		6	13
50-60	2			2	3		3	5
60-100	6			6	4		4	10
Total	**29**	**6**	**2**	**37**	**27**	**1**	**28**	**65**

Materials and Methods

84 patients (47/37 males/females, mean age:78,57±11,7 Y) with clinical suspicion of pneumonia and with ultrasound findings of peripheral lung lesions (but unable to perform chest CECT because of chronic renal failure), were investigated with CEUS for a better characterization. Final diagnosis in 19 patients was lung cancers: 16 patients performed bronchoscopy; 3 refused (non-invasive diagnosis with basal CT-scan, and positron emission tomography (PET) with fluorodeoxyglucose (FDG) [18]); in 65 patients CAP was obtained. 56 consolidations were single, 7 doubles and 2 multiples. Subdivision based on their size is expressed in Table 1.

CD was based on: New onset of cough or expectoration, or aggravation of existing symptoms of respiratory tract diseases, with or without purulent sputum, chest pain, dyspnea, or hemoptysis, Fever, Signs of pulmonary consolidation and/or moist rales; Peripheral white blood cell count (WBC)>10^*10^9/L or <4 3 10^9/L, with or without a left shift [19, 20]; CXR was executed in two projections in the emergency department; ultrasound was performed bed-side when patient entered the Internal Medicine Department; bedside LUS was performed by a single skilled operator (with approximately 30 years of ultrasound experience) during the clinic visit, using a handheld system (CERBERO version 4.0, ATL Milan, Italy). This system is composed by a portable ultrasound probe, comprising a miniconvex probe (abdominal and cardiological), and a linear probe. It uses two types of WiFi and USB wired connection, it works with a mobile app compatible with most iOS, Android and Windows devices; Image transmission is via internal 5G Wi-Fi and no external networks are required. We used the method described by Soldati et al [21] to perform the LUS, with division of the lung in 13 areas subjected to ultrasound exploration. At LUS Pneumonia appears as a hypoechogenic area with poorly defined borders and with the presence of B-lines at the far-field margin. The pleural line is less echogenic in the area affected by lung consolidation and lung sliding is reduced or absent (Figure 1).

Pneumonia can be represented as a consolidation: we can observe small (Figure 2a), big (Figure 2b) or "hepatized" consolidation (Figure 2c) (when the consolidation appears to have the consistency of hepatic parenchyma). In the case of consolidations, branching echogenic structures – representing air bronchograms – are seen in the infected area (Figure 2c). Air bronchograms may show intrinsic dynamic centrifugal movements due to breathing. This finding is called dynamic air bronchogram: it attests bronchial patency and rules out obstructive atelectasis. Multiple lenticular echoes, representing air trapped in the smaller airways, are also frequently observed. Fluid bronchograms (Figure 2d), described in post obstructive pneumonia, are identified as anechoic tubular structures with hyperechoic walls but without color Doppler signals. Fluid bronchograms are frequently observed in pneumonia in children.

Pleural effusion is easily detected on LUS and appears as an anechoic area in the pleural space (Figure 2d,e). A honeycomb organization of fibrin is observed in pleural empyema [23] (Figure 2f).

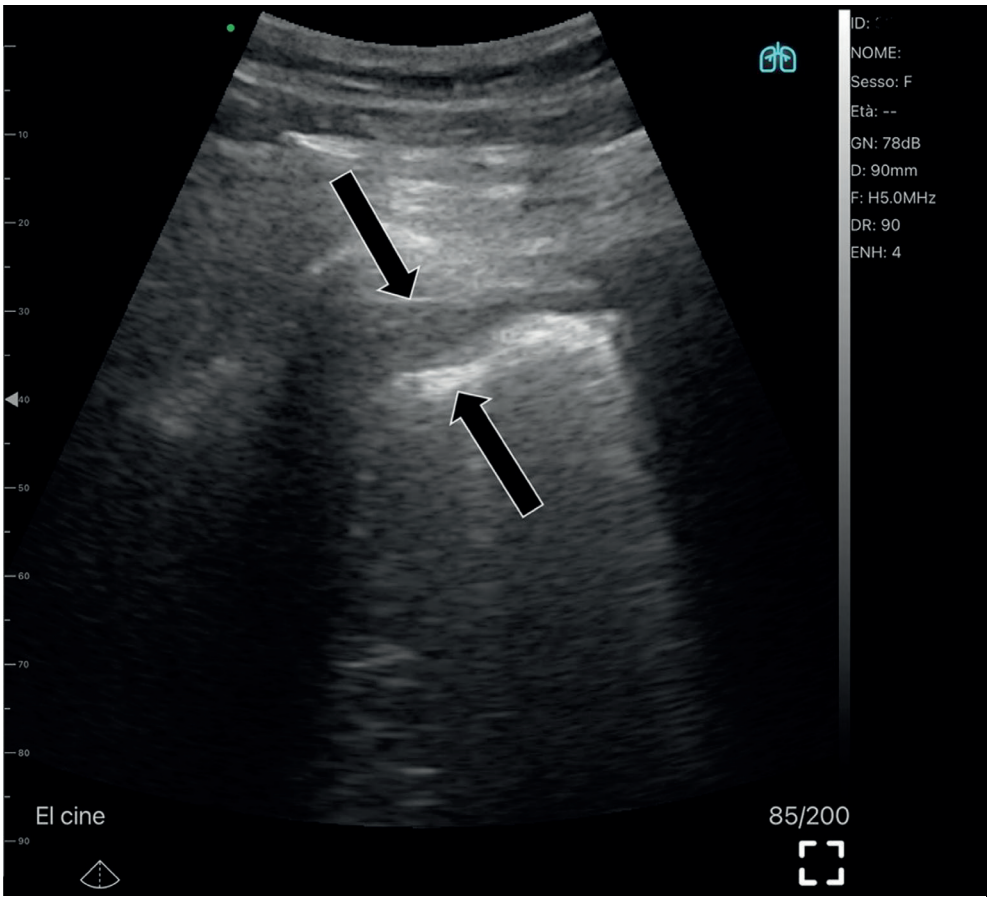

Figure 1. Interstitial Pneumonia: hypoechogenic area with poorly defined borders (arrows) and with the presence of B-lines at the far-field margin; in details, this margin, separating the tissue-like lung consolidation from the normal lung, is fragmented and fuzzy (shred sign) [22].

Pneumonia is characterized by a marked treelike vascularity on color-doppler system (CDS) (Figure 3).

Vessels seen in pneumonia correspond to branches of the pulmonary artery, where, as a result of the hypoxic situation, a different extent of vasoconstriction occurs (Figure 3a and 3b). On CDS, an enhanced Resistive Index (RI) indicates the degree of pulmonary vasoconstriction. Therefore, high RI values in CDS of the pulmonary artery are seen in complete pneumonic lung consolidation (Figure 3c). In contrast, bronchial arteries react to hypoxemia with vasodilatation, similar to the response of systemic arteries. Typically, an arterial monophasic flow profile with low RI values, indicative of bronchial arteries, could also be seen in pneumonia [24]. Sometimes, LUS is not able to distinguish pneumonia from cancer (Figure 4)

CEUS was performed bed-side with portable system, a commercially available ultrasound machine, equipped with Plane wave technology, was used for this study (MINDRAY MX7, Shenzhen Mindray Bio-Medical Electronics Co., China), that works with a new ultrasound technology called zone sonography [25, 26] and based on Plane-Wave Imaging (PWI) [27] with Pixel compounding [28]. Conventional (baseline and contrast-enhanced) ultrasonography is based technically on Delay and Sum (DAS) technique [29]; the DAS technique uses several transmissions of US signals focused in one or more regions to scan the entire area to be analyzed and to form the scan lines that will be used to reconstruct the final image. This process is time-consuming and limits the frame rate to approximately 30 to 40 frames per second. Zone sonography yields

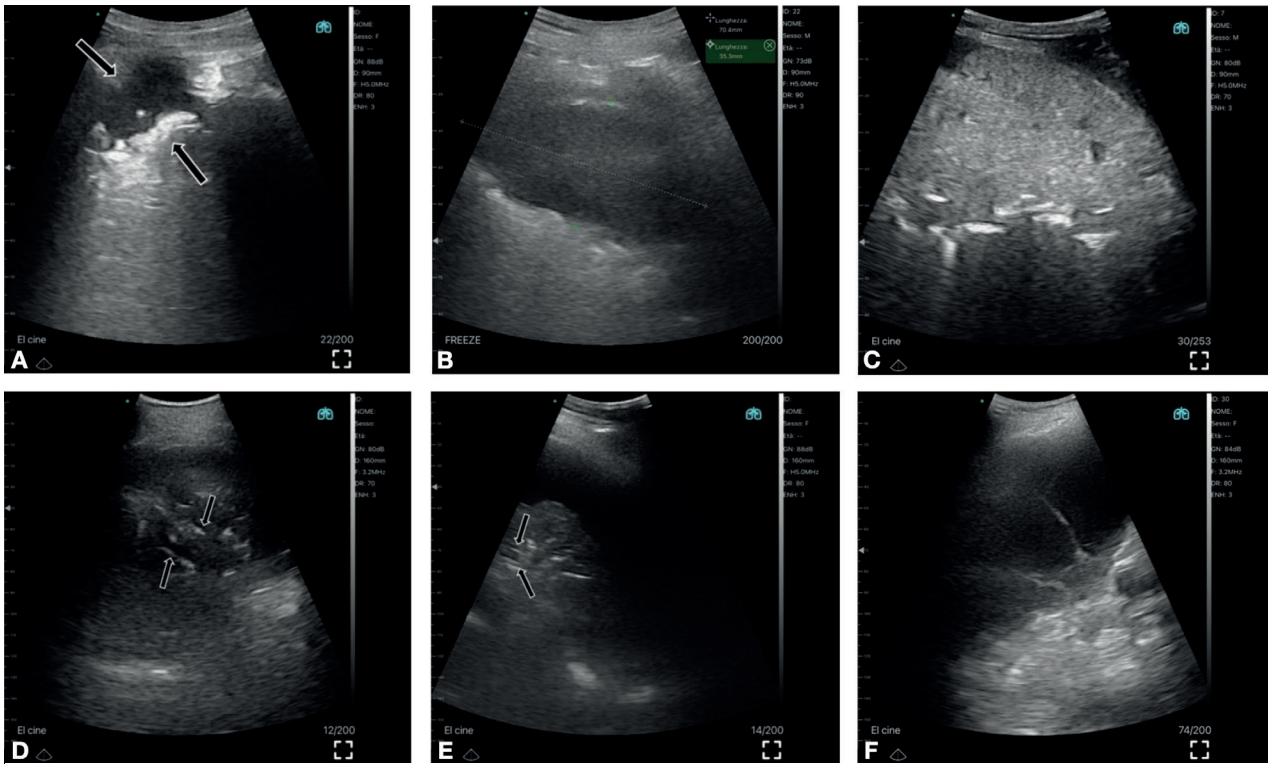

Figure 2. B-MODE typical aspects of Pneumonia at LUS: small (arrows) (a) and big size Consolidation (b); "hepatized" pneumonia (c); Air bronchogram (arrows) (d); liquid bronchogram (e); small, intermediate and big amount of pleural effusion (d, e, f); honeycomb organization, typical of pleural empyema (f)

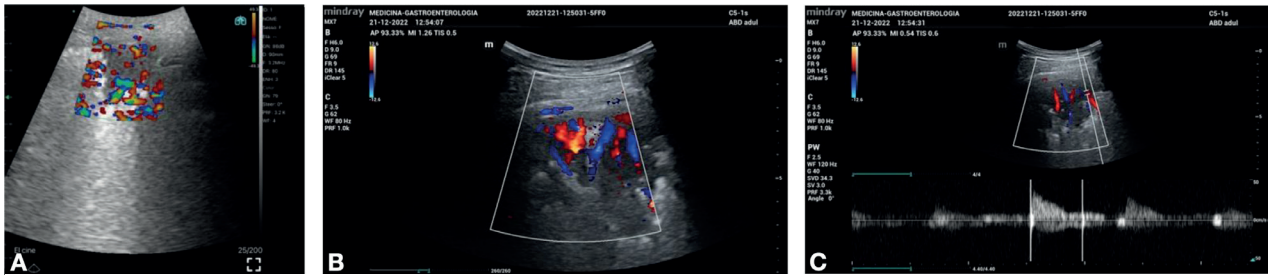

Figure 3. Color- and pulsed-doppler typical aspects of Pneumonia at LUS: small (a) and big size vascularized consolidation (b); High resistive Index (RI) at pulsed doppler examination of arteries inside pneumonia consolidation (c)

framerates as high as several thousands of images per second with a low frame rate (around 10 FPS). The system works with the simultaneous excitation of all available elements in a certain transducer to transmit and collect ultrasonic signals; At first this increase in framerate was obtained at the expense of reduced contrast and resolution. However, this drawback was skillfully addressed by Coherent Plane-Wave Compounding (CPWC) for very high frame rate ultrasonography, which introduced a trade-off between framerate and image quality; coherent plane-wave compounding has many advantages because it provides an image of a full region of interest for each ultrasonic transmission using all array elements [30]. 0.8-1.2 ml of contrast media (SonoVue, Bracco, Italy) was used. CEUS diagnosis of acute pneumonia is determined by early pulmonary arterial (PA) enhancement; marked homogeneous enhancement in all phases without parenchymal washout [13] (Figure 5).

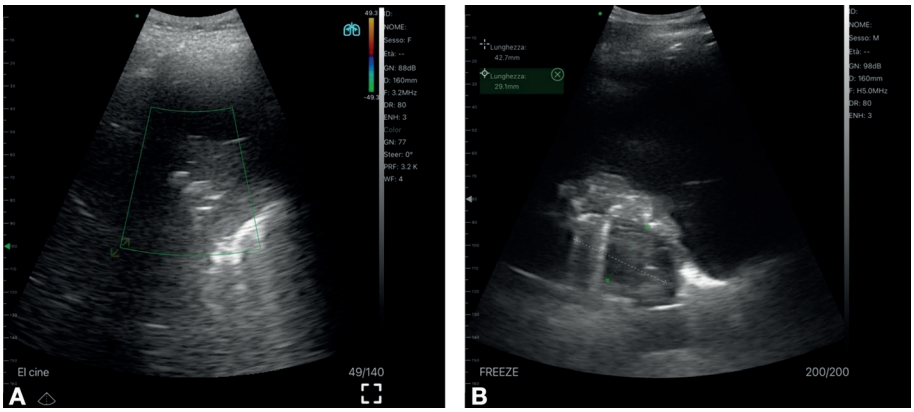

Figure 4. Hypoechoic consolidation in elderly with cough, but no fever; no vascularization at colordoppler examination: final diagnosis was pneumonia (a): hypoechoic consolidation in elderly with cough, but no fever; no vascularization at colordoppler examination: final diagnosis was lung cancer (b).

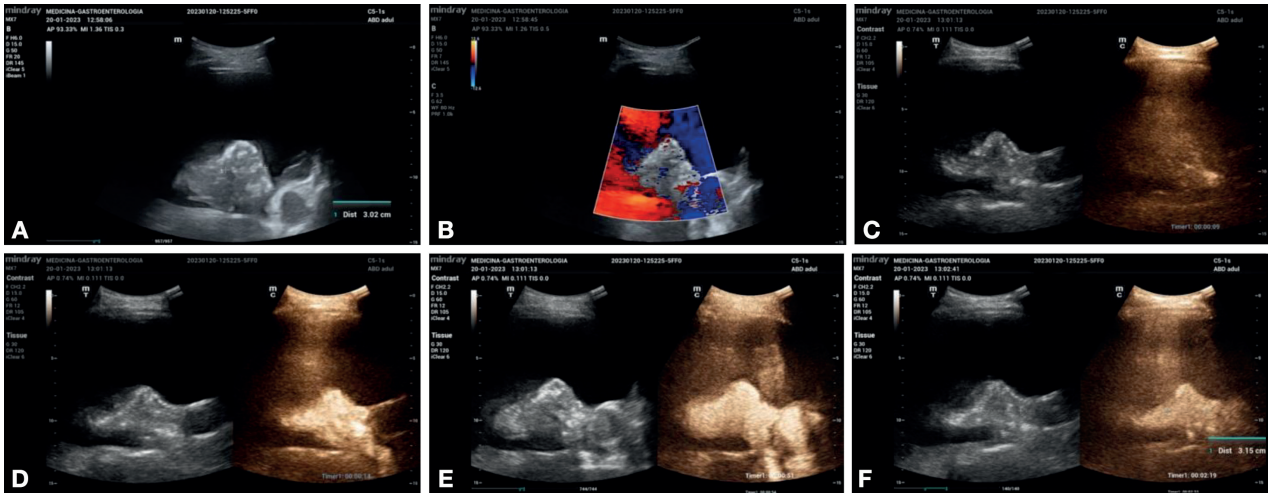

Figure 5. 86 y old male with dyspnea and cough (with history of ischemic heart disease and smoking) CXR negative for pneumonia, but with pleural effusion. LUS demonstrated a small inhomogeneous nodule (a), negative at color-doppler examination (b); CEUS examination demonstrated an early arterial vascularization (c) and subsequent hyper-enhancement (d), with persistent vascularization in portal (e) and late phase (f).

Statistics

we evaluated true positive diagnoses (positive corresponding US- and final- diagnosis), true negative ones (negative corresponding US- and final- diagnosis), False positive ones (positive false US-diagnosis and final negative ones) and false negative ones (negative false US-diagnosis and final positive ones), evaluating sensitivity, specificity, overall diagnostic accuracy (ODA), Positive Predictive Value (PPV), Negative Predictive Value (NPV) [31]. The confidence interval is calculated using the continuity-corrected score method described by Newcombe [32]. Finally, corresponding area under the curve of Receiver Operating Characteristic (AU-ROC) was calculated [33]. Correlations were calculated with X_2, with a significant value when $p<0.005$.

Results

The CD of CAP started as dyspnea and cough in 22/65 (33,8%) patients, fever in 20/65 (30,7%), fever, cough and dyspnea in 14/65 (21,5%), fever and syncope in 7/65 (10,7%), fever, cough and stinging thoracic pain only in 2/65 (3%). Clinical examination had signs of pulmonary consolidation in only 23 patients, while no significant signs were in 42. Laboratory tests had inflammation signs only in 35 pts. 9/65 (13%) patients died, of these 7/9 with older age (86,42±1,61 Y vs 78,46; p<0,001) and heart disease as comorbidity.

CXR had 29/65 (44,6%) false negative diagnoses: percentage of radiological diagnoses depended on the size of the pneumonia and varied from 28.6% to 70% (Table 2). The average radiological diagnosis of CAP in elderly patients in our series was 53.4%

In particular, the average diameter of radiolucent pneumonias was smaller than that of radiopaque pneumonias: 36 mm versus 44 mm (p<0.001). Pneumonia site distribution was greater at the base (49 pts) and at the apex (1 pt) in older people (average: 81.83 years) compared to younger people (average: 69 years), where the main site was the middle field (15 pts) (p<0.001).

US: consolidation in LUS diagnosis of pneumonia was in 56/65 (86.1%). The air/fluid bronchogram was overall present in 30/65 (46.15%) of cases; it increased progressively with increasing size (p<0.05). Arterial vascularization was present only in 29/65 (44.6%) of cases and increased with increasing size (from 25% to 90%) (p<0.001). 28/65 (43%) pneumonia hadn't bronchogram neither vascularization (Table 3).

In 20/29 (70%) radiolucent pneumonias, a bronchogram was absent on LUS. This data was significantly correlated (p<0.005). Pleural effusion was present in 46/65 (70.7%) cases (mean age: 80.93+/- 10.33 years) and was absent in 19 cases (mean age: 74.32+/- 12.71 years). The presence of effusion was directly correlated with older age (p<0.05).

CEUS: The diagnosis of pneumonia included early arterial vascularization (< 6 sec), present in 44/65 patients (67.9%), while in 21 the arterial vascularization was >10 sec because either they had heart disease (14/65, i.e. 21 .5%), or bed rest or cancer (3/65, i.e. 4.6% for each), or COPD (1/65, i.e. 1.5%) In 63 cases the late CEUS vascularization presented contrast's persistence, in 2 cases (final diagnosis: organized pneumonia [34]) there was a wash out, mistakenly diagnosed as a malignant lesion [13] (Figure 6).

Finally, we evaluated the ability of CD, CXR, LUS and CEUS in the characterization of lung consolidations. We therefore evaluated 19 neoplastic lung consolidations as negative: CD diagnosed only 23/65 (35,4%), CXR diagnosed 36/65 patients (55.4%), LUS 59/65 (90,8%) patients; Overall, CEUS allowed diagnosis in 63/65 patients (96.9%) (Table 4).

CEUS arterial vasculature was predominantly homogeneous up to pneumonias of 5-6 cm, then becomes predominantly inhomogeneous (p<0.001). A vascularization on color Doppler was not correlated with death, while a non-homogeneous arterial vascularization on CEUS was predictive of death (p<0.05); Indeed, only 8% of the vasculatures were homogeneous vs 31% of the non-homogeneous ones in died

Table 2. Number of negative and positive pneumonia at chest X-Ray in comparison with consolidation dimensions: bigger was the consolidation and bigger the percentage of X-ray positivity.

	Chest X-ray diagnosis of pneumonia			
Dimensions (mm)	**Negative**	**Positive**	**Total**	**% radiological diagnosis of pneumonia**
10-20	5	2	7	28,57%
20-30	2	2	4	50,00%
30-40	12	14	26	53,85%
40-50	5	8	13	61,54%
50-60	2	3	5	60,00%
60-100	3	7	10	70,00%
Total	**29**	**36**	**65**	55,38%

Table 3. Diameter of pneumonia consolidations in comparison with bronchogram and vascularization at LUS.

Bronchogram, vascularization and us diagnosis of pneumonia										
Dimensions (mm)	**Both Not**	**(%)**	**Bronchogram (Yes)**	**(%)**	**Vascularization (Yes)**	**(%)**	**Both Yes**	**(%)**	**Total**	**Total (%)**
10-20	**4**	6,15%	**1**	1,54%	**2**	3,08%	**0**	0,00%	**7**	**10,77%**
20-30	**2**	3,08%	**0**	0,00%	**1**	1,54%	**1**	1,54%	**4**	**6,15%**
30-40	**16**	24,62%	**2**	3,08%	**3**	4,62%	**5**	7,69%	**26**	**40,00%**
40-50	**5**	7,69%	**2**	3,08%	**0**	0,00%	**6**	9,23%	**13**	**20,00%**
50-60	**1**	1,54%	**0**	0,00%	**0**	0,00%	**4**	6,15%	**5**	**7,69%**
60-100	**0**	0,00%	**3**	4,62%	**1**	1,54%	**6**	9,23%	**10**	**15,38%**
Total	**28**	43,08%	**8**	12,31%	**7**	10,77%	**22**	33,85%	**65**	**100,00%**

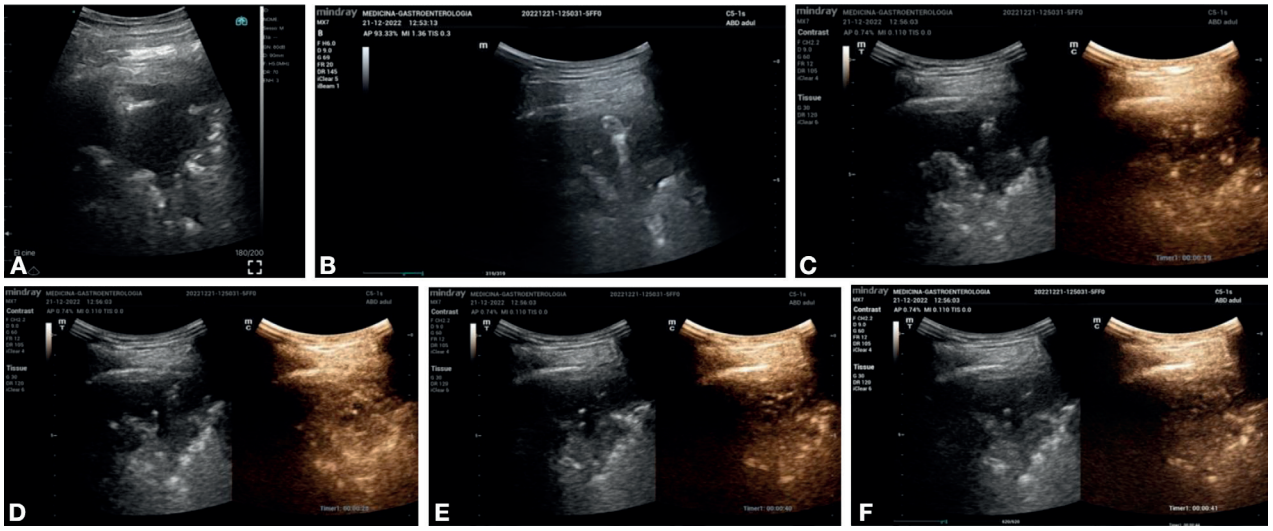

Figure 6. 82 y old male with dyspnea and fever (with history of ischemic heart disease and smoking) CXR negative for pneumonia. Hand-held LUS demonstrated a small inhomogeneous nodule (a), negative at color-doppler examination, for which CEUS was performed at the patient's bedside; conventional ultrasound confirms the lesion (b). CEUS: arterial phase demonstrates initial enhancement after 19 seconds (c), with inhomogeneous vascularization after 28 seconds (d) and weak wash-out in portal (e) and late phase (f). CEUS diagnosis of malignant lesion; after 7 days of intravenous antibiotic therapy the lesion disappeared.

patients. This data can be indirectly explained by the fact that the vascularization is imbalanced especially in larger lesions.

Discussion

The gold standard for diagnosing community-acquired pneumonia should be the identification of a microbiological pathogen isolated directly from the lung tissue. However, such a test (for example, lung puncture or biopsy) is rarely undertaken for the routine diagnosis of community-acquired pneumonia [35]. An alternative gold standard could be based on a combination of clinical symptoms; radiographic, laboratory, and microbiological findings [1]; clinical symptoms were considered inappropriate, and If the clinical setting includes sicker patients and the baseline prevalence of pneumonia is about to 10%, the revised probability of pneumonia ranges from 32% to 60% for

Table 4. True positive (True+), true Negative (True-), False Positive (False+) and False negative (False-) of clinical diagnosis, Chest X-RAY, Ultrasound and CEUS are summarized in this table. The corresponding values of Sensitivity, Specificity, Overall Diagnostic accuracy, Positive Predictive Value and Negative Predictive values are expressed. Finally, AUC ROC curves were calculated.

	True+	True-	False +	False-	Tot	
Clinical D.	23	17	2	42	84	
Chest X-Ray	36	14	5	29	84	
Us	59	14	5	6	84	
Ceus	63	19	0	2	84	
	Sens	**Spec**	**Diagnostic ACC**	**PPV**	**NPV**	**AUC**
Clinical D.	35,4%	89,5%	10%	92%	28,8%	0,46±0,076
Chest X-Ray	55,4%	73,7%	32%	87,5%	32,66%	0,645±0,068
Us	90,8%	73,7%	84,9%	92,2%	70%	0,9417±0,024
Ceus	96,9%	100%	97,5%	100%	90,5%	0,98±0,01

a patient with cough, fever, tachycardia, and crackles [35]. Although chest X-ray is widely recognized as a crucial step in the diagnosis of pneumonia, this technique has several limitations and two recent metanalysis demonstrated a low sensibility (from 54% to 60%) and a low specificity (from 57 to 60%) in the detection of pneumonia [9, 10]. Nowadays, Chest CT scan is considered to be more sensitive than radiography in detecting the presence of lung infiltrates and may also be useful in evaluating other conditions such as empyema, lung cancer, cavitations and multifocal infiltrates [36]. Although CT could be considered the "gold standard" technique in the diagnosis of pneumonia, it cannot be used as a first-line radiological examination in all patients with suspected pneumonia [36]. This is mainly due to the fact that it is often not available, it involves a high radiation dose, requires normal kidney function and it is costly [37]. The increased sensitivity of ultra-low-dose chest CT compared to CXR is of added value in vulnerable and immunocompromised patients [38]. Against, it was demonstrated recently that pulmonary imaging, in patients with suspected infection but no respiratory symptoms or signs, can result in the detection of clinically significant pneumonia [38]. CAP may be diagnosed and followed up by LUS, a technique that shows excellent sensitivity. LUS may be performed with any abdomen-sonography device. Therefore, LUS is a readily available diagnostic tool that does not involve radiation exposure and has wide applications especially in situations where X-ray is not available and/ or not applicable [23, 36]. LUS was useful in predicting a diagnosis of CAP, the bacterial etiology of CAP, and favorable outcome in patients with CAP [12]. Anyway, Two different metanalyses demonstrated high values of sensitivity for detection of pneumonia but a relatively low specificity (from 72 to 86%) for their characterization [9, 10]; also our series demonstrated an high sensitivity but a relatively low specificity (73,7%); in these cases CT of the chest should be performed. This technique, anyway, cannot be technically performed due to the high incidence of renal failure in an elderly population, up to 34% acute kidney failure during pneumonia in a recent study [39]. CEUS was demonstrated useful for diagnosis of pulmonary nodules [8] and also for pneumonia [9, 10]. Typically, CEUS diagnosis is based on arterial and parenchymal hyperenhancement with nearly no decrease of enhancement, but the value of CEUS is based on the reliable visualization of non-perfused areas within the pneumonia in terms of necrosis, abscess and infarction, as well as differentiation between lung consolidation and organized pleural effusion as part of complicated parapneumonic effusion/ pleural empyema [13]. Our experience demonstrated a high diagnostic accuracy, with high values of sensitivity and specificity in doubtful nodules detected by conventional LUS, that in our series (in older people) was high (about 43%). Two patients demonstrated an

atypical vascularization, mimicking a cancer; the nodules were organized Pneumonia. The main result, furthermore, was to perform a microvascularization study at bedside (with a portable us-machine), in a fragile and weak population, such as that of those over eighty, employing a safe and cheap contrast media [40]. Our experience demonstrate that CEUS may be useful in the correct characterization of pneumonia in elderly population, where LUS has no ultrasonographic signs of CAP, without having the need to use a chest CT scan with contrast medium.

The clinical relevance of the use of pulmonary CEUS in people over eighty is evident: it allows the characterization of peripheral nodules that are doubtful on conventional LUS (relatively high percentage in our series), allowing for an early diagnosis and consequent adequate therapy; this method is performed safely, even in cases of renal failure (where spiral CT is not possible) and can also be performed at the patient's bedside, with consequent saving of time and optimization of resources. Pulmonary CEUS does not replace LUS, but can simply complete it in those cases of difficult diagnosis. It is therefore possible to consider adding CEUS to the diagnostic flow chart of CAP pneumonia when the clinical, radiological and ultrasound diagnosis alone are not conclusive. In our experience this happened in 43% of cases, in a very elderly population, with many comorbidities and with the impossibility of performing a contrast-enhanced CT scan. According to the WFSUMB guidelines, recommended uses and applications of CEUS are limited only to peripheral lesions visible on thoracic US[13], so we cannot say that CEUS can replace chest CECT. For the same reason, CEUS cannot also be used as a exhaustive lung staging method, reserved to contrast-enhenced spiral CT.

The main limitations of this publication are the relatively small sample and the single center study: recent experiences (with high sample size) obtained different results about utility of CEUS in the characterization of peripheral lung nodules: Shen [41] obtained that CEUS enhancement mode is different between benign and malignant pulmonary lesions. Using dynamic CEUS (including time intensity curves -TIC-), Quarato et al [42] obtained that dynamic CEUS parameters cannot effectively differentiate between benign and malignant nodules; instead, Li et al [43] demonstrated that CEUS (and TIC) is useful and that CEUS and CECT had similar diagnostic accuracies of 80.16% and 81.75%, respectively. Quarato's experience [42] differs from ours due to the younger age of population (52 vs 78 years) and the use of older ultrasound technology, while Li's one [43] is more similar to ours, due to the older age (60 years) and to a more recent ultrasound system. These two authors also analyzed the various TIC-parameters, in order to "objectify" the various qualitative ultrasound parameters, used in our experience and described by the latest WFUMB guidelines [13].

Conclusion

In conclusions, our paper demonstrated, for the first time, clinical usefulness of CEUS in the characterization of peripheral lung nodules, especially when clinical suspicion is pneumonia in elderly population, where gold standard imaging (CECT) often can't be performed.

Abbreviations:

CAP: Community-acquired pneumonia
US: Ultrasound
CXR: Chest X Ray
CEUS: Contrast Enhanced Ultrasound

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Lung ultrasound in respiratory therapy: a global reflective survey

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ABSTRACT

Background: Lung ultrasound (LUS) is a noninvasive point-of-care diagnostic tool used to assess the presence and severity of various lung disorders and has been widely used in acute care settings for more than two decades. Respiratory therapists (RTs) play a vital role in managing patients on ventilation and other patients requiring respiratory support. However, the incorporation of LUS into the scope of practice of RTs has not been well highlighted despite the prominence of their practice in acute care. This international cross-sectional survey was specifically designed to evaluate the knowledge, attitude, and practice of RTs with respect to lung ultrasonography.
Methods: This observational cross-sectional study was conducted among RTs from different parts of the world using a questionnaire-based study tool. In total, 514 RTs responded to all the questions and were considered for statistical analysis. Descriptive statistics, analysis of variance, Fisher's exact, Chi-square, Bonferroni *post-hoc* analysis, and binomial logistic regression analyses were performed to identify the significance of the data.
Results: The majority of the 514 RTs who responded to the survey were from Middle Eastern countries. Out of the 514 responders, 44.9% of the responders were in the age group of 23-30 years; 67.1% were bachelor's degree holders; and 40.9% of participants had more than 10 years of experience. The knowledge-based questions revealed that RTs with higher experience and academic qualification provided more positive responses while in the attitude-related domain it was observed that standardized training in LUS helps them to enhance the current practice and to add LUS to the academic curriculum of respiratory therapy schools. However, barriers to practice LUS remains based on their responses. The practice-based questions revealed that RTs expected some additional seminars/workshops/webinars to be conducted on LUS. More than half of the participants were found to be knowledgeable with a positive attitude and working towards the inclusion of LUS in the respiratory therapy profession.
Conclusion: RTs have a positive attribute towards the inclusion of LUS in their clinical practice. Providing more structured training for professional RTs and including LUS modules in the respiratory therapy school curriculum may facilitate mastering their diagnostic skills, thereby expanding the scope of practice.

Key words: Respiratory therapists; Lung ultrasound; Survey; Knowledge; Attitude; Practice

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Ethics approval and consent to participate: The study was approved by the institutional ethical committee of Srinivas University, India (SUEC:2018/001). An informed consent was obtained from all the participants.

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Background

Over the past two decades, the utility of lung ultrasound (LUS) has revolutionized and is now an inevitable tool in assessing and managing critically ill patients [1]. LUS is a radiation-free imaging tool that is noninvasive, portable, and rapid, allowing the real-time examination of pulmonary and related structures. Many studies, including meta-analyses, that compared LUS with chest X-ray suggested its higher sensitivity and similar specificity in detecting disorders such as pleural effusion, pneumonia, pneumothorax, and pulmonary edema [2-5]. LUS also provides vital information at the bedside on lung aeration, ventilation distribution, and respiratory complications in ventilated patients [6-10]. Moreover, a comprehensive ultrasonographic approach, including LUS, echocardiography, and diaphragmatic ultrasound, offers detailed information that could help clinicians individualize ventilator settings in these patients.

Apart from acute care areas, LUS is found to be beneficial in other related clinical settings such as cardiology and rheumatology to assess the presence and severity of diverse related lung conditions. Integrating LUS with traditional echocardiography provides an integrated cardiopulmonary analysis and facilitates cardiologists in the diagnosis and management of acute and chronic cardiopulmonary conditions [11]. Similarly, LUS was also found to have a high diagnostic accuracy and significant correlation with the high-resolution computed tomography findings, thereby playing an important role in the diagnosis and management of rheumatoid disorders like interstitial lung diseases [12].

Respiratory therapists (RTs) are healthcare professionals who specialize in the evaluation and treatment of patients of diverse age groups presenting with respiratory and related disorders. They possess the knowledge, skill, and ability to offer a wide scope of diagnostic and therapeutic procedures based on the requirements. Evidence supports the importance of RTs and RT-driven care in improving patient outcomes and reducing morbidities [13-15]. It is also of interest that an outcome with decreasing costs and increased compliance with established practice guidelines without any increase in adverse events was observed in RT-driven care compared to the care directed by physicians [16]. RTs, as one of the primary practitioners of mechanical ventilation, play a pivotal role in identifying and fixing various ventilator/ventilation-related disorders, and LUS may facilitate their diagnostic abilities in the diagnosis of various respiratory derangements such as pneumothorax, pulmonary edema, etc. [17]. Nevertheless, it is not currently included as one of the standard practices in respiratory therapy profession.

Despite the paucity of literature on international consensus on education, assessment of competencies, and certification on LUS, these available studies described the need for training sessions of 1-3 days with alternating theoretical and hands-on sessions [18-21]. Anecdotal studies have also shown the positive outcomes of a 1-day training for physicians [22], 2-day training session for paramedics [23], and 0-12 hours of training for nurses and medical students resulting in the identification of B-lines and pleural effusions [24]. Another training study on a multidisciplinary group of professionals including physicians and RTs concluded the effectiveness of LUS training with a 2-hour video lecture, followed by 25 supervised scans [25].

In one of the pioneering studies on LUS training for RTs, the authors concluded that RTs trained in ultrasound are independently capable of performing LUS with an accuracy of > 95% [26]. Another recently published study concluded that a 2-day (16 hours) of training resulted in a post-test outcome of > 60% of the total score in 96% of the participants, reflecting the importance of didactic theory sessions and practical sessions [27]. A scoping review published on the involvement of RTs in LUS identified seven papers that incorporated different approaches of ultrasound training for RTs and concluded that training LUS skills for RTs seems feasible but needs global standardization [28].

It is evident that despite the increasing trend of the potential of LUS in the diagnostics and therapeutic areas of respiratory care, a global standardization of including this tool within the scope of practice of RTs is yet to be achieved. Therefore, this first cross-sectional international survey designed specifically for RTs was performed to set a benchmark regarding their insights on the knowledge, attitude, and practice regarding LUS. We understand that such a survey will

give understanding to the global practice, and specific measures might be considered to include this imaging tool within the scope of practice of RTs. We also anticipate that the outcome of this project will serve as a point of reference for policy makers and for the upcoming investigations related to the subject matter.

Methods

Study design

This observational cross-sectional survey adopted snowball sampling techniques through emails, professional social networks, respiratory therapy professional societies, and RTs of various countries. The survey targeted RTs worldwide with diverse educational backgrounds, age groups, and sex. We developed the survey on an online survey platform (Google Forms). The study was conducted from January 2022 to May 2022. The study was approved by the institutional ethical committee of Srinivas University, India (SUEC:2018/001).

Study participants

The targeted participants were RTs with no restrictions to age, sex, educational background, professional experience, and country where they work. An informed consent was obtained from all the participants. RTs who gave the consent to participate and were working in academic and clinical settings were included in the study. RTs who denied the consent to participate and those who did not complete the survey were automatically excluded from the study.

Questionnaire development

The survey questionnaire was created in English. Previous studies describing the applications of LUS and the competencies required were reviewed [14-18]. The authors and two critical care physicians, who are experienced in LUS and research, developed the questionnaire to investigate the objectives of the study. A five-member panel of experienced critical care physicians and senior RTs carried out the content validation of the questionnaire. The panel examined the core content, language, appropriateness of questions for various domains, scoring patterns, etc. A pilot survey was conducted with an experimental group of 20 randomly selected participants of various ages, sex, qualification, and experience. The internal consistency of the responses to the questions of knowledge, attitude, and practice domains in the pilot group was analyzed using Cronbach's alpha reliability test, with an acceptable result of 0.736 (> 0.6).

The survey was segregated into the demographic and questionnaire segments. In the demographic segment, respondents' basic information such as sex, age, nationality, geographical location, educational qualification, and work experience in years were collected. The questionnaire segment contained 18 questions, with 6 questions each in knowledge, attitude, and practice sections. The objective of the questionnaire (Supplementary file 1) was to assess the knowledge, attitude, and practice of RTs regarding LUS, to compare the knowledge, attitude, and practice regarding LUS amongst RTs across the world, and to investigate the factors that can facilitate LUS practice in the RT profession.

1. Knowledge: This domain focused on the technical and clinical knowledge of RTs in LUS.
2. Attitude: This domain focused on the subjective perspectives of the RTs regarding the training, clinical, and future application of LUS.
3. Practice: The practice domain focused on the subjective exposure, training, and practice sessions of the RTs with LUS.

Data analysis

All data was populated in Microsoft Excel (2013, Redmond, WA, United States) and then transferred to SPSS statistical software (SPSS, v.28; IBM, Armonk, NY, United States) for analysis. The distribution of all qualitative variables, both demographic and other variables (i.e., close-ended) of samples were examined with frequency tables. The descriptive statistics was done using mean and standard deviation or median and quartile deviation. The mean score of survey domains were

compared between sexes using independent sample *t*-test. Analysis of variance (ANOVA) was used to find the difference among demographic information such as age, work country, educational qualifications, and their experience based on knowledge, attitude, and practice scores. Bonferroni *post-hoc* analysis was performed to determine the significant difference between groups. Chi-square and Fisher's exact tests were performed to find the association between demographic domains and the 'barriers to practice' related question. Statistical significance was set at p (two-tailed) < 0.05. Binomial logistic regression analysis was also performed between the dependent and independent variables to explore the values of the study outcome.

Results

A total of 514 RTs from 22 countries responded to this survey. The age of the participants ranged from 23-50, and most respondents were between 23-30 years (n = 231, 44.9%). The sex distribution was comparable between males (n = 250, 48.6%) and females (n = 260, 50.6%), with four respondents preferring not to disclose their sex. Most of the respondents were bachelor's degree holders (n = 345, 67.1%) followed by diploma holders. Though the group was small, there were doctorate degree holders (n = 7, 1.4%) among the respondents. Most RTs were highly experienced with more than 10 years (n = 210, 40.9%). More RTs working in the Kingdom of Saudi Arabia responded to the survey (n = 109, 21.2%), followed by the United Arab Emirates, India, the United States, and Canada. The distribution of the demographic variables (age, sex, academic qualification, years of experience, and work country) were examined with frequency tables presented in Table 1.

Descriptive statistics were calculated with mean and standard deviation for the knowledge domain questions. The correct answer rates of the six questions on the LUS knowledge questions ranged between 0-100%. The mean knowledge score was 2.80 ± 1.49 (range: 0-6) suggesting an overall 46.60% correct rate on the knowledge domain. Median and quartile deviation was calculated for attitude and practice-based questions as these domains were measured on an ordinal scale (Table 2). One of the attitude-based questions (Q. 12) related to the 'barriers' was analyzed separately due to its nature.

The frequency for each question under knowledge, attitude, and practice were calculated and presented in Table 3. The right and wrong answers in the

Table 1. Demographic details of the participants.

Demographic characteristics	Frequency	Percentage
Age		
23-30	231	44.9
>30-40	187	36.4
>40-50	78	15.2
> 50	18	3.5
Sex		
Male	250	48.6
Female	260	50.6
Prefer not to say	4	0.8
Academic qualification		
Bachelor's	345	67.1
Diploma/Associate's	83	16.1
Intern	15	2.9
Master's	57	11.1
On-the-job trainee	7	1.4
Ph.D.	7	1.4
Years of experience		
0-2 years	104	20.2
>2-5 years	99	19.3
>5-10 years	101	19.6
>10 years	210	40.9
Country where the respondent currently works		
Bahrain	11	2.1
Canada	56	10.9
India	86	16.7
KSA	109	21.2
Philippines	18	3.5
Qatar	44	8.6
UAE	89	17.3
USA	75	14.6
Others	26	5.1

Ph.D., Doctor of Philosophy; KSA, Kingdom of Saudi Arabia; UAE, United Arab Emirates; USA, United States of America.

Table 2. Response rate of the participants.

Dependent variables	Mean ± SD	Median (Quartile Deviation)
Knowledge	2.80 ± 1.49	
Attitude	4.18 ± 1.29	5.00 (4.00-5.00)
Practice	2.19 ± 1.73	2.00 (1.00-4.00)

SD, Standard deviation.

Table 3. Knowledge, attitude, and practice questionnaire analysis.

Knowledge-based questions	Correct, *n* (%)	Incorrect, *n* (%)
Q1: LUS emits radiation (No)	387 (75.3)	127 (24.7)
Q2: Image identification (Pleural reverberation artifacts)	164 (31.9)	350 (68.1)
Q3: Image identification (Bat sign)	276 (53.7)	238 (46.3)
Q4: Image identification (Pleural effusion)	214 (41.6)	300 (58.4)
Q5: Image identification (Pulmonary edema)	198 (38.5)	316 (61.5)
Q6: Sea shore in M-mode (Normal lung)	198 (38.5)	316 (61.5)
Attitude-based questions	**Yes, *n* (%)**	**No/not sure, *n* (%)**
Q7: LUS within the scope of RTs?	430 (83.7)	84 (16.3)
Q8: LUS promotes safety culture?	439 (85.4)	75 (14.6)
Q9: Need of training for RTs?	454 (88.3)	60 (11.7)
Q10: RTs are competent to do LUS?	377 (73.3)	137 (26.7)
Q11: LUS module in RT school curriculum?	446 (86.8)	68 (13.2)
Q12: Barriers for RTs to do LUS?		
Practice-based questions	**Yes, *n* (%)**	**No, *n* (%)**
Q13: Previous learning in LUS?	267 (51.9)	247 (48.1)
Q14: Any formal certification in LUS?	36 (7.0)	478 (93.0)
Q15: Any hands-on experience in LUS?	134 (26.1)	380 (73.9)
Q16: Any feedback on your experience in LUS?	176 (34.2)	338 (65.8)
Q17: Any assistance offered to others in LUS?	244 (47.5)	270 (52.5)
Q18: Ever been an advocate for LUS in RT profession?	269 (52.3)	245 (47.7)

LUS, Lung ultrasound; RT, Respiratory therapist.

knowledge-based domain and the responses of the attitude-based and practice-based domains were recorded individually with frequency and percentage to validate the strength of each question.

In question 1, the majority of the respondents were aware that LUS does not emit radiation (*n* = 387, 75.3%). Question 9 regarding the requirement of LUS training for RTs (*n* = 454, 88.3%) and question 11 on the inclusion of an LUS module to RT school curriculum (*n* = 446, 86.8%) were found to have a more positive attitude in the group of attitude-based questions. Similarly, among the practice-based questions, question 18 on the advocacy of LUS in the RT profession (*n* = 269, 52.3%) and question 13 regarding previous learning in LUS (*n* = 267, 51.9%) reflected the keenness of the respondents to learn LUS and involve LUS in their practices. More than half of the participants were found to be knowledgeable with positive attitudes and working towards including LUS in the RT profession.

The mean score of knowledge, attitude, and practice were compared between male and female sexes

Table 4. Comparison of sex in the knowledge, attitude, and practice scores.

Domain	Sex	*n*	Mean	SD	*t*	*p*
Knowledge	Male	250	2.6080	1.55951	2.55	0.01*
	Female	260	2.9423	1.39516		
Attitude	Male	250	4.0280	1.49538	3.23	0.001*
	Female	260	4.3808	0.91175		
Practice	Male	250	2.3680	1.69590	2.06	0.04*
	Female	260	2.0538	1.74786		

*, Statistically significant. SD, Standard deviation.

Table 5. Comparison of age groups in the knowledge, attitude, and practice scores.

Domain	Age Group	*n*	Mean	SD	SE	*F*	*p*
Knowledge	23-30	231	2.6797	1.54398	0.10159	1.68	0.17
	>30-40	187	2.8075	1.44257	0.10549		
	>40-50	78	2.9872	1.46379	0.16574		
	>51	18	3.3333	1.37199	0.32338		
	Total	514	2.7957	1.49303	0.06585		
Attitude	23-30	231	4.1602	1.18519	0.07798	0.05	0.98
	>30-40	187	4.1872	1.39208	0.10180		
	>40-50	78	4.1667	1.39029	0.15742		
	>51	18	4.2778	1.22741	0.28930		
	Total	514	4.1751	1.29344	0.05705		
Practice	23-30	231	2.4156	1.74469	0.11479	4.92	0.002*
	>30-40	187	2.1979	1.74701	0.12775		
	>40-50	78	1.7051	1.59633	0.18075		
	>51	18	1.3333	1.37199	0.32338		
	Total	514	2.1907	1.73223	0.07641		

*, Statistically significant. SD, Standard deviation; SE, Standard error.

using independent sample *t*-test (Table 4). Knowledge, attitude, and practice scores significantly differed between males and females ($p < 0.05$). Knowledge and attitude scores regarding LUS were highest among females: (2.94 ± 1.40) and (4.38 ± 0.91), respectively. Practice scores on LUS were higher for males (2.37 ± 1.70). The mean scores of knowledge, attitude, and practice were compared between age groups using ANOVA (Table 5). There was a significant difference ($p < 0.05$) between age groups for practice scores regarding LUS. The youngest age group (23-30) had a higher mean score (2.42 ± 1.74) than other age groups. Multiple comparisons between the age groups on the responses of various domains were performed using Bonferroni *post-hoc* analysis. We observed a significant difference in the responses of the practice domain between the age groups of 23-30 and 41-50 ($p < 0.05$). The comparison between the rest of the groups was not significant. Knowledge, attitude, and practice scores significantly differed between work countries ($p < 0.05$) by applying ANOVA (Table 6). The mean scores of participants from India were found to be highest in all the domains such as knowledge (3.24 ± 1.45), attitude (4.51 ± 0.84), and practice (3.34 ± 1.51) compared to participants from the rest of the countries. The *post-hoc* analysis revealed a significant difference in the

Table 6. Comparison of country in the knowledge, attitude, and practice scores.

Domains	Work country	*n*	Mean	SD	*F*	*p*
Knowledge	Bahrain	11	2.2727	1.61808	3.92	< 0.001*
	Canada	56	3.0536	1.36741		
	India	86	3.2442	1.45470		
	KSA	109	2.3394	1.34178		
	Philippines	18	1.8333	1.09813		
	Qatar	44	2.8636	1.19283		
	UAE	89	2.8764	1.62243		
	USA	75	2.8133	1.51295		
	Others	26	3.1154	1.90425		
	Total	514	2.7957	1.49303		
Attitude	Bahrain	11	3.8182	1.16775	7.77	< 0.001*
	Canada	56	4.6250	.61975		
	India	86	4.5116	.83658		
	KSA	109	3.5413	1.69166		
	Philippines	18	4.3333	.48507		
	Qatar	44	4.5227	.90190		
	UAE	89	3.8202	1.51928		
	USA	75	4.5333	1.08221		
	Others	26	4.3846	1.13409		
	Total	514	4.1751	1.29344		
Practice	Bahrain	11	2.0909	1.51357	8.58	< 0.001*
	Canada	56	1.7500	1.68685		
	India	86	3.3372	1.50771		
	KSA	109	1.8532	1.60915		
	Philippines	18	1.7222	1.40610		
	Qatar	44	2.0909	1.50686		
	UAE	89	1.6067	1.74263		
	USA	75	2.3467	1.69653		
	Others	26	2.8462	1.91191		
	Total	514	2.1907	1.73223		

*, Statistically significant. SD, Standard deviation; KSA, Kingdom of Saudi Arabia; UAE, United Arab Emirates; USA, United States of America.

response was observed between India and the Kingdom of Saudi Arabia and the Philippines ($p < 0.05$), and the differences among the other countries were insignificant among the responses in the knowledge domain. In the attitude domain, a significant difference was observed between Canada and the Kingdom of Saudi Arabia and the United Arab Emirates, India and the Kingdom of Saudi Arabia and the United Arab Emirates, the Kingdom of Saudi Arabia and Qatar, and the United Arab Emirates and the United States ($p < 0.05$). In the practice domain, we observed a significant difference between India and Canada, the Kingdom of Saudi Arabia, the Philippines, Qatar, the United Arab Emirates, and the United States ($p < 0.05$). ANOVA was applied to qualifications and domains. Knowledge and practice scores were

Table 7. Comparison of academic qualification in knowledge, attitude, and practice scores.

Domains	Academic qualification	*n*	Mean	SD	*F*	*p*
Knowledge	Bachelor's	345	2.6696	1.50419	6.11	< 0.001*
	Diploma/associate	83	2.7108	1.33005		
	Intern	15	2.3333	1.44749		
	Master's	57	3.7544	1.37945		
	Trainee	7	2.5714	0.97590		
	Ph.D.	7	3.4286	1.51186		
	Total	514	2.7957	1.49303		
Attitude	Bachelors	345	4.0464	1.39482	2.85	0.02*
	Diploma/Associate	83	4.5181	0.83171		
	Intern	15	4.4667	0.63994		
	Masters	57	4.4035	1.23722		
	Trainee	7	3.5714	1.51186		
	Ph.D.	7	4.5714	0.78680		
	Total	514	4.1751	1.29344		
Practice	Bachelors	345	2.1797	1.69203	5.08	< 0.001*
	Diploma/Associate	83	1.7711	1.72729		
	Intern	15	1.9333	1.22280		
	Masters	57	3.1228	1.85232		
	Trainee	7	1.4286	1.13389		
	Ph.D.	7	1.4286	1.61835		
	Total	514	2.1907	1.73223		

*, Statistically significant. SD, Standard deviation; Ph.D., Doctor of Philosophy.

the highest among respondents with master's degree (3.75 ± 1.38 and 3.12 ± 1.85, respectively), whereas the attitude score was the highest among the Ph.D. group (4.57 ± 0.79) (Table 7).

After *post-hoc* analysis, we observed a significant difference in the responses of the practice domain between master's degrees and interns, diploma, and bachelor's degrees ($p < 0.05$). A significant difference in the attitude responses was observed between bachelor's degree holders and diploma holders ($p < 0.05$). In the practice domain, there was a significant difference between master's degree holders and diploma and bachelor's degree holders ($p < 0.05$). There was a significant difference ($p < 0.05$) in knowledge regarding LUS. We observed that respondents with more than 10 years of experience had a higher score (3.02 ± 1.47) than the other groups. The group with 6-10 years of experience scored higher than other groups in the practice questions. Attitude scores were not correlated with years of experience. We observed a significant difference in the practice responses between the 0-2 years of experience and > 10 years of experience ($p < 0.05$) after *post-hoc* analysis. No statistical significance was observed in the attitude responses amongst the groups of years of experience ($p > 0.05$). In the practice domain, there was a significant difference between those with 6-10 years and > 10 years of experience ($p < 0.05$) (Table 8). Logistic regression analysis was performed between the dependent and independent variables to predict the values of the study outcome. The dependent variables were years of experience (up to 5 years and above 5 years of experience) and academic qualifications (qualifications less than bachelor's degree and bachelor's degree and above). The independent variables were the knowledge, attitude, and practice scores. We attained a regression

Table 8. Comparison of years of experience in knowledge, attitude, and practice scores.

Domains	Years of experience	*n*	Mean	SD	*F*	*p*
Knowledge	0-2	104	2.5288	1.56389	2.99	0.03*
	>2-5	99	2.6869	1.59493		
	>5-10	101	2.7129	1.31405		
	>10	210	3.0190	1.46722		
	Total	514	2.7957	1.49303		
Attitude	0-2	104	3.8942	1.37183	2.34	0.07
	>2-5	99	4.2222	1.13888		
	>5-10	101	4.3465	1.22013		
	>10	210	4.2095	1.34268		
	Total	514	4.1751	1.29344		
Practice	0-2	104	2.4519	1.61233	3.98	0.01*
	>2-5	99	2.1212	1.76284		
	>5-10	101	2.5446	1.81397		
	>10	210	1.9238	1.69827		
	Total	514	2.1907	1.73223		

*, Statistically significant. SD, Standard deviation.

Table 9. Regression analysis among knowledge, attitude, and practice scores and years of experience.

Independent variable	B	SE	Wald	Degrees of freedom	*p*	Odds Ratio	95% CI	
							Lower	Upper
Knowledge	0.155	0.064	5.920	1	0.015*	1.167	1.031	1.322
Attitude	0.121	0.072	2.847	1	0.092	1.128	0.981	1.298
Practice	-0.105	0.055	3.634	1	0.057	0.900	0.808	1.003
Constant	-0.272	0.330	0.680	1	0.410	0.762	NA	NA

*, Statistically significant. CI, Confidence interval; SE, Standard error.
NA, Not applicable.

Table 10. Regression analysis among knowledge, attitude, and practice scores and academic qualifications.

Independent variable	B	SE	Wald	Degrees of freedom	*p*	Odds Ratio	95% CI	
							Lower	Upper
Knowledge	0.065	0.080	0.655	1	0.418	1.067	0.912	1.247
Attitude	-0.343	0.114	9.023	1	0.003*	0.710	0.568	0.888
Practice	0.224	0.071	9.848	1	0.002*	1.251	1.088	1.439
Constant	2.200	0.524	17.625	1	0.000	9.021		

*, Statistically significant. CI, Confidence interval; SE, Standard error.

output that concluded knowledge and attitude had a positive impact on the years of experience, as higher experience resulted in an increase in knowledge and attitude, whereas practice questions had a negative impact on the years of experience (Table 9). Regression analysis with academic qualification concluded that knowledge and practice have a positive impact with the higher academic qualification, whereas attitude has a negative impact with the academic qualification (Table 10).

Question on barriers to practice LUS

There was a question in the attitude domain as follows: "*If formally certified in lung ultrasound to enhance the scope of practice, do you think that there will be barriers for RTs to perform lung ultrasound?*" The options were: *a) Yes b) No c) Not sure.* Table 11 shows that 50% of the respondents mentioned that there might be barriers for the RTs to practice LUS, even if they were formally certified. All the independent variables such as demographic details were analyzed against the attitude-based question on barriers to practice LUS. Fisher's exact test was applied to find the association between age groups and barriers to practice. No significant difference (Fisher's exact test = 11.59; p value = 0.07) was found between these two variables, concluding that there was no association between age group of the RTs and barriers to practice LUS (Figure 1, Table 12). The association between sex and barriers to practice was analyzed using the chi-square test. Overall, 52.4% of the male and 48.8% of the female RTs reported that there were barriers to LUS. No significant difference (Chi-square = 5.44; p = 0.07) was observed, concluding that there was no association between sex and perception of barriers to practice LUS (Figure 2, Table 13). Fisher's exact test was performed to find the association between academic qualifications and the barriers to practice-related question. A significant difference (Fisher's exact = 18.73; p = 0.04) was found indicating that there is an association between academic qualification of the RTs and barriers to practice LUS (Figure 3, Table 14). The association between the years of experience of the RTs and their attitude towards the barriers to practice LUS was assessed using the chi-square test. RTs who had more than 10 years of experience in the field agreed that barriers to practicing LUS remain even though they are experienced. We identified a significant difference (p < 0.05) between the years of experience and the attitude towards barriers to practice LUS (Figure 4, Table 15). Fisher's exact test was applied to find the association between work countries and barriers to practice-related question. Nearly 50.2% of the RTs reported that barriers exist for them to use the LUS irrespective of the work country, while 27.0% of them responded that there were no barriers. The remaining respondents were unsure. There was a significant difference (Fisher's exact = 46.68; p = 0.001) (Figure 5, Table 16).

Table 11. Attitude domain question on barriers to practice lung ultrasound.

Answer	Frequency	Percent
No	139	27.0
Not sure	117	22.8
Yes	258	50.2
Total	514	100.0

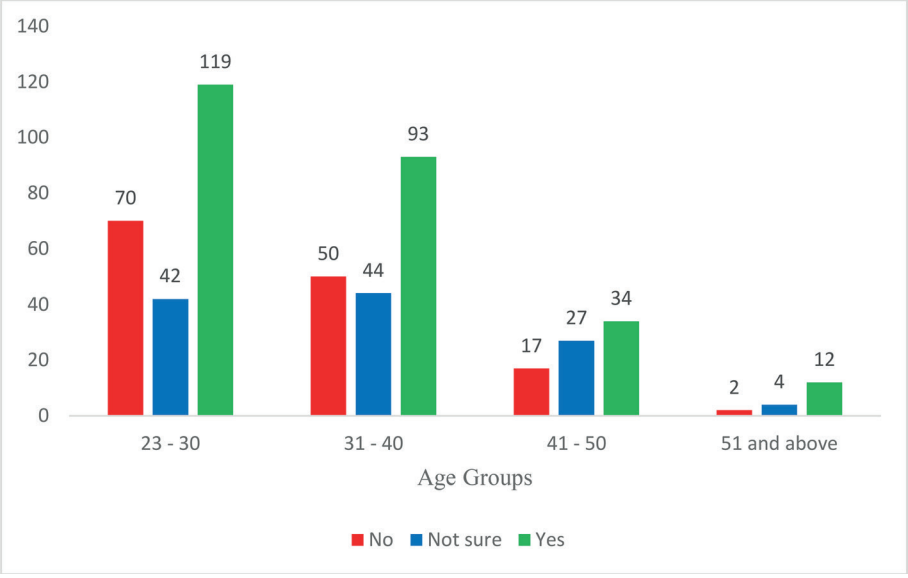

Figure 1. Insight of respondents on the barriers to practice lung ultrasound based on age groups.

Table 12. Cross tabulation between age and barrier-related question.

Parameter		If formally certified in lung ultrasound to enhance the scope of practice, do you think that there will be barriers for respiratory therapists to use this diagnostic tool?			Total
		No	Not Sure	Yes	
Age group in years	23-30	70 (30.3)	42 (18.2)	119 (51.5)	231
	>30-40	50 (26.7)	44 (23.5)	93 (49.7)	187
	>40-50	17 (21.8)	27 (34.6)	34 (43.6)	78
	>51	2 (11.1)	4 (22.2)	12 (66.7)	18
Total		139	117	258	514

Fisher's exact test = 11.59; $p = 0.07$.

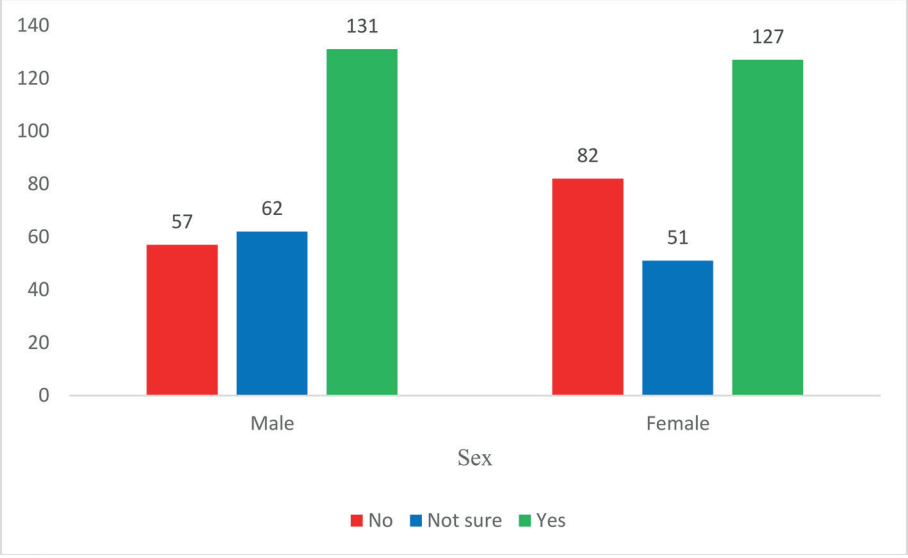

Figure 2. Insight of respondents on the barriers to practice lung ultrasound based on sex.

Table 13. Cross tabulation between sex and barrier-related question.

Sex	If formally certified in lung ultrasound to enhance the scope of practice, do you think that there will be barriers for respiratory therapists to use this diagnostic tool?			Total
	No	Not sure	Yes	
Male	57 (22.8)	62 (24.8)	131 (52.4)	250
Female	82 (31.5)	51 (19.6)	127 (48.8)	260
Total	139 (27.3)	113 (22.2)	258 (50.6)	510

Chi-square = 5.44; $p = 0.07$.

Discussion

The scope of practice of RTs has been expanding with the evolution of new related technologies in medicine. LUS appears to be a promising tool in the diagnostic and prognostic aspects of respiratory disorders, especially in acute care settings. Considering the pivotal role of RTs in acute care settings, it is recommended that RTs should master the knowledge and skills related to LUS [28, 29]. It is suggested that as the primary caregivers of ventilated patients, RTs trained in LUS will have specific beneficial outcomes in terms of early recognition of pneumothorax, facilitation of weaning, and optimization of the positive-end expiratory pressure in worsening acute respiratory distress syndrome patients [28].

This study was the first international survey specifically conducted for RTs to capture a diverse range of practices, challenges, and insights, offering a comprehensive view of how LUS is utilized worldwide by RTs. Even though the sample size was small compared

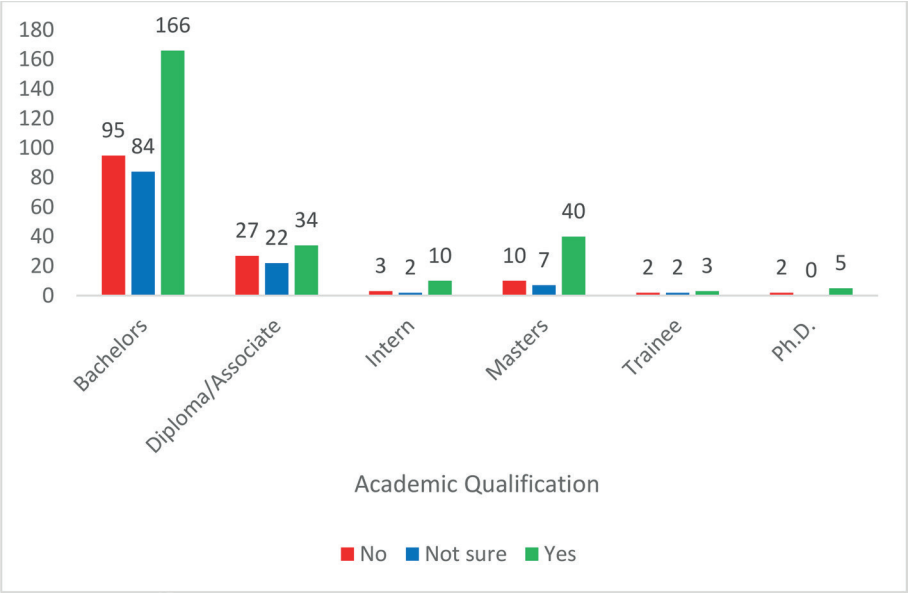

Figure 3. Insight of respondents on the barriers to practice lung ultrasound based on educational qualifications (Ph.D., Doctor of Philosophy).

Table 14. Cross tabulation between qualification and barrier-related question.

	If formally certified in lung ultrasound to enhance the scope of practice, do you think that there will be barriers for respiratory therapists to use this diagnostic tool?			
Academic qualification	**No**	**Not sure**	**Yes**	**Total**
Bachelors	95 (27.5)	84 (24.3)	166 (48.1)	345
Diploma/Associate	27 (32.5)	22 (26.5)	34 (41.0)	83
Intern	3 (20.0)	2 (13.3)	10 (66.7)	15
Master's	10 (17.5)	7 (12.3)	40 (70.2)	57
Trainee	2 (28.6)	2 (28.6)	3 (42.9)	7
Ph.D.	2 (28.6)	0 (0)	5 (71.4)	7
Total	139	117	258	514

Fisher's exact = 18.73; $p = 0.04$. Ph.D., Doctor of Philosophy.

to the number of RTs globally, the survey had participation from many countries where the practice exists, providing important insights into their shared perspectives on LUS. The survey reflected all age groups, with considerable participation from the young RTs. Sex-wise, the samples were comparable. RTs with diverse qualifications participated in the survey, with prominent representation from bachelor's degree holders. From an experience perspective, the groups with less than 10 years were comparable, but a striking participation was noted from the senior RTs with more than 10 years of experience. RTs working in diverse geographical regions responded to the survey, with higher responses from the Middle Eastern countries.

From the knowledge domain analysis, the mean score of 2.80 ± 1.49 (range: 0-6) reflected the insufficiency of LUS knowledge that the RTs possess. One of the alarming parts of the knowledge domain was about the 'seashore sign,' in which only 38.5% of the RTs correctly mentioned it as a normal lung pattern

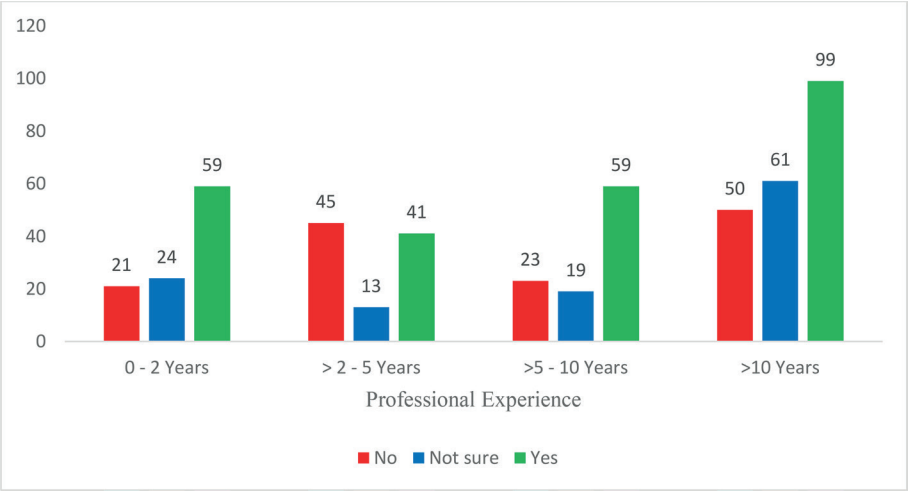

Figure 4. Insight of respondents on the barriers to practice lung ultrasound based on years of experience.

Table 15. Cross tabulation between years of experience and barrier-related question.

	If formally certified in lung ultrasound to enhance the scope of practice, do you think that there will be barriers for respiratory therapists to use this diagnostic tool?			
Years of experience	**No**	**Not sure**	**Yes**	**Total**
0-2	21 (20.2)	24 (23.1)	59 (56.7)	104
>2-5	45 (45.5)	13 (13.1)	41 (41.4)	99
>5-10	23 (22.8)	19 (18.8)	59 (58.4)	101
> 10	50 (23.8)	61 (29.0)	99 (47.1)	210
Total	139	117	258	514

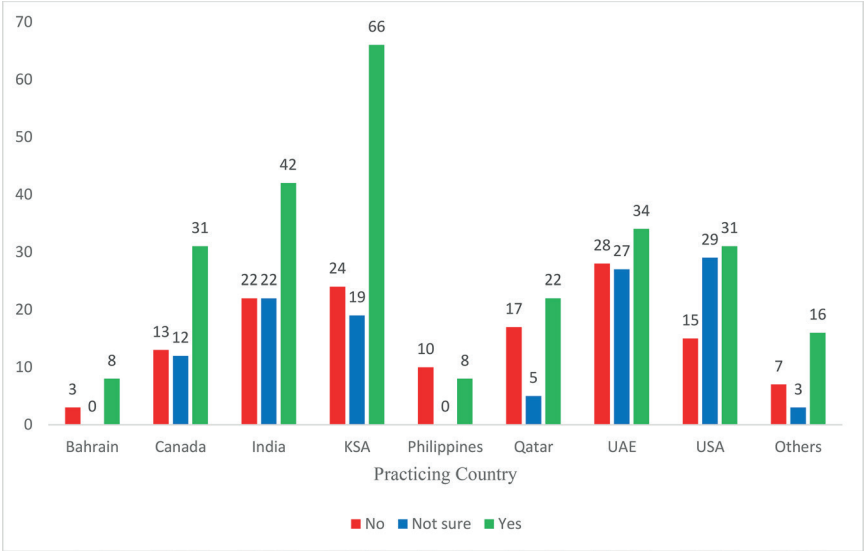

Figure 5. Insight of respondents on the barriers to practice lung ultrasound based on the country they work. (KSA, Kingdom of Saudi Arabia; UAE, United Arab Emirates; USA: United States of America).

Table 16. Cross tabulation between work country and barriers for lung ultrasound.

Country where the respondent currently works	If formally certified in lung ultrasound to enhance the scope of practice, do you think that there will be barriers for respiratory therapists to use this diagnostic tool?			Total
	No	Not sure	Yes	
Bahrain	3 (27.3)	0 (0)	8 (72.7)	11
Canada	13 (23.3)	12 (21.4)	31 (55.4)	56
India	22 (25.6)	22 (25.6)	42 (48.8)	86
KSA	24 (22.0)	19 (17.4)	66 (60.6)	109
Philippines	10 (55.6)	0 (0)	8 (44.4)	18
Qatar	17 (38.6)	5 (11.4)	22 (50.0)	44
UAE	28 (31.5)	27 (30.3)	34 (38.2)	89
USA	15 (20.0)	29 (38.7)	31 (41.3)	75
Others	7 (26.9)	3 (11.5)	16 (61.5)	26
Total	139 (27.0)	117 (22.8)	258 (50.2)	514

Fisher's exact = 46.68; $p = 0.000$. KSA, Kingdom of Saudi Arabia; UAE, United Arab Emirates; USA, United States of America.

from the options given. It is understood that the paucity of focused training and position statements specific for the RTs to perform LUS might have led to the ambiguity as reflected in the responses of the knowledge domain. Additionally, this uncertainty in the knowledge-related domain of RTs might perpetuate considering their naiveness in LUS and the infancy of the profession in some parts of the world [30].

The mean attitude score in this survey was 4.18 ± 1.29 (range: 0-5) reflecting the positive approach of RTs toward LUS. The majority (83.7%) stand with the idea of including LUS within their scope of practice. In general, the attitude of respondents was suggestive of the need to empower the RTs with LUS with proper training to enhance patient care and safety culture. We agree with a previous similar study that such an extended scope can be developed only through proper training pathways to set up a clear structure focusing on the outcome, i.e., patient care.

The mean practice score was 2.19 ± 1.73 (range: 0-6), indicating an insufficient exposure and practice of LUS by the RTs. It is of great interest that 51.9% of RTs have initiated efforts to practice LUS by learning through workshops/ journals/ textbooks/ webinars/ YouTube. However, only 7.0% of the RTs have some certification in LUS, with only 26.1% of them having hands-on experience. The enthusiasm to learn LUS and their interest to include LUS in the profession was visible in their responses related to assisting the LUS-related procedures and their interaction on LUS with other healthcare professionals.

In our study, the positively attributed responses in the knowledge and practice domains were high among the RTs who have completed their master's and Ph.D. This corresponded to the years of clinical exposure they possess. This reflects that the learning trajectory in any areas such as LUS progresses from basic principles and techniques to more advanced concepts and skills [31]. Like any other technique, the process of the LUS learning curve typically starts with exploring the technical aspects of the equipment and by obtaining and interpreting basic ultrasound images. With experience, they may move on to more advanced techniques, such as using ultrasound to guide procedures or to assess specific respiratory conditions.

The results obtained from knowledge-based questions was comparable to a prospective cohort study conducted by See et al., in which RT trainees were examined with the same pre-performance and post-performance-based test in identifying ultrasound images after undergoing a didactic session, self-learning module, and practical assessment. It was found that the trainees were 95% successful in interpreting the images, and the performance score was directly

proportional to the number of training cases attended by the trainees [26]. Hence, systematic training and practice are essential to master LUS, as the goal of LUS training is to enable healthcare professionals like RTs to use ultrasound effectively and confidently in their clinical practice [32].

The attitude of the working professional RT regarding the need for the inclusion of LUS curriculum in RT school reflected the necessity of the same. This finding was backed by another cross-sectional study that focused on the RTs working in Saudi Arabia where the results showed the need of integrating LUS into RT curriculum [30].

Hands-on experience is an important part of training in LUS [33], and we applaud the positive responses of our respondents related to attitude and practice reflecting their interest towards the learning process. One of the ways RTs can gain hands-on experience in LUS includes the observation of experienced practitioners while they perform LUS exams, which can provide valuable insight into the technique and help to build an understanding of the process [34]. Another method is to practice LUS on simulated models, which helps to develop technical skills and confidence [35].

The practice-based responses in our study are in accordance with a study where the trainees including RTs were exposed to a didactic session with video lecture, hands-on session at the bedside, and practical assessments of LUS. When the trainee's knowledge was assessed, almost 80% of the trainees were able to identify the normal lungs and lungs with interstitial-alveolar syndrome after a few examinations and supervisions, reflecting the importance of exposure and training [25]. The most comprehensive way to gain hands-on experience in LUS is to perform supervised exams or performance-based assessment on real patients. This can provide valuable experience in working with patients and applying the knowledge and skills learned [36].

To address the identified gaps noted from our survey, regarding knowledge and practice of RTs, it is important to implement comprehensive and targeted professional development programs. Strategies to facilitate this include standardized training programs with a comprehensive curriculum, hands-on workshops, and simulation-based education [37, 38]. Additionally, continuing education programs such as workshops, online courses, and certification programs are crucial [39, 40]. Interdisciplinary training through collaborative learning with other professionals and case-based learning can also enhance RTs' skills [41, 42]. Moreover, mentorship and peer learning opportunities should be provided to support ongoing professional growth [43, 44].

An area of concern identified was the barriers to practice LUS. In our study, irrespective of diverse demographic details, half of the total respondents agreed that there might exist barriers for the RTs to practice LUS, and the other half had mixed opinions. Even though the survey did not subcategorize the types of expected barriers, the potential barriers to RTs' involvement in LUS practice, as reflected from the literature include lack of formal training and curriculum, lack of resources and mentors, time constraints, lack of accreditation or standardization, resistance to practice, and lack of confidence [30]. Strategies to overcome these barriers include investing in equipment and resource sharing, providing integrated training sessions and hybrid self-paced programs, implementing standardized training guidelines and tailored certification programs, offering evidence-based education and inclusive approaches, and providing frequent practice opportunities and mentorship [37, 39, 40, 43]. If RTs, even with formal certification, continue to have barriers to practice, then this points at the need of competency assessments with the endorsement from the respective professional societies or regulatory bodies.

Due to the nature of their educational background and professional practice, RTs are eligible candidates to learn and practice LUS. However, the extent and duration of training/learning, the frequency of scans to be done, and the competency-based assessment specific to RTs are still unknown with some repositioned statements related to other professions.

It has been reported from a few anecdotal experiences and conference abstracts that LUS skills can be satisfactorily achieved with a training duration ranging from 2 hours to 4 months and with 20-80 supervised scans [36, 45-47]. Even though the learning curve associated with the application of LUS is relatively short, the diagnostic yield of LUS depends primarily on the

clinician's expertise [48-50]. It was highlighted from a multicentered study with multidisciplinary trainees including RTs that a training curriculum consisting of theoretical modules and 25 LUS exams under expert supervision is optimal to attain the basic skills for identifying normal lung aeration, interstitial-alveolar syndrome, and consolidation in acutely ill patients [25].

There is evidence to support the involvement of non-physician healthcare professionals such as nurses, paramedics, and physiotherapists in the practice of ultrasonography [51-53], and some articles reflect the need of inclusion of LUS into the scope of practice of RTs [17, 28-30]. It was reiterated in these articles that considering the nature of the profession, equipping RTs with LUS knowledge will be an added value in improving the quality of patient care and patient safety.

Conclusion

Foreseeing professional advancement and better patient outcomes, this study suggested that RTs perceive value in the inclusion of a comprehensive respiratory care-related ultrasound training module within existing respiratory therapy curriculums internationally. This study also suggests that a well-structured respiratory-related ultrasound training module for the practicing RTs may serve to augment their technical and clinical decision-making skills for safer practice. Building on this broader understanding, additional study on LUS is warranted in specific countries/healthcare authorities to understand the nuances of RT practice in those contexts. Barriers to implement the practice of routine use of LUS ultrasonography by the RTs remains. However, the involvement of professional organizations of the respective countries, medical education departments, and credentialing and privileging committees play a pivotal role in this process to reflect the benefit-risk ratio of including RTs in the imaging taskforce.

Need of future research

This study aimed at exploring the potential and the outlook of RTs in the practice of LUS. Although LUS clearly has an impact on respiratory care practices, there are substantial gaps, as identified from the available literature. Future research focusing on randomized controlled academic and clinical trials with the inclusion of LUS as a tool of practice for RTs is highly recommended. There also exists a need for multicentered prospective studies to propose and standardize the training and competency requirement in LUS for RTs. Everything starts at the school level, and we highlight the need to include LUS modules in respiratory therapy curriculum across the globe.

Strengths and limitations of this study

This is the first international survey conducted to explore the objective and subjective responses of RTs on LUS. Since this survey only addressed qualified respiratory therapy professionals, the responses might be considered as their global feedback on this imaging tool. However, we consider the number of participants in this study to be low compared to the worldwide number of RTs. We assume this to be due to the specific nature of the topic, where the practice of LUS by the RTs is still naïve in many parts of the world. This might have led to a bias of interest in the topic. Another reason might be survey fatigue as the coronavirus disease 2019 pandemic caused a surge in survey-based research activities.

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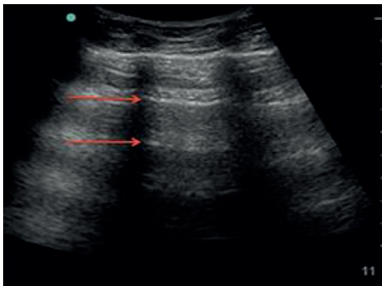
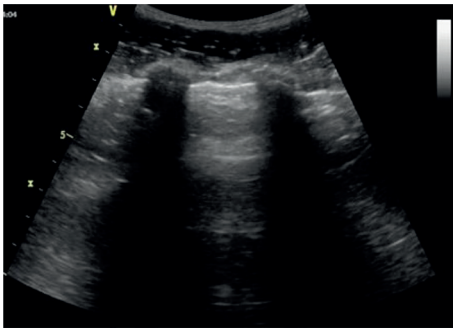
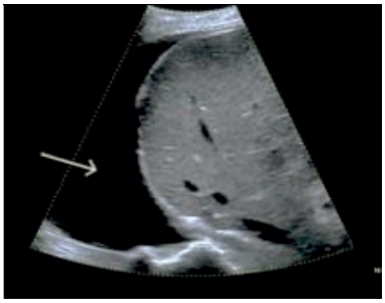
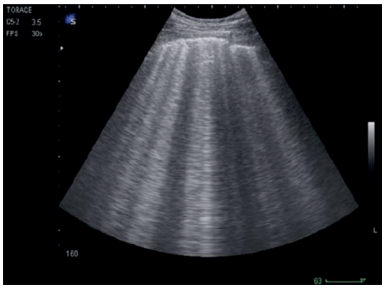
APPENDIX

SUPPLEMENTARY FILE 1: SURVEY QUESTIONNAIRE

	Questions Knowledge-Based Questions	Answer Options [Italic Bold-Correct Answer]
Q1	Lung ultrasound emits radiation.	a. Yes b. ***No*** c. Maybe
Q2	The bright horizontal lines represented by the arrows indicates _____ 	a. Lung tissue artifacts b. ***Pleural reverberation artifacts*** c. Endotracheal Tube artifacts d. Rib shadows
Q3	What normal / abnormal sign is visible in the following lung ultrasound image? 	a. Seashore sign b. ***Bat sign*** c. Quad sign d. B-lines
Q4	What normal/ abnormal sign is indicated by the arrow? 	a. Pulmonary Edema b. ***Pleural Effusion*** c. Pneumothorax d. Atelectasis

Questions		Answer Options [Italic Bold-Correct Answer]
Knowledge-Based Questions		
Q5	What is the most likely clinical condition reflected by the vertical lines in this lung ultrasound image of a patient in respiratory distress? 	a. ***Pulmonary Edema*** b. Pleural Effusion c. Pneumothorax d. Normal Lung
Q6	Seashore sign in M-mode of Lung ultrasound indicates _____	a. Pulmonary Edema b. Pleural Effusion c. Pneumothorax d. ***Normal Lung***
Attitude-Based Questions		**Answer Options**
Q7	Do you think that Lung Ultrasound should be included within the scope of practice of RTs?	a. Yes b. No c. Not sure
Q8	Do you think that RT performed lung ultrasound can promote safety culture in ICU, especially in case of ventilated patients?	a. Yes b. No c. Not sure
Q9	Do you think that there is a need of development of training-based certification on Lung Ultrasound for the currently practicing RTs?	a. Yes b. No c. Not sure
Q10	Do you think that your academic and clinical knowledge can make you competent to perform lung ultrasound?	a. Yes b. No c. Not sure
Q11	Do you think that lung ultrasound needs to be included in the curriculum of RT schools?	a. Yes b. No c. Not sure
Q12	If formally certified in lung ultrasound to enhance the scope of practice, do you think that there will be barriers for RTs to perform lung ultrasound?	a. Yes b. No c. Not sure
Practice-Based Questions		**Answer Options**
Q13	Have you ever learnt about Lung Ultrasound in any workshops/ journals/ textbooks/ webinars/ YouTube?	a. Yes b. No
Q14	Do you have any formal certification in Lung Ultrasound?	a. Yes b. No
Q15	Do you have any hands-on experience in Lung Ultrasound?	a. Yes b. No
Q16	Have you ever been asked by the Physicians/ Nurses/ Other Healthcare Professionals, regarding your knowledge on Lung Ultrasound?	a. Yes b. No
Q17	Have you ever assisted the Physicians in performing Lung Ultrasound/ prepared the Ultrasound Machine?	a. Yes b. No
Q18	Have you ever interacted/ recommended the scope of Lung Ultrasound in RT Profession, to Colleagues/ Supervisors/ Other Healthcare Professionals/ Management?	a. Yes b. No

Original research article

Ant-waist surgery adversely affects lung function: a cross-sectional study

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ABSTRACT

Background: Body contouring surgery for the removal of the 11th and 12th ribs is undertaken for aesthetic appeal in female and transgender populations. The potential adverse effects of the surgery on lung function and respiratory muscle strength have not been previously studied. Therefore, this study aimed to determine the effects of 'Ant-waist' surgery on lung function and respiratory muscle strength in individuals who had undergone surgery.

Methods: This was a cross-sectional study with two groups, an Anti-waist group who had undergone surgery and an age and gender matched control group. Participants performed lung function tests to determine measurements of FEV_1, FVC, FEV_1/FVC, PEF, MIP, and MEP. Independent t-tests were performed to determine between-group differences in outcomes and Pearson's correlation coefficients determined the relationship between lung function and respiratory muscle strength, and number of years since surgery.

Results: There was a significant between-group difference in FEV_1 (-0.83; 95%CI -1.30, -0.36; p<0.001), FEV_1%pred. (-34.91; 95%CI -48.92, -20.90; p<0.001), FVC%pred. (-22.73; 95%CI -32.84, -12.62; p<0.001), PEF%pred. (-44.18; 95%CI -61.52, -26.84; p<0.001) and MEP (-68.27; -102.48, -34.07; p<0.001). There were significantly large, negative correlations (r>0.5) between the number of years after surgery and FEV_1 (p=0.002), FEV_1%pred. (p=0.0001); and PEF%pred. (p=0.032).

Conclusions: This study has identified that aesthetic surgery for the removal of ribs 11 and 12 had a significant adverse effect on lung function and respiratory muscle strength in Jordanian females. The potential adverse effects should be carefully explained by surgeons to patients considering the surgery.

Keywords: respiratory; lung function; Ant-waist surgery; floating ribs removal surgery

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Authors' contributions: AA, MZD contributed to the study conception. MZD, AA and RB designed and prepared the study. RB, AAA, and AMS collected the data. SL and AA analysed the data. MZD, AA and SL wrote the first draft of the manuscript. All authors commented on previous versions of the manuscript, read, and approved the final manuscript.

Ethics approval and consent to participate: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. (Ethical approval from the Research Ethics Committee at the Faculty of Allied Medical Sciences at Applied Science No: AMS-2024-3). Private University (Reference No: AMS-2024-3) was undertaken. Signed informed consents were obtained from the participants.

Consent for publication: Written informed consent was obtained from all individuals participating in the study and all authors in this study provided formal consent for publication.

Availability of data and material: Available upon request.

Conflict of interest: Authors declare no competing interests related to this paper.

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Introduction

Perceptions of physical attraction and beauty may be influences by geographical location, ethnicity, culture, and demographic factors [1] and social media [2]. Consequently, body contouring surgery, a specialised field within plastic surgery has undergone significant advancements in recent years, influenced by the success of bariatric procedures, pharmacological interventions for patients experiencing substantial weight loss, and the refinement of lipomodelling techniques [3]. Numerous invasive and non-invasive procedures have been developed to enhance aesthetic appearance, such as correction of excess skin laxity and subcutaneous fat, which involves techniques such as liposuction and abdominoplasty [4]. These procedures refine the abdominal musculature and reduce waist circumference [3], whilst procedures such buttock augmentation involving liposuction, lipofilling, and intramuscular silicone implant placement are undertaken to achieve optimal buttock aesthetics [5].

The term "Ant-waist" has gained in popularity to describe the ideal waist-to-hip ratio for maximum aesthetic appeal, particularly in women and transgender populations, with post-surgical resection of the 11th and 12th rib (floating ribs) [5, 6]. A waist-to-hip ratio ranging from 0.65 to 0.70 has been reported to be the most highly attractive [1, 7]. Some individuals struggle to attain the desired waist-to-hip ratio after abdominoplasty and buttock augmentation surgeries due to inherent bony structures [5], therefore the surgical removal of the floating ribs to decrease waist-to-hip ratio may be considered [5].

The knowledge base related to the efficacy and safety of rib resection solely for aesthetic purposes is limited [6]. In a case-series report, Verdugo et al. [8], reported a low complication rate of two pneumothoraces in 104 patients who had undergone surgery across an 8-year period. However, only 10 of these patients had undergone exclusive rib removal surgery, with the majority undergoing a combination of resection, liposuction, and abdominoplasty.

A significant (p<0.01) post-operative decrease in forced vital capacity (FVC) has been reported in patients who have had multiple ribs removed during thoracic wall resection surgery for tumours [9]. Therefore, it is plausible that Ant-waist surgery may lead to respiratory complications due to several factors: 1) the floating ribs play a crucial role in protecting vital organs, including the lungs; 2) these ribs facilitate the expansion and retraction of the thoracic cavity during breathing as they are attachment sites for the external obliques, internal oblique, and transversus abdominis muscles that stabilise the thoracic cage and spine, 3) removal of the floating ribs alters the structural integrity of the rib cage, potentially impacting respiratory mechanics, such as decreased bucket handle movement [10].

Bucket handle movement contributes to the dynamic process of breathing by altering the dimensions of the thoracic cavity, allowing for effective ventilation of the lungs [10, 11]. During inspiration, bucket handle movement involves the lower ribs, but particularly the floating ribs, moving upwards and outwards, which increases the transverse diameter of the thoracic cage, effectively expanding the chest cavity laterally. The volume of the thoracic cavity increases, creating a negative pressure environment which facilitates the intake of air into the lungs [10]. Conversely, during expiration, the bucket handle movement reverses, with the lower ribs moving downwards and inwards, such that the transverse diameter of the thoracic cage decreases causing the chest cavity to contract laterally. The reduction in thoracic cavity volume increases the pressure within the lungs facilitating the expulsion of air [10, 11].

Surgical removal of the floating ribs may alter the mechanics of breathing and have an adverse effect on lung function. However, there are no published research that has assessed lung function or respiratory muscle strength in people who have undergone this surgery. Therefore, the aim of this study was to assess the effects of Ant-waist surgery on lung function and respiratory muscle strength.

Methods

Study design

A cross-sectional study with ethical approval from the Research Ethics Committee at the Faculty of Allied Medical Sciences at Applied Science Private University (Reference No: AMS-2024-3) was

undertaken. The study included an age and gender matched Ant-waist group and control group.

Recruitment of participants

Participants in the Ant-waist group were recruited through plastic surgery clinics in Jordan. Additionally, an invitation to participate in this study was posted on social media (e.g. Facebook and Instagram) to enhance the recruitment strategy. Due to the limited published data on Ant-waist surgery, a power-calculation to determine sample size was not undertaken.

Inclusion and exclusion criteria

Participants in the Ant-waist group were included if: 1) they had undergone the surgical removal of the 11^{th} and 12^{th} ribs; 2) surgery was not less than six months before the start of the study; 3) aged 18 years and over. Exclusion criteria for both groups included smokers; pregnancy; diagnosed cardiac, respiratory, musculoskeletal, or neurological conditions; or the individual had undergone any other surgery that might limit their exercise capacity or ability to perform spirometry.

Outcome measures

Spirometry

The gold standard lung function test, spirometry, was assessed using a calibrated spirometer (BTL Spirometry, United Kingdom) and in accordance with the American Thoracic Society & European Respiratory Society (ATS/ERS) standardised guidelines [12]. The best of three consecutive maximal expiratory manoeuvres were used to obtain the forced expiratory volume in the first second (FEV_1), FVC and the FEV_1/FVC ratio [12]. Results were compared with Global Lung Initiative normative multi-ethnic reference equations for age 3-95 years [13].

Respiratory muscle strength

Respiratory muscle strength was estimated by measuring maximal inspiratory pressure (MIP) and maximum expiratory pressure (MEP) using a portable mouth pressure device (MicroRPM, Cardinal Healthcare, UK). Participants were instructed to maximally and forcefully exhale after a maximal inhalation manoeuvre [14, 15].

Statistical analysis

All raw data were digitally retrieved and exported into a Microsoft Excel® spreadsheet (Redmond, Washington, USA), with FEV_1 and FVC data converted to percentage predicted (%pred.) using GLI 2012 Desktop Software for Large Data Sets [16]. Data were transferred for statistical analyses using IBM® SPSS® Statistics 24.0 (Chicago, IL, USA). The Shapiro–Wilk Test ($p>0.05$) was used to assess for the normal distribution of data, and comparisons of between-group spirometry data were performed using independent t-tests [17]. Numerical data are presented as mean, standard deviation (SD), and 95% confidence intervals (95%CI), with statistical significance established as $p\leq0.05$, unless otherwise stated. To explore the correlations, if any, between lung function, respiratory muscle strength, and number of years since surgery, bi-variate correlational analysis was conducted using the Pearson's correlation coefficient (r), such that $r<0.10$ was considered a small effect, $r>0.10$ to $r<0.50$ considered a moderate effect size, and $r>0.50$ a large effect size [18].

Results

A total of twenty-two (n=22) female Jordanian participants were recruited, with eleven (n=11) participants allocated to the Ant-waist group and eleven (n=11) age and gender matched participants allocated to the control group. All data were collected between March 2024 - April 2024. Table 1 shows the anthropometric data of the groups.

Lung function

Table 2 shows that there were significant between-group differences in FEV_1, FEV_1%pred., FVC%pred., FEV_1/FVC and PEF%pred., with the Ant-waist group demonstrating the lowest scores.

Table 1. Anthropometric results for both groups (n=22).

Variable	Ant-waist group	Control group	Mean difference (95%CI)*	*p*
Age	33.27±2.69	33.27±2.69	1.64 (-2.54, -2.54)	0.99
BMI (kg/m^2)	20.16±1.59	22.26±3.12	1.39 (-0.24, 4.44)	0.07
Years since surgery	3.00±1.18	-		

*Ant-waist group minus control group.

Table 2. Differences between Ant-waist group and control group in spirometry results.

Variable	Ant-waist group	Control group	Mean difference (95%CI)*	*p*
FEV_1 (L)	2.73±0.50	3.56±0.55	-0.83 (-1.30, -0.36)	<0.001**
FEV_1%pred.	69.64±8.42	104.55±20.62	-34.91 (-48.92, -20.90)	<0.001*
FVC (L)	4.16±0.83	4.30±0.59	-0.14 (-0.79, 0.50)	0.65
FVC%pred.	82.64±8.39	105.36±13.71	-22.73 (-32.84, -12.62)	<0.001**
FEV_1/FVC	0.67±0.17	0.83±0.64	-0.15 (-0.27, -0.04)	0.01**
PEF (L)	404.55±120.87	478.91±147.12	-76.36 (-196.41, 43.68)	0.20
PEF%pred.	70.73±16.08	114.91±22.39	-44.18 (-61.52, -26.84)	<0.001**

*Ant-waist group minus control group; **statistically significant.
FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; PEF, Peak expiratory flow.

Table 3. Difference in respiratory muscle strength results (mouth pressure) in both groups (n=22).

Variable	Ant-waist group	Control group	Mean difference (95%CI)*	*p*
MIP (cmH_2O)	109.18±25.40	104.18±25.40	5.00 (-20.52, 30.52)	0.69
MEP (cmH_2O)	70.45±11.71	191.18±39.52	-68.27 (-102.48, -34.07)	<0.001**

*Ant-waist group minus control group; **statistically significant.
MIP, Maximal inspiratory pressure; MEP, Maximal expiratory pressure; cmH_2O, centimetre of water.

Respiratory muscles strength

MIP was slightly higher in the Ant-waist group, but this difference was not significant. However, MEP was significantly lower (p<0.001) in the Ant-waist group, which may suggest greater respiratory muscle weakness (Table 3).

Correlations with years since Ant-waist surgery

The results of Pearson's correlation coefficient tests (Table 4) showed significant, negative, and large effects of number of years post-surgery and FEV_1 (*p*=0.002), FEV_1%pred. (p=0.0001); and PEF%pred. (p=0.032).

Discussion

This is the first study that has investigated the effects of Ant-waist surgeries on lung function and respiratory muscle strength, and the results showed that the surgery had a significant adverse effect on lung function and respiratory muscle strength. The study also showed that there were significant negative correlations between lung function and years since surgery in the Ant-waist group. These results suggest that that the negative impact of the surgery progresses with time and this impact should be explained to individuals considering this surgery.

It is difficult to draw comparisons due to the limited knowledge bank, however Hatano et al. [19], used

Table 4. Correlations between years since surgery and respiratory function in the Ant-waist group (n-11).

Variable		Years since Ant-waist surgery
FEV_1 (L)	*r*	-0.921*
	p	0.0001**
FEV_1%pred.	*r*	-0.813*
	p	0.002**
FVC (L)	*r*	-0.392
	p	0.233
FVC%pred.	*r*	-0.443
	p	0.172
FEV_1/FVC	*r*	-0.421
	p	0.198
PEF (L)	*r*	-0.394
	p	0.231
PEF%pred.	*r*	-0.646*
	p	0.032**
MIP (cmH_2O)	*r*	-0.067
	p	0.844
MEP (cmH_2O)	*r*	-0.238
	p	0.481

*Large effect size; **statistically significant.
FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; PEF, Peak expiratory flow; MIP, Maximal inspiratory pressure; MEP, Maximal expiratory pressure; cmH_2O, centimetre of water.

a three-dimensional computer simulation model to evaluate the biomechanical relationship between the location of rib defects and loss of respiratory function using data from 10 participants commuted tomography scans. Hatano et al. [19], reported that that the loss of lung function was greatest in the lateral-inferior part of the thorax, where the floating ribs are located. The rationale being that during inhalation, the ribs elevate and the external intercostal muscles contract, to increase the transverse diameter of the lungs causing the bucket handle movement of the ribs [10, 11]. The absence of the 11^{th} and 12^{th} ribs would likely limit the ability to inhale to total inspiratory capacity, as was demonstrated in this cross-sectional study, with the ant-waist group recording significantly lower FVC.

In a 25-years retrospective study (1975-2000) of chest wall-resections and reconstruction, Mansour et al. [20] evaluated the outcomes of 200 patients to determine the most common complications of the surgeries. Pneumonia (14%), acute respiratory distress syndrome (6%), and infection/sepsis (5%) were the most common adverse events recorded, with lung function impairment resulting from rib defects also reported. These findings were in contradiction to those reported by of Chiu et al. [5], who reported the effects of the surgical resection of the floating ribs in 5 patients (n=3, female; n=2, transgender) had minimal impact on lung function and no adverse effects were observed. However, given the sample size of this study, caution should be applied when comparing the results to the larger Mansour et al. [20] study, particularly as the Chiu et al. [5] relied on commentary from qualitative patient questionnaires and a survey related to dyspnoea, and did not assess lung function or respiratory muscles strength.

Strengths and limitations

The strength of this study is that it is the first to demonstrate a clear negative relationship between lung function and respiratory muscle strength in women who have undergone surgical removal of the 11^{th} and 12^{th} ribs. The outcomes of this study may be useful to surgeons and other clinicians when discussing the potential adverse effects of the surgery. However, it is important to consider the limitations of this study as the sample size was small and limited to Jordanian females only, and pre-surgical data related to lung function and respiratory muscle function were unavailable. Therefore, generalisability to the wider population should be judiciously considered. Nevertheless, the results of this study would suggest that more research in this area is warranted, particularly focussed on determining the differences between pre- and post-surgical effects on lung function.

Conclusion

This study has identified that aesthetic surgery for the removal of the floating ribs had an adverse effect on lung function and respiratory muscle strength in Jordanian females. These findings are important as

they may impact the decision-making of individuals considering this type of surgery, and the potential adverse effects should be carefully explained by surgeons. Further research is warranted, with a focus on multicentre and multi-national data so that robust comparisons can be made.

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Original research article

Impact of biological therapies on laboratory outcomes and FEV_1 in patients with severe eosinophilic asthma with chronic rhinosinusitis: a real-life study from Saudi Arabia

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ABSTRACT

Background: Few studies have addressed the effects of biological therapies on laboratory outcomes and changes in FEV_1 in patients with severe asthma (SA) and chronic rhinosinusitis (CRS). We aimed to study the effect of three biological therapies on laboratory outcomes and FEV_1 in Saudi Arabian patients with SA and CRS.

Methods: From March to September 2022, a retrospective observational cohort study was undertaken at the severe asthma clinics of the Armed Forces Hospital—Southern Region (AFHSR) and King Khalid University Hospital, Abha, Saudi Arabia, to delineate the effects of 3 biological therapies (benralizumab, dupilumab, and omalizumab) in adults with SA and concomitant CRS in terms of FEV_1 and laboratory parameters (serum IgE and eosinophilic counts).

Results: Eighty patients were enrolled, with a mean age of 46.68. There were 45 (56%) females and 35 (44%) males. There were significant improvements in FEV_1 and laboratory parameters (serum IgE and eosinophilic counts) after 6 & 12 months of biological therapies compared to pre-biological therapies ($p<0.001$, each). The response was different among different biological therapies. The improvements in FEV_1, serum IgE, and eosinophilic counts were manifest with benralizumab and dupilumab but not with omalizumab.

Conclusions: Results from the first study from two large Saudi Arabian tertiary centers for patients with severe asthma and chronic rhinosinusitis agree with and support those of worldwide real-life ones. One-year follow up of patients with SA and CRS showed the effectiveness of benralizumab and dupilumab, but not omalizumab, regarding FEV_1, serum IgE, and eosinophilic counts. Further prospective multicenter studies are warranted.

Key words: Severe asthma, chronic rhinosinusitis, FEV_1, IgE, eosinophils, outcomes, retrospective

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Ethics approval and consent to participate: The Armed Forces Hospital Southern Region (AFHSR) Institutional Review Board (IRB) approved the study, with Approval number AFHSRMREC/2022/PULMONOLOGY-INTERNAL MEDICINE/681. Since the study was a retrospective analysis, the IRB waived the need for written informed consent.

Availability of data and material: For the current study, the data are available from the corresponding author upon reasonable request from the requester(s).

Conflict of interest: The authors declare that they have no competing interests.

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Introduction

The definition of severe asthma (SA) is "asthma that requires therapy with high-dose inhaled corticosteroids (ICS) plus a second controller (e.g., long-acting beta-2 agonist (LABA), long-acting muscarinic antagonist (LAMA), leukotriene modifier and/o oral corticosteroids (OCS) to prevent it from becoming "uncontrolled" or that remains uncontrolled despite such therapy" [1,2]. SA affects 3-10% of asthma patients and is associated with increased mortality, hospitalization, decreased quality of life, and higher healthcare costs [1].

Chronic rhinosinusitis (CRS) affects patients worldwide, with a prevalence rate of 6.95–13% [3], and the burden of medical expenses caused by it is exceptionally high. Depending on the presence or absence of nasal polyps (NPs), CRS can be classified as CRS with NPs (CRSwNP) or CRS without NPs (CRSsNP) [4].

Chronic Rhinosinusitis with nasal polyposis (CRSwNP) coexists in over 30% of persons with severe asthma, with or without aspirin-exacerbated respiratory disease (AERD) [5]. CRSwNP has a high rate of recurrence after sinonasal surgery, can be refractory to topical nasal therapies, and can be effectively treated by biologics, with dupilumab, omalizumab, and mepolizumab having a regulatory indication separate from asthma [6].

Many worldwide studies have addressed the impact of biological therapies in patients with SA combined with CRS [7-9]. However, few studies have focused on the effects of those therapies in terms of laboratory outcomes and changes in FEV_1 [10]. Recently, an interesting systematic review of the literature was conducted to address the role of biological therapies in lung function and quality of life in patients with SA and CRSwNP [11]. It concluded that using biological therapies is associated with significant improvements in lung function and quality of life in patients with SA and CRSwNP.

To the best of our knowledge, no studies addressed the impact of biological therapies on laboratory outcomes and FEV_1 in Saudi Arabian patients with SA and CRS. Therefore, the current research aims to study the effect of three biological therapies on laboratory outcomes and FEV_1 in Saudi Arabian patients with SA and CRS admitted to two large tertiary centers.

Materials and methods

Study design and population

The current research is a retrospective observational cohort study undertaken at the severe asthma clinics of the Armed Forces Hospital—Southern Region (AFHSR) and King Khalid University Hospital, Abha, Saudi Arabia, from March to September 2022. This study aimed to delineate the effects of biological therapy in adults with severe eosinophilic asthma and concomitant CRS who were maintained on medium to high ICS, LABA, and LAMA, with some receiving montelukast, in terms of laboratory outcomes and FEV_1. Outcomes assessed included routine clinic evaluations, exacerbation frequency, hospitalization rates, oral corticosteroid (OC) use, Asthma Control Test (ACT) scores, FEV_1, serum IgE, and eosinophilic counts from the year before to the year after initiating biological therapy.

Inclusion and exclusion criteria

Participants were adults (≥ 18 years) diagnosed with SA as per the diagnostic criteria of the Global Initiative for Asthma; GINA 2023 guidelines [1] and concomitant Rhinosinusitis, meeting criteria from Orlandi et al. [2]. Exclusion criteria were chest X-ray abnormalities suggestive of interstitial lung disease (ILD), Type 2 low asthma, patients with allergic bronchopulmonary aspergillosis (ABPA), patients with eosinophilic granulomatosis with polyangiitis (EGPA) or having positive anti-nuclear cytoplasmic antibodies (ANCA), patients with hemoglobin <10 g/dl, those with significant cardiac or autoimmune conditions, fixed or irreversible airway obstruction, paradoxical vocal fold motion, and those with documented history or high resolution computed tomography (HRCT) findings of bronchiectasis or ILD.

Assessments

Clinical Assessment: Routine clinic evaluations included biannual serum eosinophils, IgE measurements, and pulmonary function tests (PFTs). ACT scores were recorded semiannually and retrieved from the patient's medical records. Chronic Rhinosinusitis (CRS) was assessed per the criteria from Orlandi et al. [2].

ACT: ACT scores, ranging from 5 to 25, assessed asthma control levels, with higher scores indicating better management [12]. FEV_1: Pulmonary function was measured using spirometry equipment according to ATS recommendations [13]. For FEV_1, the largest values from three acceptable efforts were recorded. Serum IgE and eosinophilic count were assessed one year before, six months after, and twelve months after biological therapies.

Biological therapy indication: biological therapy followed the ERS/ATS 2020 recommendations [14], with the anti-IL-5 benralizumab initiated at eosinophil counts ≥150 μL–1 and omalizumab considered at counts ≥260 μL–1. Dupilumab served as an adjunct for those inadequately controlled on conventional regimens.

Outcome measures and data collection

Data encompassing demographics, clinical evaluations, laboratory results, FEV_1, and treatment histories were systematically extracted from electronic health records for analysis.

Ethical considerations

The Armed Forces Hospital Southern Region (AFHSR) Institutional Review Board (IRB) approved the study, with Approval number AFHSRMREC/2022/PULMONOLOGY-INTERNAL MEDICINE/681. Since the study was a retrospective analysis, the IRB waived the need for written informed consent.

Statistical analyses

Descriptive data were expressed as mean±SD for normally distributed variables and median (IQR) for non-normally distributed ones, while frequencies and percentages were used with categorical variables. The three biological treatment groups were compared using One-way ANOVA or the Kruskal-Wallis test for numerical variables. In contrast, the Chi-square test was utilized for categorical variables. Treatment response before biological therapy, six months, and 12 months after biologic therapy was compared using repeated measures ANOVA for numerical variables, or Cochrane Q test for categorical variables, while the comparison between pre-treatment and 12 months after was done using paired-samples t-test, Wilcoxon signed rank test or McNemar test. $P < 0.05$ is statistically significant, and IBM SPSS for Windows version 29 was used for the statistical analysis.

Results

Baseline (pre-biologics) demographics, laboratory, and FEV_1 characteristics

Eighty patients were enrolled in the current study, with a mean age of 46.68 ± 12.81 years, and they were 45 (56%) females and 35 (44%) males. The mean body mass index (BMI) was 31.14 ± 4.68 kg/m^2, with obesity found in 49 (61%) patients. Chronic rhinosinusitis (CRS) was a comorbid disease in all patients. The following most common comorbidities were nasal polyps (34/80,42%) and gastro-oesophageal reflux disease, GERD (28/80,35%), respectively.

Table 1. Baseline demographics, laboratory, and FEV_1 characteristics of the enrolled patients (N=80).

		N (%)
Age	Mean ± SD	46.68 ± 12.81
	Min - Max	18 - 83
Sex	Male	35 (43.75%)
	Female	45 (56.25%)
BMI	Mean ± SD	31.14 ± 4.68
	Min - Max	18.57 - 46.2
Obesity	No	31 (38.75%)
	Yes	49 (61.25%)
	Min - Max	1 - 5
Asthma duration (years)	Mean ± SD	9.25 ± 4.76
	Min - Max	1 - 25
Exacerbations/year (before the biologics)	Mean ± SD	2.35 ± 0.92
	Min - Max	1 - 5
Comorbidities		
GERD		28 (35.44%)
Anxiety		27 (33.75%)
ACO		4 (5%)
Chronic rhinosinusitis		80 (100%)
OSA		10 (12.5%)
Nasal polyps		34 (42.5%)
Pre FEV_1%	Mean ± SD	54.82 ± 8.83
	Min - Max	33 - 78
Pre IgE	Mean ± SD	353.81 ± 249.81
	Min - Max	21 - 1150
Pre Eosinophils	Mean ± SD	666.23 ± 352.27
	Min - Max	100 - 1600

BMI, Body mass index; GERD, gastroesophageal reflux disease; ACO, Asthma-COPD overlap; OSA, obstructive sleep apnea; OCS, oral corticosteroid; ICS, inhaled corticosteroids; LABA, long-acting beta-2 agonist; LAMA, long-acting muscarinic antagonist.

The mean baseline FEV_1 values were 54.82 ± 8.83 ml. The mean serum IgE and eosinophilic counts were 353.81 ± 249.81 IU/ml and 666.23 ± 352.27 μL–1, respectively. Table 1 shows these results.

Asthma medications and biological therapies

Before biological therapies, all the study subjects received the standard therapies for severe asthma: high-dose ICs, LABA, and LAMA. Remarkably, all patients received OCs.

Regarding biological therapies, omalizumab, benralizumab, and dupilumab were used in 8 (10.0%), 22 (27.5%), and 50 (62.5%) patients, respectively (Table 2).

Characteristically, we noticed no significant differences in demographics, comorbidities, or asthma exacerbations per year among patients who received omalizumab, benralizumab, or dupilumab, respectively. Only for pre-treatment serum IgE, there was a significant difference among patients who used benralizumab, dupilumab, and omalizumab (p=0.024), respectively. The pre-treatment mean serum IgE level was the highest in patients who received dupilumab (405.43 ± 291.09 IU/ml), while it was the lowest in those who received benralizumab (259.36 ± 121.76 IU/ml), and it was 290.88 ± 122.61 IU/ml in those who received omalizumab, respectively. (Table 2)

Treatment response (before and after biological therapies)

There were significant improvements in FEV_1 and laboratory parameters (serum IgE and eosinophilic counts) after 6 &12 months of biological therapies compared to pre-biological therapies (p<0.001, each). There was a significant increase of pre-biologics FEV_1 from 54.82 ± 8.83 ml to 65.47 ± 9.49 ml and 68.44 ± 8.04 ml after 6 &12 months of biological therapies, respectively (p<0.001). There was a significant decrease of pre-biologics serum IgE from 353.81±249.81 IU/ml to 161.91±144.69 IU/ml and 115.10±93.21 IU/ml, after 6 &12 months of biological therapies, respectively (p<0.001). Also, there was a significant decrease of pre-biologics serum eosinophilic counts from 666.23 ± 352.27 μL–1 to 339.08 ± 321.48 μL–1 and 242.25 ± 212.01 μL–1 after 6 &12 months of biological therapies, respectively (p<0.001) (Table 3).

Treatment response before and after individual biological therapies

There was a significant increase in the FEV_1 6 and 12 months after, compared to the year before benralizumab and dupilumab (p<0.001). There were statistically significant decreases in serum IgE and eosinophilic counts 6 and 12 months after, compared to

Table 2. General characteristics, FEV_1, and lab findings according to the used biologic drugs.

		Benralizumab (N=22)	Dupilumab (N=50)	Omalizumab (N=8)	P
Age (years)	Mean ± SD	45.64 ± 8.52	46.56 ± 13.93	50.25 ± 16.08	0.685[+]
BMI	Mean ± SD	32.75 ± 3.46	30.52 ± 4.27	30.52 ± 8.49	0.099[+]
Sex	Male	9 (40.9%)	23 (46%)	3 (37.5%)	0.838[+++]
	Female	13 (59.1%)	27 (54%)	5 (62.5%)	
Exacerbations/year (pre)	Mean ± SD	2.51 ± 0.82	2.32 ± 0.94	2.13 ± 1.13	0.572[+]
BA duration years	Mean ± SD	8.05 ± 1.96	9.26 ± 5.28	12.5 ± 5.73	0.079[+]
Pre Eosinophils	Median (IQR)	666.23 (274.75)	563.5 (639.25)	415 (315)	0.149[++]
Pre IgE	Mean ± SD	259.36 ± 121.76	405.43 ± 291.09	290.88 ± 122.61	0.024[+]
Pre FEV_1%	Median (IQR)	54.82 (10)	55 (12)	52 (21.25)	0.641[++]

[+] One-way ANOVA test, [++] Kruskal Wallis test, [+++] Chi-square test, Games-Howell method was used for *post-hoc* pairwise comparison.

Table 3. Treatment response before, compared to 6 and 12 months after biological therapies.

	Before the biological therapy	6 months after the biological therapy	12 months after the biological therapy	P
ACT (Mean ± SD)	13.40±2.32	19.12±2.83	19.25±2.54	<0.001
Frequency of exacerbation Median (IQR)	2 (1)		0 (0)	<0.001
Frequency of hospitalization Median (IQR)	1 (0)		0 (0)	<0.001
OCs use, N(%)	80(100%)	9(11.3%)	3(3.8%)	<0.001
FEV_1%	54.82 ± 8.83	65.47 ± 9.49	68.44 ± 8.04	<0.001
IgE	353.81±249.81	161.91±144.69	115.10±93.21	<0.001
Eosinophils	666.23 ± 352.27	339.08 ± 321.48	242.25 ± 212.01	<0.001

the year before benralizumab and dupilumab (p<0.001, each).

On the other hand, there were no statistical differences in FEV_1 6 and 12 months after compared to the year before omalizumab (p=0.286). There was a borderline statistically insignificant decrease in serum IgE (p=0.053) and a non-significant decrease in the eosinophilic count (p=0.131), 6 and 12 months after compared to the year before omalizumab, respectively (Table 4 details these results).

Discussion

To the best of our knowledge, this is the first real-world study that addresses the impacts of biological therapies on FEV_1 and laboratory outcomes in patients with severe asthma combined with CRS in Saudi Arabia, followed at two large tertiary centers. The current study followed patients with severe asthma who received biological therapies for 12 months. Interestingly, previous studies had shorter follow up durations [10].

Current advances in our understanding of asthma heterogeneity and the molecular mechanisms underlying airway inflammation have led us to treat asthma as subtypes based on inflammatory mechanisms or endotypes [15]. The paradigm of 2 endotypes, type 2 high and type 2 low, has emerged in recent years [15,16]. Type 2 (T2) immune responses, attributed to subsets of CD4 + T cells known as T helper two cells (Th2) that produce interleukins 4, 5, and 13 (IL4, IL5, IL13), have classically been associated with

Table 4. Treatment response before 6 months, and 12 months after biologic therapy in different treatments.

	Before the biologic therapy	6 months after the biologic therapy	12 months after the biologic therapy	P
Benralizumab				
ACT	13.89±2.17	18.91±2.29	19.01±1.72	<0.001
OCs use	22 (100%)	0 (0%)	0 (0%)	<0.001
FEV_1%	56.86±6.34	67.34±9.56	71.76±6.93	<0.001
IgE	259.36±121.76	214.1±132.4	135.68±81.39	<0.001
Eosinophils	746.78±350.15	152.65±124.19	94.83±86.87	<0.001
Dupilumab				
ACT	13.63±2.62	18.13±1.55	19±1.85	<0.001
OCs use	50 (100%)	6 (12%)	2 (4%)	<0.001
FEV_1%	53.58±9.05	65.11±8.82	67.05±7.07	<0.001
IgE	405.43±291.09	131.93±149.33	96.11±94.88	<0.001
Eosinophils	657.79±363.24		295.77±198.90	<0.001
Omalizumab				
ACT	13.63±2.62	18.13±1.55	19±1.85	<0.001
OCs use	8 (100%)	3 (37.5%)	1 (12.5%)	0.004
FEV_1%	57.00±12.49	62.63±13.30	68.00±13.66	0.286
IgE	290.88±122.61	205.76±101.96	177.25±82.69	0.053
Eosinophils	497.50±235.78	-	313.13±336.46	0.131

eosinophilic airway inflammation and atopic disease [16]. This study showed significant improvements in FEV_1 and laboratory parameters after 6 & 12 months of biological therapies compared to those before use. Recently, a systematic search was conducted to address the effectiveness of biologics in terms of lung function as well as quality of life in patients with severe asthma and CRSwNP [11].

Results revealed that significant FEV_1 improvements were consistently observed after 24 weeks of treatment, as shown in real-world studies that enrolled variable proportions of patients with severe asthma/CRSwNP [11].

Our results agree with and support the effectiveness of biological therapies in addressing the underlying inflammatory processes driving severe uncontrolled asthma and CRSwNP. Improving lung function is crucial as it is associated with reduced symptoms, enhanced exercise capacity, and improved quality of life for asthma patients [7-10]. Our study showed a significant decrease in pre-biologics serum IgE and eosinophilic counts after 6 and 12 months of biological therapies, respectively.

These results are in concordance with previous ones [7,8,10,17]. In their study, Khan and colleagues [10] observed that, after six months, biological treatment for 30 patients significantly reduced eosinophils (540 cells/μL to 290 cells/μL) and IgE levels (410 IU/mL to 280 IU/mL). Notably, the reduction in eosinophil levels post-biologic therapy is consistent with the mechanism of action of these agents, which specifically target eosinophilic inflammation [5, 6, 9].

The combination of severe asthma with chronic rhinosinusitis (CRS), particularly CRS with nasal polyposis (CRSwNP), presents a unique phenotype, and the relationship between asthma and CRSwNP is not just a simple association. Core pathophysiological mechanisms are shared, with T2 inflammation being the cornerstone of these disorders. This T2 inflammation strongly impacts the symptoms and burdens of both diseases. Thus, patients who have severe asthma will often experience severe CRSwNP symptoms, too,

and vice versa [4,18]. Consequently, one may expect a better response to biological treatment in patients with SA and CRSwNP. This is evident in reducing asthma exacerbations, using maintenance steroids, and improving lung function, control, and quality of life [18,19].

In the current study, the results of treatment response before and after individual biological therapies were interesting.

Laboratory outcomes and FEV_1 were significantly improved after 6 and 12 months of benralizumab and dupilumb. However, for omalizumab, there were no statistical differences in FEV_1 after its use. There was a borderline statistically insignificant decrease in serum IgE and a non-significant decrease in the eosinophilic count after its use compared to the year before omalizumab, respectively. The clinician should consider these differences in response among biological therapies when choosing a particular biologic for a patient category. Previous reports had demonstrated differences in responses among patients with severe asthma and those with SA and CRS for different biological therapies [11, 17, 20].

Recent reports have shown that dupilumab may be more effective than omalizumab and mepolizumab in decreasing asthma-related exacerbations and improving lung function [20, 21]. The greater effectiveness of dupilumab may be related to its mechanism of action. Dupilumab is a broad-spectrum type 2" biologic. It blocks IL-4 and IL-13 signaling, decreasing the B-cell class switch to IgE.33 In addition, it prevents differentiation of naive TH cells to TH2 cells, thus decreasing canonical TH2 cytokines such as IL-5– and IL-5–induced eosinophil recruitment, the mechanism deployed by the anti–IL–5, mepolizumab [6, 9, 21]. By blocking IL-13, dupilumab may also affect airway hyperreactivity, goblet cell hyperplasia, and smooth muscle dysfunction associated with asthma, and it may account for dupilumab's remarkable effect in improving prebronchodilator FEV_1 value [6, 9, 21].

In a real-world study from Italy [22], 137 patients with late-onset asthma were treated with benralizumab for 24 weeks. Among them, 79 (57.7%) presented with CRwNP. Again, a real-life study from Italy [23] included 123 severe asthma patients, of whom 17 (13.8%) had comorbid CRSwNP. After using omalizumab, there was no significant difference in ACQ, FEV_1, or annual exacerbation rate between those with CRSwNP and those without NP. However, the proportion of patients who improved all three outcomes was numerically more significant in the CRSwNP group (35.7% vs. 23.0%) [23].

On the other hand, in another real-life study [24] with 24 patients with severe allergic asthma and CRSwNP, a 6-month treatment with omalizumab resulted in significant improvements in asthma outcomes (symptoms, rescue medication, ACT, lung function, exacerbations) and sinonasal symptoms but not on nasal polyp endoscopic score [24].

Overall, the results of the current study have important implications for daily clinical practice. Applying a multidisciplinary approach to managing patients with SA and CRS is still a challenge and an unmet need. Given the lack of recommendations for joint management in current clinical practice guidelines [1,4], an evidence-based approach could help decision-making processes.

Given the importance of including lung function and QOL among the primary outcomes of studies in patients with asthma and CRSwNP, future research could analyze the potential correlation between these outcomes.

Our study has many strengths. It is the first Saudi Arabian real-world study on biologics' effectiveness in FEV_1, laboratory, and nasal outcomes in patients with severe asthma and chronic Rhinosinusitis. Our one-year follow up period was also more extended than most similar studies. The number of enrolled patients gives the results considerable robustness. However, our study has several limitations. This is a retrospective study, which is affected by the limitations of retrospective studies. Also, fractional exhaled nitric oxide (FeNO) was not available to assess the enrolled subjects. Further Saudi studies are needed to provide an in-depth understanding of the baseline characteristics of patients with multimorbid conditions and allow a more comprehensive evaluation of the effect of biologics in patients with both SA and CRS.

Conclusions

Results from the first study from two large Saudi Arabian tertiary centers for patients with severe asthma

and chronic rhinosinusitis agree with and support those of worldwide real-life ones. One-year follow up of patients with SA and CRS showed the effectiveness of benralizumab and dupilumab regarding FEV_1, serum IgE, and eosinophilic counts. For omalizumab, there were neither improvements in FEV_1 nor eosinophilic counts and a borderline decrease in serum IgE, respectively. Further prospective multicenter studies are warranted.

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Original Article

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Inter-societal Survey on the topical nasal treatments in Italy

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ABSTRACT

Topical nasal therapy represents a widespread opportunity to treat upper airway diseases. As a result, specialists in different areas (mainly ENT, pediatrics, and allergology) and general practitioners prescribe intranasal compounds. However, a myriad of products and devices are available, as well as respiratory disorders. Consequently, this matter is debatable, and no guideline organically addresses this issue.

Considering these premises, a restricted panel of qualified experts promoted an initial multidisciplinary survey involving only Fellows of some Scientific Societies belonging to ENT, pediatrics, and allergology areas. The survey included a series of queries concerning practical aspects of topical nasal therapy (treated disease, devices, and agents). A web platform served to participate in this survey. Each participant anonymously completed the questionnaire.

Four hundred and forty-five doctors participated in the survey. There was a homogeneous distribution in Italy. Most participants were pediatricians (37%), followed by allergologists (31%) and ENT specialists (24%). Almost all doctors (95%) used topical nasal therapy. The most common diseases topically treated were allergic rhinitis (79%), chronic rhinosinusitis (73%), and non-allergic rhinitis. The most popular devices were pre-dosed spray both for nasal irrigation (67%) and nebulization (66%). Corticosteroids (67%), isotonic saline (63%), hyaluronic acid, hypertonic saline, and antihistamines (39%) were the most common agents used for intranasal therapy. Combined antihistamine/corticosteroids were also commonly used (38%). The most frequent schedule was the cyclic treatment. Most doctors (89%) claim they adequately spend time educating patients on this matter.

In conclusion, topical nasal therapy is commonly used to manage upper respiratory diseases. However, the disagreement about some issues requires greater knowledge of the topics and the need to develop new studies, including pragmatic ones.

Key words: topical nasal therapy, device, upper respiratory diseases, agents, survey

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Ethics approval and consent to participate: It was a Delphi Consensus among doctors.

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Introduction

The nose is a gateway for pathogens, pollutants, allergens, and harmful substances, so inflammatory and infectious disorders are expected to happen in the nose and may spread to respiratory airways. However, the nose presents the advantage of being topically treated. Namely, topical nasal therapy is an approach known since ancient times. As a result, topical nasal therapy represents a popular way to administer different compounds directly into the nose.

On the other hand, topical nasal therapy constitutes an extended matter regarding treated disease, used devices, and prescribed agents. Moreover, no guidelines specifically or organically address this multifaceted issue.

A recent Intersocietal Delphi Consensus evaluated some debated perspectives about topical nasal therapy [1]. This Delphi Consensus provided interesting outcomes reinforced by the participation of 14 Scientific Societies involving ENT, pediatrics, and allergology areas. However, this Delphi Consensus reported a particular discrepancy among participants' agreements. Namely, the second round involved a panel of qualified experts who discussed and voted on the statements face-to-face, reaching a high consensus on all statements. On the contrary, the third round collected agreement grades through a web platform, reducing the agreement grade on some statements. This dichotomous behavior might hypothetically depend on an incomplete knowledge of some aspects of topical nasal therapy, a prerogative of some specialists. This gap could reflect a different approach to managing upper airway disorders.

Based on this background, the steering committee of the Intersocietal Delphi Consensus on topical nasal therapy decided to conduct an initial nationwide survey involving a large number of Italian specialists on this matter. The steering committee excluded general practitioners as a further survey should specifically consider them.

Therefore, the present Intersocietal Survey faced this theme by proposing a questionnaire to doctors who are Fellows of Scientific Societies in the ENT, pediatrics, and allergology areas. This survey aimed to collect and analyze information about the practical use of topical nasal therapy in Italy.

Materials and methods

Questionnaire

A panel of experts (some authors of this article, such as A.V., L.P., I.L.M., and G.C.) came together to form an *ad hoc* steering committee. The steering committee prepared a specific questionnaire aimed at specialists involved in managing upper airway diseases. The questionnaire consisted of questions regarding the geographic area of work, postgraduate work, and specific issues on topical nasal therapy.

The survey explored three main areas of topical nasal therapy use in clinical practice, mainly concerning the diseases treated, devices used, and prescribed agents.

Table 1, in detail, reports the single questions proposed in the survey.

Table 1. Questions included in the Intersocietal Survey on use of topical nasal therapy in Italy and answers.

Questions	Main answers
In which geographical area do you practice: North-West, North-East, Centre, South, Islands?	North-West 27.2% South 25.2% Centre 21.8% North-East 13.5% Islands 11.2%
Are you a specialist in: ENT, Pediatrics, Allergology?	Pediatrics 36.6% Allergology 31.5% ENT 24.3%
Do you use topical nasal therapy?	Yes 95.3%

Questions	Main answers
In which disease you use it (% of patients): • Vasomotor rhinitis • Allergic rhinitis • Non-allergic rhinitis • Viral rhinitis • Bacterial rhinitis • Atrophic rhinitis • Acute rhinosinusitis • Chronic rhinosinusitis with nasal polyps • Chronic rhinosinusitis without nasal polyps • Acute nasopharyngitis • Chronic nasopharyngitis • Acute adenoiditis • Chronic adenoiditis	Allergic rhinitis 79.1% Chronic rhinosinusitis with nasal polyps 78.6% Chronic rhinosinusitis without nasal polyps 73.1% Non-allergic rhinitis 72.0% Chronic adenoiditis 69.2% Acute rhinosinusitis 67.9% Acute adenoiditis 62.2% Bacterial rhinitis 56.3% Viral rhinitis 54.5% Chronic nasopharyngitis 50.4% Acute nasopharyngitis 47.5% Atrophic rhinitis 46.0% Vasomotor rhinitis 44.8%
What devices do you use? If yes, in what % of patients? **<u>Nasal Irrigation:</u>** • Simple syringe • Vials • Pre-dosed sprays • High-volume and low-pressure devices • Low-volume and high-pressure devices • Pressure-less drop devices • Mechanical nebulizer • Ultra-sound nebulizer **<u>Nebulization:</u>** • Pre-dosed sprays • Atomizers as nasal spray • Atomizers as micronized douche • Nasal douches as manual micronized • Nasal douches as pneumatic micronized • Nasal hairpin (Y)	**<u>Nasal Irrigation:</u>** Pre-dosed sprays 63.6% Simple syringe 43.1% Low-volume and high-pressure devices 40.2% High-volume and low-pressure devices 38.7% Vials 30.3% Pressure-less drop devices 27.0% **<u>Nebulization:</u>** Pre-dosed sprays 66.1% Nasal douches as pneumatic micronized 46.4% Nasal douches as manual micronized 39.6% Atomizers as nasal spray 36.3% Nasal hairpin (Y) 22.2%
What substances do you prescribe? If yes, in what % of patients? • Isotonic saline solution • Hypertonic saline solution • Vasoconstrictors • Corticosteroids • Antihistamines • Combined antihistamines/corticosteroids • Antivirals • Antibacterials • Natural antiseptics • Hyaluronic acid • Natural agents	Corticosteroids 67.2% Isotonic saline solution 63.0% Hyaluronic acid 39.6% Hypertonic saline solution 39.3% Antihistamines 39.1% Combined antihistamines/corticosteroids 37.6% Antibacterials 27.9% Natural antiseptics 20.1% Natural agents 15.9% Antivirals 14.2% Vasoconstrictors 8.5%
Do you use topical treatment in cycles?	Yes 88.8%
Do you use topical therapy continuously?	No 58.2%
Do you use topical treatment as needed?	Yes 53.4%
Do you explain to the patient how to use the various devices, their maintenance and durability?	Yes 89.4%

The survey consisted of administering the questionnaire to the participants, which the steering committee approved. For this purpose, a provider agency (Lingomed: a provider of ECM) set up a web platform allowing anonymous participation.

The invited participants were the Fellows of the same Scientific Societies involved in the Delphi Consensus on topical nasal therapy. Each Society's institutional website publicized the initiative with a specific banner and a link directly to the survey's web platform. Thus, all Fellows of each Society were the target of this initiative.

Table 2 lists the Scientific Societies adhering to the present initiative.

The participants anonymously completed the questionnaire using the same platform.

After collecting and analyzing the results, the steering committee discussed the results.

The survey process was conducted between April 2024 and May 2024.

Answers assessment

The scientific committee discussed the results in a virtual meeting. The statistical analysis was descriptive.

Table 2. List of Scientific Societies adhering to the initiative of a survey on topical nasal therapy.

Associazione Italiana Otorinolaringoiatri Libero Professionisti (AIOLP)
Associazione Allergologi Immunologi Italiani Territoriali e Ospedalieri (AAIITO)
Società Italiana di Allergologia e Immunologia Pediatrica (SIAIP)
Società Italiana di Otorinolaringoiatria e Chirurgia Cervico Facciale (SIOeChCF)
Società Italiana di Allergologia e Immunologia Pediatrica (SIAIP)
Società Italiana di Otorinolaringologia Pediatrica (SIOP)
Associazione Ospedaliera Italia Centromeridionale Otorinolaringoiatrica (AOICO)
Accademia Italiana di Citologia Nasale (AICNA)
Società Italiana di Otorinolaringologia Pediatrica (SIOP)
Società Italiana per le Malattie Respiratorie Infantili (SIMRI)
Accademia Italiana di Rinologia (IAR)
Società Italiana di Otorinolaringoiatria e Chirurgia Cervico Facciale (SIOeChCF)
Società Italiana di Allergologia e Immunologia Pediatrica (SIAIP)
Società Italiana di Otorinolaringoiatria e Chirurgia Cervico Facciale (SIOeChCF)
Società Italiana di Rinologia (SIR)
Società Italiana di Otorinolaringoiatria e Chirurgia Cervico Facciale (SIOeChCF)
Società Italiana di Allergologia, Asma ed Immunologia Clinica (SIAAIC)
Società Italiana di Allergologia e Immunologia Pediatrica (SIAIP)
Società Italiana di Pediatria Preventiva e Sociale (SIPPS)
Associazione Italiana Vie Aeree Superiori (AIVAS)

Results

Table 1, in detail, reports the answers to the questions included in the survey.

The geographic distribution of participants was fairly representative of the existing population in the various geographical areas, except for the North-East, where the population is the 19.6% of the Italian nation. The most represented group of participants was pediatricians (36.6%), followed by allergologists (31.5%) and ENT specialists (24.3%). These frequencies do not reflect the real number of different specialists, as ENT specialists are more numerous than allergologists.

Almost all participants (95.3%) declared to use topical nasal therapy.

The most common respiratory diseases treated through topical nasal therapy were allergic rhinitis (79.1%), chronic rhinosinusitis (mainly if associated with nasal polyps: 78.6%), non-allergic rhinitis (72%), adenoiditis (mostly if chronic: 69.2%), acute rhinosinusitis (67.9%), bacterial rhinitis (56.3%), viral rhinitis (54.5%), chronic nasopharyngitis (50.4%), and acute nasopharyngitis (47.5%).

Regarding the devices used, two main types were considered: nasal irrigation and nebulization. As regards nasal irrigation, pre-dosed spray was the most common device (63.6%), followed by simple syringe (43.1%), low-volume and high-pressure devices (40.2%), and high-volume and low-pressure systems (38.7%).

As concerns the prescribed agents, intranasal corticosteroids were the most frequent drugs (67.2%), followed by isotonic saline (63%), hyaluronic acid (39.6%), hypertonic saline (39.3%), antihistamines (39.1%), antibacterials (27.9%), natural antiseptics (20.1%), natural agents 15.9% and antivirals (14.2%).

Combined antihistamine/corticosteroids were also commonly used (37.6%). The most frequent schedule was the cyclic treatment, as recommended by 88.8% of participants. Continuous treatment was prescribed by 41.8%, and on-demand treatment was advised by 53.4%.

Most doctors (89%) adequately spent time educating patients on this matter.

Discussion and conclusion

Topical nasal therapy has some advantages compared to systemic one as it is more rapid and effective, allows a better distribution into the nasal cavity, and considerably reduces the dosage and, consequently, side effects [2]. However, topical nasal therapy is an umbrella term that collects different diseases, devices, and agents. In addition, many specialists follow this approach, and no guideline organically faces this issue. As a result, topical nasal therapy is a complex matter and presents some controversial aspects.

The present survey aimed to portray its actual use in Italian clinical practice. This initiative followed a previous Intersocietal Delphi Consensus that involved a panel of experts in this field designed by 14 Italian Scientific Societies concerning this therapeutic area. That document reported a discrepancy in the agreement grade between qualified and other experts (manuscript submitted). This misalignment may depend on the specific knowledge of this matter owned by the different specializations. In addition, personal attitude may contribute to understanding this treatment route.

Therefore, the present survey provided information that reflects the real practice in Italy regarding this therapeutic modality.

Interestingly, pediatricians were the most represented specialists, followed by allergologists, and ENT specialists. However, it has to be underlined that many ENT specialists are surgeons; indeed, a substantial part of ENT discipline is surgical and does not concern the medical therapy.

Anyway, almost all participants (95.3%) used topical nasal therapy. This high percentage might depend on the fact that overall, doctors using topical nasal therapy participated in the survey.

Allergic and non-allergic rhinitis are frequently treated using topical agents. Despite the duration and presence of polyps, rhinosinusitis and adenoiditis consistently represent the most common diseases topically treated. The high percentage of participants who were favorable to topically treating these diseases may depend on the dissemination of specific guidelines and position papers [3-8].

Regarding the devices used for administering topical therapy, a first distinction should consider nasal irrigation and nebulization separately. As defined by several studies, nasal irrigation does not medicate the airways *per se* [9-11]. However, the saline nasal irrigation, as recently underlined by a Cochrane analysis, may reduce the symptom severity perceived by patients (children and adults) with allergic rhinitis [12].

Actually, nasal irrigation washes the nose and prepares it to better respond to treatments [13]. On the contrary, nebulization represents the correct way to administer intranasal therapy [14]. The most crucial point is the dimension of the particles generated by the different devices, such as the mass median aerodynamic diameter (MMAD). The correct diameter should be between 10 and 50 μm [15]. Accordingly, the pre-dosed spray was the most used device, as it guarantees an adequate dimension, assuring a complete distribution through the nasal cavity, but not in the nasopharynx, in the paranasal sinus and in Eustachian tube [16]. However, nasal micronized douches and some nasal atomizers are devices suitable for the treatment of nasopharynx, as it plays a pathophysiological 'carrefour' role, in respiratory diseases, being the site of: post-nasal drip, respiratory microbiome of the upper airways, possible bacterial biofilms, cause of recurrence of infections.

Compounds used in topical nasal therapy: Corticosteroids were the preferred molecules, followed by saline solution (mostly isotonic) and hyaluronic acid.

Antihistamines and combined antihistamine/corticosteroid medications were also frequently prescribed. These results are consistent with the guidelines' and position papers' recommendations to dampen inflammation, remove secretions, and relieve symptoms [2-8].

Regarding infections, a fair percentage of participants, use antibacterial and antiviral drugs, such as: antibacterials (27.9%), natural antiseptics (20.1%), natural agents (15.9%), and antivirals (14.2%). In this regard, natural antiseptics may include different substances, for example the extracts of eucalyptus, geranium, lavender, mint, niaouli, pine, rosemary, thyme, vitamin D, probiotics [17,18]. Natural agents may include a myriad of substances, including, for example, resveratrol, lactoferrin, quercetin, and glucans [19-21].

Regarding the duration of treatments, the cycle schedule is preferred, followed by on-demand suggestions. On the contrary, continuous treatments are less prescribed. These findings confirm the relevant concept of tailoring the treatment on a personalized approach that considers various aspects, e.g., the pathophysiological mechanisms involved in the specific patient, the fear of systemic side effects, the patient's preference, the seasonality of diseases (allergies, infections), and so on.

Finally, most participants acknowledged that patient education and instruction are cornerstones in managing patients topically treated.

Therefore, the present survey underlined some peculiar aspects of topical nasal therapy: inflammatory diseases are the preferred target, pre-dosed sprays are the ideal device, and corticosteroids and antihistamines are commonly prescribed.

However, this survey had some limitations, including a relatively limited number of participants and a scarce participation of ENT specialists. The questionnaire was not validated, and the results reflected the single opinion and self-allegations of participants and did not constitute robust evidence.

In conclusion, topical nasal therapy is a widespread method of treatment administration. However, the disagreement about some issues requires greater knowledge of the topics and the need to develop new studies, including pragmatic ones.

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Original research article

Awareness and practices of Speech Language Pathologists (SLPs) working with chronic cough in India: a call for action

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ABSTRACT

Objective: A cough persisting beyond eight weeks is referred as chronic cough (CC) and is a common symptom of many respiratory conditions and non-respiratory conditions. The role of a speech language pathologist (SLP) in CC is emerging and this study aimed to profile the awareness and practice patterns of SLPs practicing in India.
Study design: Cross-sectional study.
Method: An online survey was used to profile the assessment, treatment and counselling practices in CC among SLPs working in India. It sought to identify the awareness levels among SLPs regarding their role and availability of behavioural interventions for CC. Only SLPs who dealt with CC could complete the entire survey while other SLPs, filled regarding awareness and availability of behavioural interventions.
Results: 127 eligible responses obtained from SLPs working across clinical settings in India were analysed. 75.59% (n=96) of them had not seen patients with CC in their career. 47.24% (n=60) of them were aware that behavioural interventions were available for CC. Thirty-one SLPs completed the entire survey and their practice patterns indicated that few clinicians used cough-specific protocols while largely relying on voice and swallowing related assessment and treatment for CC.
Conclusion: This survey the lack of awareness of SLPs' role in CC and that their practices are dominated by existing procedures for voice and swallowing disorders. Increasing the awareness of SLP's role in CC may increase the caseload of patients referred and expand the SLP's scope of practice. Development of guidelines in CC practice and inclusion in coursework/curriculum are future considerations.

Key words: chronic cough; refractory; practice patterns; healthcare; scope of practice

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Authors' contributions: Y.V., V.A. and R.K.B. were involved in study conceptualization and design. Y.V. developed the initial version of the survey, which was reviewed and edited by D.G. and R.K.B. The survey was circulated by Y.V. The formal data analysis was done by Y.V. and R.K.B and they drafted the first version of the manuscript. Y.V., R.K.B, D.G. were involved in editing the manuscript for content and clarity. The prepared manuscript was reviewed by V.A., S.K., and D.G. All authors approved the final manuscript.

Ethics approval and consent to participate: This survey was approved by the Institutional Ethics Committee of Kasturba Medical College, Manipal Academy of Higher Education, Mangalore (IECKMCMLR-11/2022/451).

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Introduction

Cough is a common symptom of many respiratory conditions such as chronic obstructive pulmonary disease (COPD), upper airway cough syndrome (UACS), asthma, and reflux diseases [1,2]. Other non-respiratory conditions and triggers, such as drug-induced cough hypersensitivity, environmental/occupational irritants, and foreign bodies, are also linked with cough [3–5]. A cough complaint lasting more than eight weeks is called "chronic cough (CC)" [6]. Adults and children with CC are assessed and optimally treated according to standard guidelines recommended by healthcare bodies such as The American College of Chest Physicians (CHEST) [7,8] and the European Respiratory Society (ERS) [9]. Performing lung function evaluations such as spirometry, or pulmonary function tests are essential to rule out any underlying respiratory conditions before defining CC as idiopathic. However, when the cough persists beyond eight weeks, with an unidentified etiology, a normal chest X-ray, and does not respond to medical treatment for the common causes, it is labelled "refractory chronic cough (RCC)" [2,10-12] or "unexplained chronic cough (UCC)" [8,11,13].

Many terminologies are used to refer to such clinical presentations, however, recent literature has sought the broad concept of 'cough hypersensitivity' or 'neurogenic laryngeal hypersensitivity' to understand RCC/UCC [3,14,15]. Patients present with laryngeal symptoms of hypertussia and allotussia due to increased sensitivity in the neural pathways which triggers cough [16,17]. Patients undergo multiple clinic visits, assessment procedures, and treatment trials before being diagnosed with RCC/UCC and suffer from its consequences. This type of cough need not necessarily be associated with an underlying lower airway disease but could be reflective of laryngeal hypersensitivity [16]. Patients tend to have laryngeal dysfunctions such as hoarseness, throat clearing, globus sensation, itch, and tickle, which may be mistaken for symptoms of lower airway disease. Patients also experience deterioration in their physical well-being [4,18] and quality of life in social contexts, work life, and leisure [18-21]. Socioeconomic distress resulting from their perpetuating cough has also been documented [22].

CC is usually managed by medical and pharmacological interventions by ruling out common aetiologies as dictated by protocols [8,9]. The need for additional therapy to manage CC is well-founded, and research has highlighted the role of non-pharmacological interventions for CC [4,23,24]. Behavioural interventions for CC have emerged in the last two decades, usually provided by speech language pathologists (SLPs) or physiotherapists [24–28]. The role of speech language pathology and physiotherapy in the management of CC has gained attention with the advent of such behavioural interventions. These include breathing exercises, vocal hygiene and hydration, cough suppression strategies, patient education, and counselling [24–28]. The principles of these interventions were borrowed from the context of voice disorder management [17,29]. The components of patient education, vocal hygiene, and breathing exercises target reducing laryngeal irritation and improving vocal function [29]. The effectiveness of these behavioural programmes has been tested in the CC population [25,28,30,31] and were found to provide quick relief [32]. Other benefits of these behavioural programmes are their cost-effectiveness and significant improvement in quality of life [22,25,28,30].

Behavioural interventions are often recommended at later stages of treatment, more as a last resort after several rounds of pharmacological trials [31,33]. The delay in referral could be attributed to the lack of awareness of the role of the SLP in CC among physicians [34]. The CHEST guidelines recommend a trial of speech pathology treatment for UCC [8]. The ERS guidelines mention nonpharmacological therapy for patients with CC [9]. The American Speech and Hearing Association (ASHA) has included CC in its scope of practice under potential aetiology for communication disorders under 'disorders of aerodigestive tract function' [35]. In contrast, the Rehabilitation Council of India (RCI), which governs speech and hearing professionals in India, has not included CC in its scope of practice [36]. This may be due to the lack of awareness of CC among Indian SLPs. There are no published documents (position statements, review papers, guidelines) on speech pathology or behavioural management on CC in India. CC is not included in the under- or post-graduate curriculum in India. The

evidence-based literature for speech pathology treatment for CC suggests a possible expansion in the scope of practice of SLPs, which is possibly emerging in India.

Although CC is within the scope of practice of SLPs, very few have awareness and exposure to work in this speciality. The level of knowledge and clinical expertise in CC may not be extensive or uniform across SLPs practicing in India. However, with increasing awareness among professionals and sufficient evidence-base from Western literature [25,28,30,32] the client load of CC seen by SLPs is bound to increase manifold. This survey was designed to understand the practice patterns of the few SLPs working in India with CC population. We aimed to investigate the following: 1) knowledge and awareness levels of Indian SLPs in the assessment and management of CC, 2) identify the proportion of SLPs dealing with CC in India, and 3) practice protocols of CC followed by the few SLPs working with CC in India.

Method

This survey was approved by the Institutional Ethics Committee of Kasturba Medical College, Manipal Academy of Higher Education, Mangalore (IECKMCMLR-11/2022/451).

Step 1: Development and validation of the survey

Literature on CC assessment and treatment by SLPs and physiotherapists was identified and used as references to develop this survey questionnaire [24,25,27,28,30,32]. An initial version of the questionnaire was developed by the first author to collect information on current practice trends in the assessment and management of CC among SLPs practicing in India. The questions focussed on demographics, clientele, symptoms, assessment, treatment, and complementary and alternative medicine (CAM) practices for patients with CC. Close-ended questions were used to collect quantitative data (demographics, clientele, symptoms, and aetiology), and open-ended questions were used to gather qualitative perspectives on assessment/treatment/CAM. Additional probes or follow up questions, mostly open-ended, were also used in the survey.

The fourth author, with a clinical experience of 10 years in the field of voice and swallowing disorders, reviewed the survey questions and suggested modifications such as adding other relevant questions and altering the question structure/type. Differences in opinions were discussed and resolved by consensus. The questionnaire was again reviewed by the fifth author (clinical experience of 15 years in the field of voice and swallowing disorders), who was given a review form to provide inputs regarding the survey. Based on the recommendations provided in the review form, the final version of the survey questionnaire was generated. A content validation form was prepared using the systematic approach for content validation [37], which provides acceptable cut-off scores. Two SLPs validated the final version, which received a content validity index score of 0.96. This score was higher than the recommended acceptable cut-off value [37].

The developed 28-item survey questionnaire was converted to an online version by uploading it to Google Forms. It contained six sections: brief information about the survey and consent, demographics, screening based on awareness of the topic, assessment-related data, treatment-related data, counselling, and CAM. Consent to participate in the survey was obtained from the respondents in the first section and was directed to submission if not consented. Similarly, in the third section, if CC was not within the scope of the clinician, the survey was directed to a few questions on awareness about CC, followed by submission of the form. Only SLPs who worked with CC completed the entire survey. The online version of the survey was checked for ease and completion duration by running a trial with the contributing authors and ten undergraduate speech-language pathology students. The time taken to complete the entire survey was around ten minutes.

Step 2 – Administration of the survey

The survey was circulated through email lists and social media, thus adopting a convenience sampling method. Professionals working in India were targeted by selecting email addresses from the Indian Speech

and Hearing Association (ISHA) database, which has more than 3000 registered SLPs. However, not all practicing SLPs in India are registered with ISHA; hence, the surveys were circulated through social media for greater reach. The responses were collected between November 2022 and January 2023. The first author sent two reminder emails/messages to ensure more responses.

Eligibility criteria

The inclusion criteria were set as follows: a) should be a practicing SLP in India (as this study aimed to understand the awareness and practice patterns among SLPs in India), b) must have a minimum experience of one year (to avoid responses from undergraduate students), and c) must consent to participate in the survey. The exclusion criteria considered were SLPs practicing abroad or participants with no or less than one year of clinical experience.

Data analysis

The results of this survey included answers to both closed- and open-ended questions. Quantitative variables were analysed using descriptive statistics (mean and standard deviations). The answers to the open-ended questions were grouped based on similar response categories for a given question. Initial grouping was performed by the first author & cross-checked by the fifth author. If there was a difference in opinion, it was discussed until both authors agreed on the grouping category. These were then summarized using frequency–percentage analysis, depicted as percentage of responses grouped under response categories. The Jamovi software (version 2.3) (The Jamovi Project, 2022) was used to perform the statistical analyses.

Results

One hundred and fifty-two SLPs filled out the survey, of which twenty-five responses were excluded based on the eligibility criteria and consent. Only responses from SLPs working in India with at least one year of working experience were included. This has been depicted as a flowchart in Figure 1 (considering one round of emails sent). The findings have been reported in the following sub-sections as per the six sections of the survey.

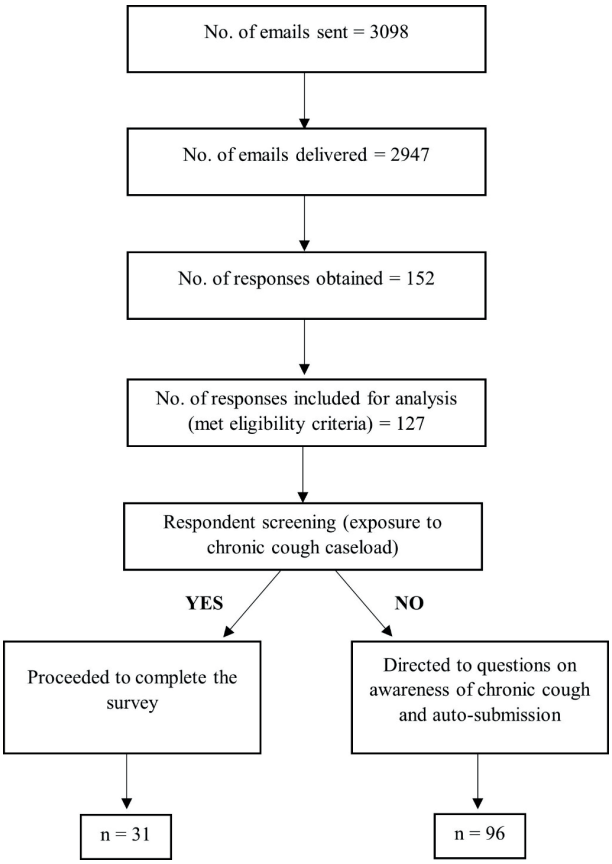

Figure 1. Survey administration and included responses depicted as a flowchart.

Consent

In the first section of the survey, the respondent's consent to partake in the study was obtained. If the respondent indicated an unwillingness to participate in the survey, the form was configured to auto-submit. Three respondents did not agree to participate in this survey and were thus excluded from the analysis.

Demographic data

The demographic section of the survey collected information on age, gender, years of experience, the city of work, and clinical work settings. Responses

Table 1. Demographic information of respondents.

Demographic information of 127 SLPs			
	Gender		
Demographic data	**Males**	**Females**	**Total respondents**
N (%)	26 (20.5%)	101 (79.5%)	127 (100%)
Age (in years) (Mean±SD) [Range]	33.65±6.11 [23-47]	30.11±7.19 [22-53]	30.84±7.11 [22-53]
Years of overall clinical experience (Mean±SD) [Range]	10.26±5.14 [1-22]	7.35±6.78 [1-35]	7.95±6.57 [1-35]
Years of clinical experience in voice (Mean±SD) [Range]	8.03±4.97 [1-20]	5.25±5.63 [1-27]	5.82±5.59 [1-27]
Demographic information of respondents 31 SLPs who worked with chronic cough population			
N (%)	10 (32.26%)	21 (67.74%)	31 (100.00%)
Age (Mean±SD) (in years) [Range]	33.80±5.78 [25-47]	30.66±7.88 [22-50]	31.67±7.33 [22-50]
Years of overall clinical experience (Mean±SD) [Range]	9.60±4.81 [3-20]	8.04±7.40 [1-28]	8.54±6.63 [1-28]
Years of clinical experience in voice (Mean±SD) [Range]	7.80±5.11 [2-20]	5.61±5.63 [1-22]	6.32±5.48 [1-22]

Note. SD, standard deviation.

from SLPs practicing abroad (n=21) or with less than 1 year clinical experience (n=1) were excluded. A final one hundred and twenty-seven responses were subjected to analysis. The mean age, gender distribution, and years of clinical experience of the respondents are shown in Table 1. The clinical work settings of the respondents yielded two hundred and four item responses. These spanned across private set-ups (34.80%, n=71), hospitals (27.45%, n=56), training institutes/colleges (23.53%, n=48), home-based set-ups (8.82%, n=18) and schools (3.92%, n=8). Additionally, three respondents mentioned online services (0.98%, n=2) and a government-related setting (0.49%, n=1).

Respondents screening

This section covered three questions, one each on CC caseload, awareness of behavioural interventions for managing CC, and the professionals involved in the same. The first question on caseload identified SLPs who dealt with the CC population based on their clinical practice. Ninety-six respondents (75.59%) had not seen patients with CC in their career and thus they were not directed to other sections of the survey. However, they could answer the remaining two questions before the form was auto-submitted. As a result, only thirty-one respondents (24.41%) proceeded to complete the entire survey.

Although most did not deal with this population, 47.24% (n=60) of the respondents were aware that behavioural interventions were available for CC. Interestingly among these 60 respondents, 73.33% (n=44) were working in a hospital and/or training institute. An array of healthcare professionals was listed by the SLPs when asked to mention the professionals who provided behavioural interventions for CC based on their knowledge and experience. Two hundred and sixty-six item responses were obtained from the participants, and this distribution is depicted in Figure 2. Fourteen (5.26%) of them reported no knowledge of the professionals involved in behavioural interventions. The frequently reported professionals were SLPs (25.56%, n=68), otorhinolaryngologists/ENTs (23.68%, n=63), and pulmonologists (16.92%, n=45).

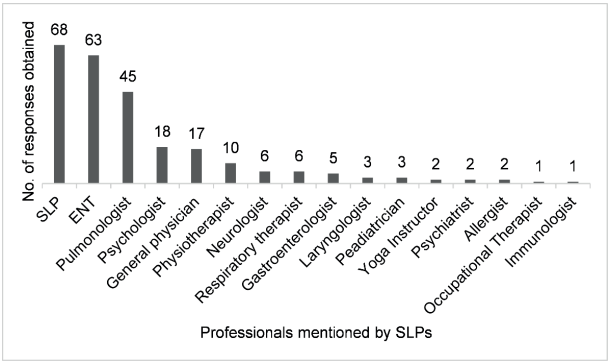

Figure 2. The professionals involved in the management of chronic cough as reported by all 127 SLPs.

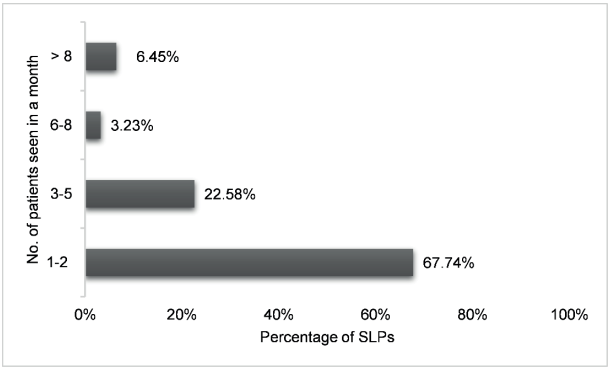

Figure 3. Chronic cough caseload per month of the 31 SLPs who completed the survey.

Respondents screened for further analysis

For the upcoming sections, thirty-one completed surveys were analysed. It included responses from twenty-one female (67.74%) and ten male (32.26%) respondents. The mean age, gender distribution, and years of clinical experience of these respondents are reported in Table 1.

Assessment related data

This section addressed seven questions on clientele-related data, referrals, signs and symptoms, etiology, and assessment procedures. The inquiries on clientele data revealed that 74.19% (n=23) of them assessed patients with CC, whereas 25.81% (n=8) did not. It is possible that these eight SLPs did not use cough specific procedures for evaluation but proceeded to intervention based on the patient's case history. The percentage of patients with CC dealt by these SLPs is illustrated in Figure 3. Most SLPs (67.74%, n=21) saw 1-2 patients monthly. For the question on referral source, sixty-one item responses were received which was predominantly from ENTs/otorhinolaryngologists (44.26%, n=27), pulmonologists (21.31%, n=13), primary care physicians (14.75%, n=9), and allergists (9.84%, n=6), among others. Two questions were on signs and symptoms presented by patients with CC. The SLPs were asked to specify how often their patients reported complaints of voice change or hoarseness, with response options ranging from always to never. The frequency of voice complaints was documented as follows: "very often" (45.16%, n=14), "sometimes" (41.94%, n=13) and "always" (12.90%, n=4). The question on "symptoms reported by patients other than cough", generated one hundred and fifty item responses, as depicted in Table 2. One SLP indicated that they had never encountered patients with such complaints. These responses reflect the symptoms as reported by the patients with CC who were seen by the SLPs.

Table 2. Common symptoms reported by patients with chronic cough as encountered by the 30 SLPs.

Symptoms	Number of responses	Percentage of item responses of 30 SLPs
Voice change	27	18.00%
Breathlessness	24	16.00%
Tiredness	20	13.33%
Pain/discomfort	20	13.33%
Impaired work life	19	12.67%
Sleep disturbances	13	8.67%
Poor social life	13	8.67%
Sleep apnea	7	4.67%
Vocal fatigue	2	1.33%
Low volume of voice	1	0.67%
More effort in speaking	1	0.67%
Voice trails off	1	0.67%
Throat clearing	1	0.67%
Poor food intake	1	0.67%

Eighty-two item responses were obtained for the open-ended question on common etiologies of CC. One SLP chose not to respond to this question.

Most reported causes were lung-related pathologies (14.46%, n=12), vocal pathologies (12.05%, n=10) gastroesophageal reflux disease (GERD; 10.84%, n=9), and asthma (9.64%, n=8) among others.

The SLPs were enquired about the tools, procedures, or questionnaires used in evaluation of CC. This yielded sixty-three item responses, with four participants not revelaing their assessment practices. Instrumental procedures related to voice (26.87%, n=18) and swallowing (5.97%, n=4), subjective measures (16.42%, n=11), case history (14.93%, n=10), and patient-reported measures (11.94%, n=8) were frequently carried out by the SLPs. Few SLPs reported using cough-specific questionnaires/checklists (5.97%, n=4). Table 3 shows the detailed breakdown of these responses.

Table 3. Procedures and tools carried out by the 27 SLPs for assessment of chronic cough.

Procedures/Tools	Number of responses	Percentage of item responses of 27 SLPs
Instrumental measures – voice related (endoscopy, stroboscopy, acoustic analysis, aerodynamic measures, EGG)	18	28.57%
Instrumental measures – swallowing related (FEES & VFS)	4	6.35%
Perceptual voice analysis & MPT	11	17.46%
History/Informal assessment	10	15.87%
PROM (VFI, VHI, VR-QoL)	8	12.70%
Cough-related assessment	4	6.35%
Swallowing related assessment	3	4.76%
Voice assessment	2	3.17%
EMST	1	1.59%
Therapeutic trials	1	1.59%
Cranial Nerve evaluation	1	1.59%

Note. FEES,Flexible Endoscopic Evaluation of Swallowing; VFS, Video Fluoroscopy, EGG, Electroglottography; MPT, Maximum Phonation Time; PROM, Patient-Reported Outcome Measures; VFI, Vocal Fatigue Index; VHI, Voice Handicap Index; VR-QoL, Voice-Related Quality of Life; EMST, Expiratory Muscle Strength Training.

Treatment-related data

The section on management practices consisted of four questions. Among the thirty-one analysed responses, 67.74% (n=21) provided treatment for CC. The next question on treatment options used by the SLPs elicited fifty-one item responses. The same ten respondents who answered "No" to the previous question, responded "Not applicable" to this question. The techniques followed by the remaining SLPs are detailed in Table 4.

SLPs delivered a varying number of behavioral therapy sessions, ranging from one session to more than six sessions. Ten respondents (32.26%) answered "Not applicable" to this question. The options chosen by the respondents are as follows: more than 6 sessions (19.35%, n=6), 1-2 sessions (16.13%, n=5), 3-4 sessions (16.13%, n=5), 5-6 sessions (12.90%, n=4), and as per patient needs (3.45%, n=1).

The final question on "the number of times you ask your patients to perform exercises or follow

Table 4. Treatment techniques used by the 21 SLPs for managing chronic cough.

Treatment techniques	Number of responses	Percentage of item responses of 21 SLPs
Vocal hygiene	10	19.61%
Voice therapy	8	15.69%
Breathing exercises	8	15.69%
Relaxation exercises	5	9.80%
Swallowing/dysphagia therapy	4	7.84%
Cough Suppression Strategies	4	7.84%
Steam inhalation	3	5.88%
Medications	3	5.88%
EMST/Respiratory training	2	3.92%
Psychoeducational counselling	1	1.96%
Diet changes	1	1.96%
Cognitive Behavioural Therapy	1	1.96%
Referral to Otorhinolaryngology	1	1.96%

Note. EMST, Expiratory Muscle Strength Training.

strategies at home" resulted in thirty-six cumulative item responses. Eight respondents (22.22%) reported "Not applicable". The most documented answers were 3 times a day (22.22%, n=8), and whenever the patient experiences cough (13.89%, n=5). This was followed by 2 times a day and patient needs (each 8.33%, n=3) and 2-3 or 3-5 times or every day (each 5.56%, n=2). Other answers were 5 times/day, 2-6 times/day, and 10-15 minutes/session (each 2.78%, n=1).

Counselling & CAM

This section had two questions on components of counselling and four questions on CAM. A significant majority of thirty SLPs (96.77%) counselled their patients about cough and its effects. Twenty-seven (87.10%) SLPs also counselled on how to avoid the persistent cough while four (12.90%) did not. To understand how SLPs aligned with utilizing CAM in treatment, they were asked if they recommended CAM to their patients. Fifteen SLPs (48.39%) responded affirmatively, stating "Yes, I believe that it may augment medications" while thirteen (41.94%) SLPs opted "No, strictly traditional methods only". One reported an integrated approach (3.23%) while two SLPs (6.45%) answered "Not applicable" to this question.

The CAM approaches mostly recommended by SLPs comprised the following - home remedies (19.57%, n=9), yoga (10.87%, n=5), steam inhalation (8.70%, n=4), homeopathy (4.35%, n=2), and lifestyle changes (4.35%, n=2) among others. Self-reports of patients seeking remedies or alternative approaches yielded forty-one item responses from twenty-two SLPs (70.97%). Majorly reported approaches included home remedies, yoga, ayurveda, and steam inhalation, among others. It is important to note that this information was recalled by SLPs as reported by their patients.

Discussion

This survey determined to gather data from three distinct aspects: i) assessing the awareness among SLPs about CC, ii) identifying the proportion of SLPs working with CC and, iii) understanding the clinical practice patterns of Indian SLPs involved in assessing and treating CC. Notably, this is the first survey conducted among SLPs in India on CC and the findings indicate that it is emerging as an new area of practice. Considering that the topic explored in this survey was relatively unfamiliar to SLPs, there is a possibility that those without prior knowledge did not partake in the survey as it involved questions about an unfamiliar caseload. Thus, the survey appears to have primarily attracted participation of only a handful of SLPs who specifically worked with the targeted clientele.

Awareness and respondent screening

The initial sub-section of the survey targeted to find how many clinicians were working with patients with CC and whether they were aware of behavioural interventions available. While most of the respondents' clientele did not include patients with CC, a considerable number were familiar with the feasibility of behavioural interventions for CC. Numerous professionals from various disciplines were mentioned as service providers for this behavioural intervention. However, the responses were based on the clinician's knowledge and experience, as this subject is not addressed in the curriculum during undergraduate or post-graduate degree courses. From these responses, it could be interpreted that SLPs were aware of behavioural interventions for CC but did not regard it within their scope of practice. This clearly showed that there is a lack of awareness of CC among SLPs, particularly about their role in assessing and managing it. This survey can serve as a steppingstone for future studies exploring this area of CC.

Assessment related data

The decreased CC caseload of SLPs could be due limited referrals from physicians owing to the insufficient knowledge of behavioural interventions, despite guideline recommendations [34]. This can be corroborated with findings from literature that patients are referred to speech language pathology late, after several investigations and treatments for their CC [31,32]. Physicians may have reservations about how

such treatments work, which has been indicated as a possibility for the delay in referral [31].

Speech pathology intervention was specified for UCC in CHEST panel and ERS guidelines [8,22]. A 2019 Indian consensus statement on cough, recommended referral to a "specialist" when the cough persists after rigorous methodical testing and patients have not benefitted from medical treatment [38]. This consensus statement has guidelines for cough of all origins but does not include information on RCC/UCC. Furthermore, it does not specify the field of the specialist or provide stepwise decision making regarding this consultation. However, a recent consensus statement on managing cough has provided definitions for UCC and RCC, and a recommendation of a trial speech therapy management for UCC [10]. This shows that awareness on the role of SLPs in managing CC has grown among physicians in the past four years. Physicians may prefer to suggest speech pathology treatment when they suspect the etiology to be laryngeal hypersensitivity than other causes [34]. In the following years, this awareness may potentially increase referrals to SLPs. This solidifies the need for SLPs to better equip themselves with the knowledge and training of CC to provide clinical services for this cough phenotype.

SLP respondents indicated that their patients with CC regularly reported voice complaints, such as hoarseness or a change in voice. This is not surprising as earlier studies have also reported on the co-occurrence of laryngeal abnormalities such as vocal cord dysfunction, paradoxical vocal fold movement, and voice hoarseness in patients with CC [26,27,39,40]. Cough is known to affect everyday activities, and the common complaints reported by patients to SLPs in this survey are similar to findings from the literature [41]. The physical symptoms encompassed breathlessness, tiredness, pain or discomfort, and sleep disturbances/apnoea. Other studies have identified additional symptoms, such as vomiting, retching, hernias, and headaches, leading to physical exhaustion/tiredness [17,42]. SLPs reported that the work life of their patients was impaired though details were not provided. Literature shows loss of job, frequent absences from work, embarrassment during meetings, and poor concentration and attention as some of the work-related complications faced by patients with CC [41–43]. SLPs frequently reported poor social life among their patients; however, specific case scenarios were not disclosed. Previous studies have highlighted social isolation due to the embarrassment of coughing in public spaces or social situations. Other compromising issues faced by patients included interference with lifestyle and leisure [42,43]. Respondents of this survey did not report psychological issues among their patients but abundant reports on depression, increased anxiety, fatigue, disrupted mood, and emotional distress are available [17,43–45].

While numerous causes are attributed to CC, the triad conditions - UACS, asthma, and GERD - have been reported as the most common etiologies [46–49]. The outcomes of this survey indicated GERD and asthma as predominant causes, along with lung-related disorders and vocal pathologies. SLPs possibly linked CC with dysphagia/voice, because for assessment, many relied on instrumental and subjective measures used in voice and/or swallowing evaluations. A scoping review on clinical assessment methods of SLPs for CC also reported that voice related measures were frequently used [50]. Only a minority of SLPs used cough related procedures, such as assessing cough triggers, cough symptoms, and quality of life and standardized cough-related checklists like Cough Symptom Index (CSI), Cough Quality of Life Questionnaire (CQLQ), Newcastle Laryngeal Hypersensitivity (NLH) questionnaire. The usage of such questionnaires is recommended in literature [51,52]. Interestingly, one response indicated attempting therapeutic trials, as recommended by the CHEST panel and ERS guidelines [8,22]. Unique responses obtained from respondents comprised performing auscultations and using Expiratory Muscle Strength Training (EMST) devices. These findings indicate that practice patterns of CC are evolving in India. SLPs predominantly used already available materials and adjunctly used cough-specific tools if they were aware.

Treatment-related data

Ten SLPs did not provide treatment or reveal their treatment techniques, but substantial variations were evident in the responses obtained from the other

respondents. SLPs predominantly indulged in techniques borrowed or adapted from voice therapy literature for treating CC [29]. This could be because both coughing and voicing mechanisms share similar anatomy. Coughing can be as harmful as phonotraumatic behaviours like screaming or talking loudly [39]. Coughing may create laryngeal irritation and dryness, thus, exacerbating the cough problem. The laryngeal structures addressed through voice treatment assist in suppressing cough, even if the physiology behind this is not exactly understood. This might be because targeting the underlying vocal pathology consequently leads to an improvement in the cough-related complaints [29].

Strategies provided by clinicians revolved around reducing laryngeal irritation, a major cause that triggers persistent cough [29]. This included giving breathing exercises, vocal hygiene tips, relaxation techniques, cough suppression strategies, steam inhalation, and dietary changes. Cough triggers originating in the laryngeal area can possibly be controlled through suitable vocal hygiene practices which minimize laryngeal irritation [39]. In some cases, patients with CC may experience physical tension or stiffness of the head, neck, or upper chest areas. They may engage in clavicular breathing or maintain abnormal postures at rest or during speech [29,39]. Clinicians possibly preferred breathing exercises to address such issues to promote relaxation of the stiff muscles of the throat, neck, and shoulders [5]. Apart from these, few clinicians reported using specific techniques to target the cough behaviour (cough suppression strategies, pursed lip breathing, psychoeducational counselling). These strategies for cough suppression or control are quite prevalent within the CC literature [25,28,30].

Most SLPs provided behavioural therapy between one to six sessions, and one SLP reported offering flexible number of sessions. Literature shows that patients are usually treated over a span of 1–2-months, across three-four sessions, although this may range between 1-7 sessions. [31,32,53]. Studies recommend that deciding the number of sessions should be based on the patient's needs and learning ability [29,54]. There was a great variability in the dosages prescribed by the SLPs for the treatment exercises or strategies. A particular treatment program for CC, provides comprehensive information on the dosage, practice conditions, and hierarchy for each exercise included [54].

Counselling & CAM

Most clinicians counselled their patients about cough, its implications, and how to avoid it. Typically, treatment programs for CC include a component on "psychoeducation" or "patient education/counselling". These are intended to cover aspects such as - differences between a medical and a behavioural approach, accepting a behavioural treatment, helping patients perceive their cough as a controllable factor and overcome it [24,25,28,54]. Patients are educated about the larynx, laryngeal well-being, identifying cough triggers, making lifestyle changes, and stress management.

Nearly half of the SLPs who completed the survey acknowledged the augmentative effects of complementary and alternative medicinal approaches on CC. The other half adhered strictly to traditional methods or opted not to not reveal their opinions. This suggests that SLPs are willing to try different modalities as much as they confine to their beliefs. There might be more willingness to endorse CAM if efficacy for treating cough is demonstrated [55]. SLPs who advocated CAM, mostly suggested home remedies, steam inhalation, and yoga. Similarly, patients self-reported using CAM such as home remedies, ayurveda, and yoga. A study on online forums showed that patients sought home remedies when conventional methods did not relieve their cough [56]. Home remedies are usually concoctions of a single or many herbal ingredient(s), each with a property that alleviates cough symptoms. These may be antitussive, anti-inflammatory, antibacterial, or mucolytic [57] in nature.

Limitations and future considerations

The major limitation of this survey would be its relatively small sample size. Although one hundred and fifty-two responses were received, only thirty-one completed responses could be analysed. The interpretations presented in this article reflect the practices of few SLPs and not representative of all SLPs in India. These findings cannot be generalized or applied across

different settings. Nonetheless, this was anticipated as many SLPs in India are not working with chronic cough. Thus, this preliminary survey highlighted the very idea it intended to - lack of awareness of CC and their role in assessing and treating CC, among SLPs in India. As for the grouping strategy followed for survey responses, categories were grouped as deemed appropriate and this could have led to some bias and thus, subsequently led to broader interpretations. Another potential limitation is the interpretation of survey responses that had binary options or open-ended questions which did not receive detailed answers. These study findings and recent advances in cough consensus statements in India should prompt contemplating behavioural management for CC. Further, CC needs to be included in the curriculum for the under- and post-graduation courses of speech language pathology. Conducting workshops and continuing education programs on CC will facilitate ongoing learning among practicing clinicians. This will enable knowledge and clinical training in CC for both speech pathology students and graduate clinicians.

Conclusion

The findings of this survey showcase the status of CC as perceived by SLPs in India. It is emerging as an area of practice among Indian SLPs. The key takeaways from this survey are: first, there is a lack of awareness regarding SLPs' role in assessing and treating CC. Second, very few SLPs deal with this population and their practices are dictated by their experience and existing procedures. There is a need for creating awareness on CC among SLPs in India, wherein working with chronic refractory cough is not yet a routine part of clinical practice. These findings may guide clinicians to develop knowledge through self-learning, continuing education programs, and workshops. Practice protocols for speech pathology treatment for CC in India may be devised in the foreseeable future if necessary measures are taken towards increasing awareness and clinical training. This will empower SLPs to facilitate the mental and physical well-being of patients with CC, thereby contributing to the overall healthcare system.

APPENDIX

*Please answer the following questions, considering patients with cough who **DO NOT** have any swallowing related (aspiration/penetration) complaints.*

1. Kindly indicate your willingness to participate - Do you consent to participate in this survey?
   a. Yes
   b. No
2. Age:
3. Gender:
4. Are you currently working in India?
5. Mention the city you are currently practicing in:
6. Please mention your overall clinical experience (in years):
7. Please mention your clinical experience working in voice & disorders (in years):
8. Please mention your clinical practice setting:
   a. Private practice
   b. Hospital
   c. Training institute/college
   d. Schools
   e. Others: _____
9. Does your caseload include patients with chronic cough?
   a. Yes
   b. No
10. Are you aware that behavioural interventions exist for managing chronic cough?
    a. Yes
    b. No
11. Based on your practice & experience, mention the professionals involved in providing behavioural management for chronic cough?
    (Respondents who answered 'No' to Q9, were directed to submit the survey after answering Q10 & 11; whereas if they answered 'Yes', they could proceed to complete the survey)
12. Does your clinical practice involve assessment of patients with chronic cough?
    a. Yes
    b. No

13. Approximately how many patients with chronic cough do you see in a month?
    a. 1-2
    b. 3-5
    c. 6-8
    d. >8
    e. NA
14. Select the professionals who refer cough patients to you? (Choose all that apply)
    a. ENT
    b. Allergist
    c. Pulmonologist
    d. Primary care physician
    e. Others: _____
15. Do your patients with chronic cough, also complain of voice change or hoarseness?
    a. Always
    b. Very often
    c. Sometimes
    d. Rarely
    e. Never
16. Please list the most common etiologies/medical conditions among the patients with chronic cough you encounter?
17. What are the other symptoms reported by your patients with chronic cough apart from cough? (Choose all that apply)
    a. Tiredness
    b. Breathlessness
    c. Sleep disturbances
    d. Voice change
    e. Pain/ Discomfort
    f. Impaired work life
    g. Poor social life
    h. Others: _____
18. Please mention the assessment procedures you generally carry out for a patient with chronic cough. Kindly list all tools, procedures or questionnaires you may use in your practice:
19. Do you provide treatment for patients with chronic cough?
    a. Yes
    b. No
20. If YES, please mention the treatment options you choose for your patients with chronic cough.
21. How many sessions do you typically provide therapy for a patient with chronic cough?
    a. 1-2
    b. 3-4
    c. 5-6
    d. >6
    e. NA
22. Kindly mention the number of times (frequency) you ask your patients to perform exercises or follow strategies at home (e.g. 5 times a day/whenever they are experiencing cough/ throughout the day)?
23. Do you counsel your patients about cough and its effects?
    a. Yes
    b. No
24. Do you also counsel on how to avoid the persistent cough?
    a. Yes
    b. No
25. Do you recommend your patients to try complementary and alternative methods (CAM) to manage their cough, such as yoga, pranayama, ayurveda, etc.?
    a. Yes, it may augment medications/therapy
    b. No, strictly traditional methods only
    c. Other opinions (Please state them)
26. If yes, what are some of the CAM you recommend to your patient? Please list them.
27. Do any of your patients' self-report on use of CAM for their cough complaints?
28. Please state the commonly reported CAM measures used by your patients.

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Case report

Gorham-Stout disease and multiple cervical lymphangiomas: case report

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ABSTRACT

Introduction: Gorham-Stout disease is a rare condition characterized by extensive bone loss due to the proliferation of new vascular and lymphatic structures. It can occur in any bone and cause pathologic fractures with poor bone healing. Complications such as effusions and lymphangiomas can also develop. Gorham-Stout disease pathogenesis is still being studied, and treatment options are limited, but sirolimus has shown promise in stabilizing or reducing symptoms.

Case presentation: We present a case of a 19-year-old male with Gorham-Stout disease, multiple cervical lymphangiomas, and several thoracic complications successfully treated with sirolimus.

Conclusions: Rare lymphatic diseases should be considered as a potential cause in adult patients with bone involvement and multiple cystic lesions in the neck, axillary, or abdominal regions after excluding more common causes. The complexity of diagnosing Gorham-Stout disease should be emphasized.

Key words: Lymphangioma; Gorham-Stout Disease; Pleural Effusion; Sirolimus

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Introduction

Gorham-Stout disease (GSD), or Vanishing Bone Disease, is a rare benign condition of unknown origin that causes extensive bone loss due to the non-cancerous proliferation of new vascular and lymphatic structures. The disease can affect the whole body, but it generally affects the ribs, scapula, humerus, pelvis, and femur, leading to pathologic fractures and a lack of bone healing. Complications such as pleural and pericardial effusion and chylothorax can also occur, and some patients may develop lymphangiomas in different parts of the body.

While most lymphangiomas are congenital and typically occur in childhood [1,2], some may be associated with rare diseases like GSD. New lymphangiomas rarely develop in adults. Therefore, investigating complex lymphatic diseases is crucial [3,4]. Diagnosing GSD is primarily based on clinical information and radiographic findings, with confirmation made by irregularly dilated lymphoid tissue lined by endothelium on bone biopsy [5]. It is essential to exclude other possible causes of osteolysis and lymphangiomas that are more common, such as osteomyelitis, cancer, rheumatoid arthritis, renal disorders, and hyperparathyroidism [4]. A mammalian target of rapamycin (mTOR) inhibitor, such as sirolimus [6], has been described as a promising treatment option [7].

The development of lymphangiomas secondary to GSD has been previously described, primarily in the abdominal region [8]. Approximately 200 cases of GSD have been reported worldwide, with no cases reported in Colombia. We present a case of a patient with GSD and multiple cervical lymphangiomas. This case highlights the importance of considering rare diseases in the differential diagnosis of adult patients with multiple osteolysis and unexplained development of lymphangiomas after a thorough clinical evaluation.

Case presentation

This case report describes a 19-year-old African American male nursing student with a complex medical history. The patient had a left cervical lymphangioma, confirmed by biopsy and surgically treated during childhood. Additionally, he experienced pathologic fractures of the humerus and femur, which were treated with osteosynthesis. At the age of 14, the patient had an episode of bilateral chylothorax that required bilateral pleurodesis. Later, he developed recurrent left chylothorax, leading to multiple hospitalizations, pleurodeses, and ultimately thoracic duct ligation. The patient denied past exposure to cigarettes, allergies, and prescriptions. However, his family history revealed that his mother had hypertension and systemic lupus erythematosus. No other diseases were reported among the family members.

The patient presented to the emergency department with a two-day history of fever, greenish expectoration, dry cough, and dyspnea at rest, accompanied by pain during inspiration in the left cervical and thoracic region. Upon admission, the patient exhibited fever (38.3°C), hypotension (112/63 mmHg), tachycardia (125 beats/minute), and tachypnea (22 breaths/minute), with an oxygen saturation of 96%. Physical examination revealed dyspnea at rest using accessory muscles, pale conjunctivae, and a non-pulsatile soft mass in the left supraclavicular area without inflammatory changes. This mass was interpreted as a recurrence of the previously surgically treated lymphangioma from childhood. The heart exhibited rhythmic tachycardia, while diminished respiratory sounds were noted in the left hemithorax. Abdominal examination revealed no masses, and the extremities had regular pulses. The neurological examination was unremarkable. Laboratory test results are provided in (Table 1).

An initial chest X-ray (CXR) (Figure 1) depicted a left pleural effusion and diffuse thickening of the left pleural space with complete atelectasis of the lower lobe and mixed opacities with predominant alveolar involvement affecting the left upper lobe. Also, multiple lytic lesions with sclerotic and well-defined edges were observed in bone structures. A chest CT scan was performed (Figure 2), confirming the left pleural thickening and pleural effusion, as well as revealing a cystic lesion occupying the supraclavicular fossa and extending to the left axillary region. The thoracic wall showed multiple lytic lesions and sclerotic margins involving vertebral bodies, bilateral costal arches, and the scapulae. Blunting on the left costophrenic angle and pleural thickening suggested a superinfected pleural

Table 1. Laboratory results.

Test	Reference values	At admission, ED	At admission, ICU	Before discharge, ICU
Hemogram				
WBC (×103/μL)	4.23 – 9.07	21.58	10.45	11.61
Neutrophils (×103/μL)	1.78 – 5.38	20.25	9.93	6.58
Hemoglobin (g/dL)	13.7 – 17.5	9	13.7	12.3
Hematocrit (%)	40.1 – 51	43	40.9	37.7
Platelet count (×103/μL)	163 – 337	308	276	529
C-reactive protein (mg/dl)	0 – 0.5	23.35	-	2.86
Lactic acid (mmol/L)	0.5 – 2.2	-	3.79	-
Renal function				
Serum creatinine (mg/dl)	0.67 – 1.17	0.98	1.45	-
BUN (mg/dl)	6 – 20	9.80	20.40	-
Arterial blood gases (ABG)				
pH	7.35 – 7.45	-	7.33	7.43
$PaCO_2$ (mmHg)	35 – 48	-	29.1	43.9
PaO_2 (mmHg)	83 – 108	-	126.9	94.8
SO_2 (%)	94 – 98	-	98.7	97.9
HCO_3 (mmol/L)	21 – 28	-	15.1	28.8

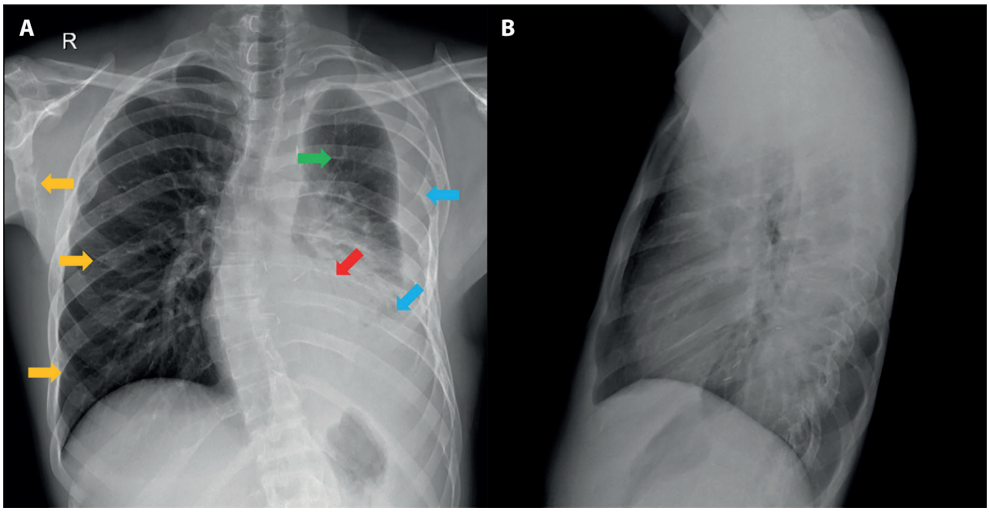

Figure 1. Chest X-ray. A. Posteroanterior projection (R= right side). Right thoracic scoliosis. Central trachea with patent source bronchi. The right lung hilum has a normal configuration, the left lung hilum cannot be assessed. Pleural effusion on the left side is evident. The cardiac silhouette is appreciated with limited evaluation due to haziness of the left lung field (red arrow). Diffuse thickening of the left pleural space with complete atelectasis of the lower lobe is observed (blue arrow). There are mixed opacities with predominant alveolar involvement affecting the left upper lobe (green arrow). Multiple lytic lesions with sclerotic and well-defined edges are seen in bone structures (yellow arrows). B. Lateral projection.

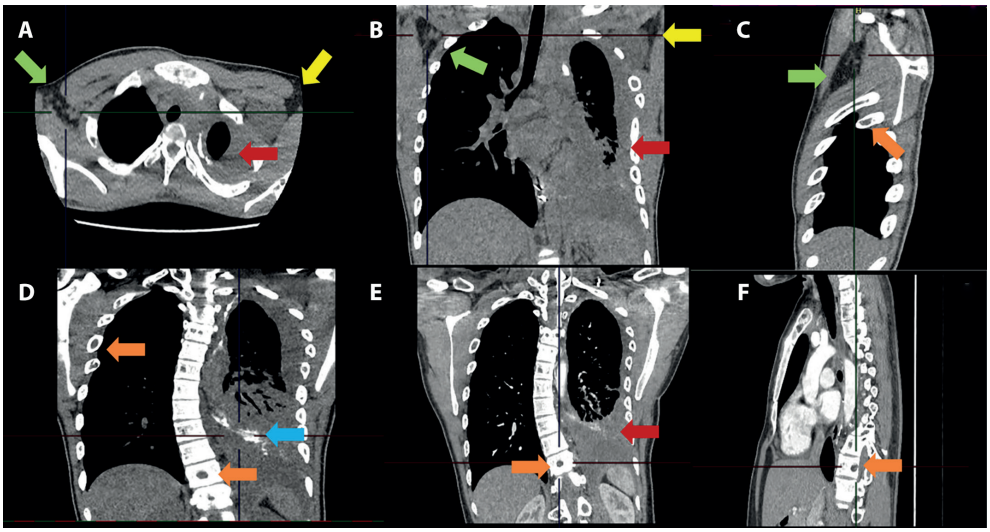

Figure 2. Chest CT scan, mediastinal window. A, B, C, D, E, F. Diffuse pleural thickening and pleural effusion with an average density of 18 Hounsfield units (HU) are observed on the left side (red arrows), calcifications of the visceral pleura in the left lower lobe (blue arrow). Cystic lesions with poorly defined borders extending into the axillary area are seen in the supraclavicular fossae, identified with green arrows on the left side and yellow arrows on the right side. Additionally, there is scoliosis with convexity to the right and multiple lytic lesions in the ribs and vertebral bodies (orange arrows).

effusion. Broad-spectrum antibiotic therapy was initiated with intravenous (IV) vancomycin 1 gram twice daily, in addition to IV cefepime 1 gram three times daily.

The patient's clinical status deteriorated a few hours later, as evidenced by a decrease in blood pressure to 77/48 mmHg and the laboratory results presented in Table 1. A subsequent CXR (Figure 3) revealed worsening of the left pleural effusion. This was further confirmed by posterior chest computed tomography (CT) (Figure 4). The patient was transferred to the intensive care unit (ICU) and diagnosed with septic shock from pulmonary origin. Ultrasound-guided thoracentesis was performed to drain and examine the pleural fluid, revealing characteristics consistent with empyema (Table 2). Hemocultures reported sensitive *Streptococcus pyogenes*, prompting the initiation of IV ceftriaxone 2 gram daily. Over the following days, the patient gradually improved, and was subsequently transferred to the hospitalization floor.

While hospitalized, the patient developed a new slow-growing lesion in the right cervical region, which was warm and painful to the touch. A multicystic lesion measuring 5.8 x 2.8 cm, along with two smaller lateral cysts, was observed behind the right sternocleidomastoid muscle during a soft tissue ultrasound. Additionally, a cystic lesion of 2.8 x 1 cm was detected in the suprasternal region (Figure 5). Due to the previous history of lymphangiomas and the characteristics of the new lesion, the possibility of it being a lymphangioma was high. However, an underlying infectious process was suspected due to inflammatory changes. Therefore, the current antibiotic therapy was extended to 21 days.

The diagnosis of GSD was suspected based on multiple osteolytic lesions in the thoracic cage, along with the previous pathologic fractures of the humerus and femur, and the recurrent chylothorax and superinfected pleural effusion. An extra-institutional bone biopsy was reviewed by a pathologist, who identified findings consistent with osteolysis, fibrosis, and reactive vascular proliferation, confirming the diagnosis and highlighting the complex diagnostic process required for GSD.

After the patient recovered from the infection, sirolimus was initiated at a dose of 2 mg/day and gradually increased until blood levels reached 5 ng/ml for a week. Once the target blood level was

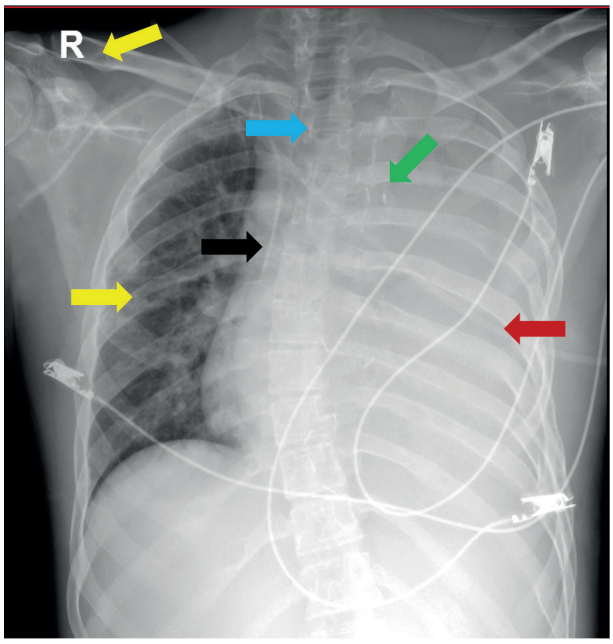

Figure 3. Chest X-ray, anteroposterior projection (R= right side). The trachea deviates to the right (blue arrow), with a non-evaluable cardiac silhouette. Compared to the previous X-ray, there is a marked increase in opacification of the left hemithorax due to pleural effusion, with underlying lung alterations unable to be ruled out (red arrow). Multiple metallic clips from a previous operation are projected onto the midline and mediastinum (green arrow). Right subclavian catheter with its tip projected into the superior vena cava (black arrow). No signs of pneumothorax are present. Multiple hypodense lesions with a lytic appearance are observed in the clavicle, scapulae, and rib cage (yellow arrow).

achieved, the dose was adjusted to 4 mg/day, and the patient was discharged. During the follow up appointment a month later, the patient reported experiencing acne as a side effect of the medication, and sirolimus blood levels were at 5 ng/ml. Consequently, the dose was reduced to 2 mg/day, improving the skin lesions. The patient was monitored over the following year, during which GSD symptoms were well-controlled with the current therapy. A CXR showed improvement in the pleural effusion as well as the lytic lesions (Figure 6).

Discussion

GSD is a bone disease characterized by abnormal vascular and lymphatic vessel proliferation throughout the body, resulting in massive osteolysis. It mainly affects children and young adults with no sex or ethnic predilection [3,9]. The development of lymphangiomas has been described before in these patients, mainly in the pelvic and abdominal regions [8].

Lymphangiomas are typically benign, congenital lesions derived from lymphatic malformations, frequently diagnosed before the age of two [1]. They are commonly found as unilateral head and neck lesions, unlike GSD, which may present with multiple lymphangiomas throughout the body at any age [8]. In this

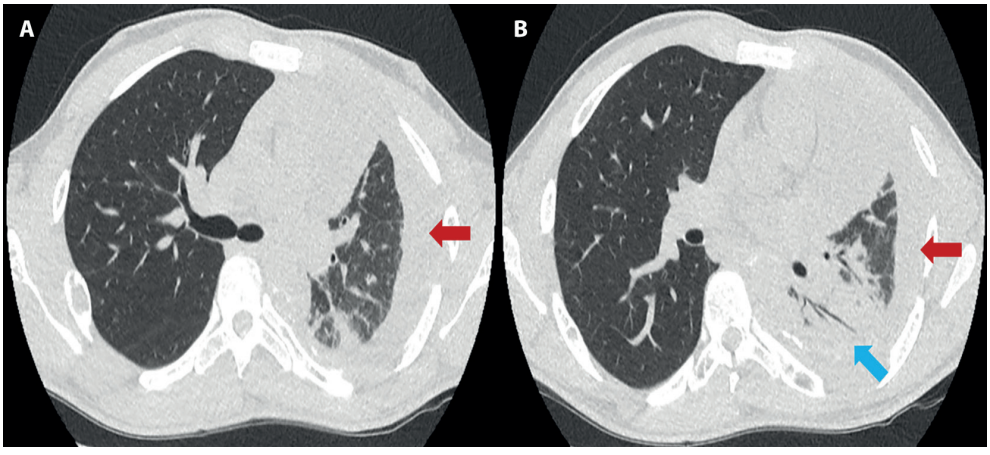

Figure 4. Chest CT scan, lung window. A, B. There is a loss of volume in the left hemithorax, left pleural effusion (red arrows), and infiltrates of alveolar occupation with consolidation of the apical segment of the left lower lobe (blue arrow).

case, the patient presented with multiple cystic lesions in the neck, which is uncommon as lymphangiomas are usually unilateral and rarely develop in adults [3,4].

Lymphangiomas in the neck are usually slow-growing and asymptomatic [10]. Pain may indicate infection, hemorrhage, or compression of the lesion. Imaging studies are necessary for assessment, and ultrasound is commonly used [11]. Sclerotherapy and surgical resection are the main treatment options [10]. However, some lesions tend to recur [8]. In this case, the patient had surgical treatment for a left cervical lymphangioma during childhood, which later recurred. The treatment for lymphangiomas secondary to lymphatic complex anomalies is to treat the primary disease.

Table 2. Pleural fluid.

	Results	Reference values
Pleural fluid		
Glucose (mg/dl)	55	-
LDH (µ/l)	440	-
Proteins (g/dl)	2.9	-
Serum		
LDH (µ/l)	177	135 - 225
Total proteins (µ/l)	5	6.4 - 8.3

LDH, Lactate dehydrogenase.

The diagnosis of GSD is complex and requires a high level of clinical suspicion. It is essential to exclude other causes of osteolysis, such as osteomyelitis, cancer, rheumatoid arthritis, hyperparathyroidism, among others, before suspecting GSD [12]. Diagnosis is based on clinical information and histopathologic and radiographic findings [5]. In the early stages, GSD may be asymptomatic, and routine laboratory tests are usually normal, except for slightly elevated serum alkaline phosphatase levels [9]. Radiographs, magnetic resonance imaging (MRI), and CT scans may show

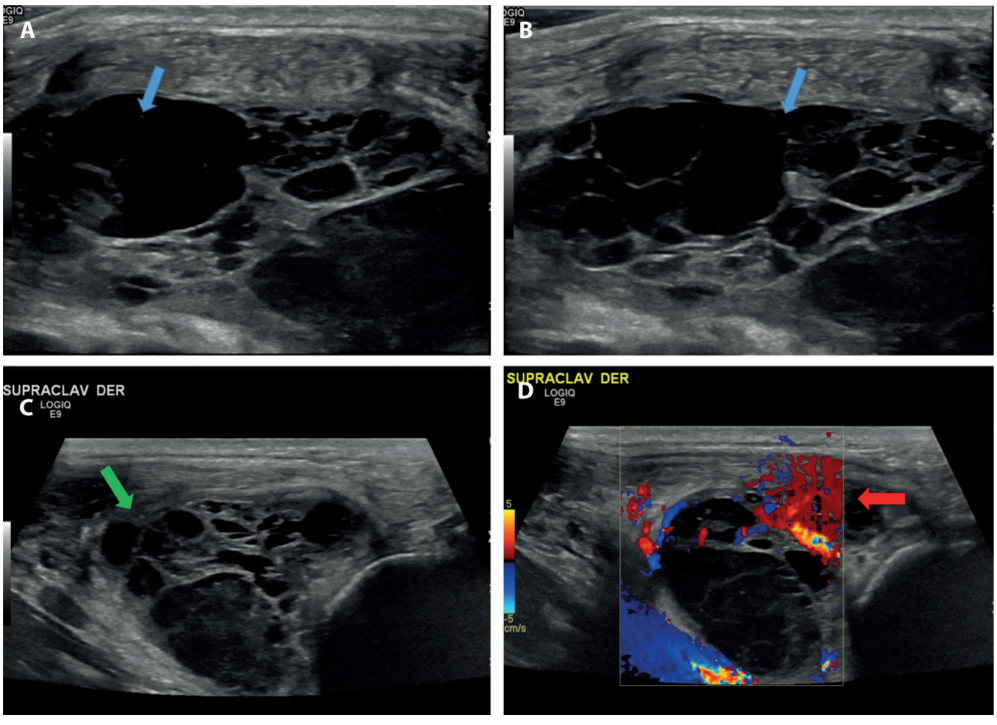

Figure 5. Soft-tissue ultrasound of the right supraclavicular region. A, B, C, D. (Blue arrow) Behind the right sternocleidomastoid muscle is a 5.8 x 2.8 cm multi-cystic lesion with multiple septations, filled with anechoic and heteroechoic content and (Red arrow) some vascular structures crossing it. Two other lateral smaller cysts, less than 9 mm in size, accompany the lesion. (Green arrow**)** There is another cystic lesion in the suprasternal region of 2.8 x 1cm.

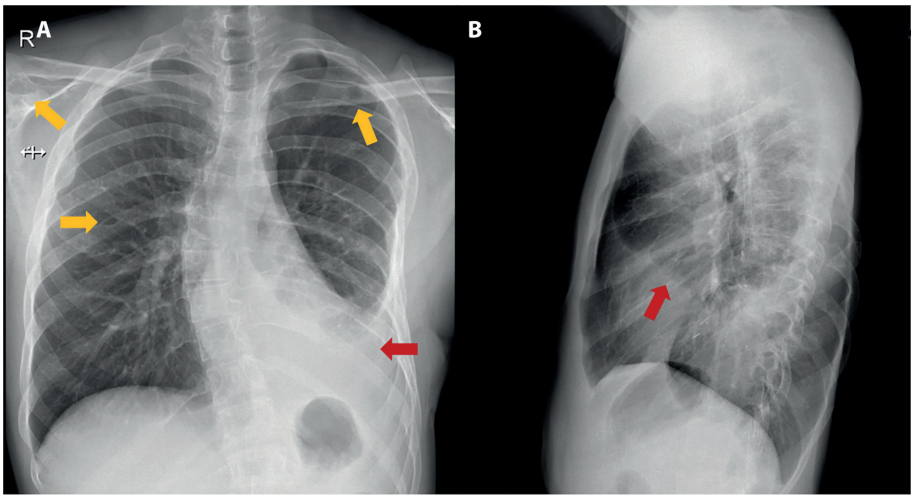

Figure 6. Chest X-ray. A. Posteroanterior projection. B. Lateral projection. Image corresponding to the latest medical check-up showing moderate residual free pleural effusion in the left lung field (red arrow), with fewer lytic lesions observed compared to the onset of the disease (yellow arrow).

osteolytic bone changes [8,13], and osteoporotic findings are common due to increased bone resorption [4]. A bone biopsy with replacement of normal bone with fibrous tissue and non-neoplastic proliferation of capillary or cavernous blood vessels usually confirms the diagnosis.

The natural history of the disease is unpredictable and can be progressive, leading to serious complications, such as pericardial effusion, pleural effusion, and chylothorax when the thoracic bones are involved [14], although there have been rare cases of spontaneous resolution [15]. The patient in this case had recurrent chylothorax due to thoracic bone involvement and persistent pleural effusion, which are further manifestations of GSD. This underscores the importance of heightened awareness of this rare disease entity, particularly when encountering patients with unexplained bone lesions and lymphatic complications after exhausting other diagnostic options.

There is no standard therapy available for the disease, and different therapeutic options have been proposed, including medications, radiation, and surgery, either alone or in combination [16]. Reported therapeutic options include interferon, bisphosphonates, bevacizumab, and mTOR inhibitors, such as sirolimus, which has been described as a promising treatment option for GSD and other complex lymphatic anomalies. A clinical trial using oral sirolimus showed improved disease in 83% of cases, with symptomatic or functional improvement in most patients [6]. Adverse effects related to sirolimus are less than 21%, with oral mucositis having the highest incidence [17,18].

Conclusion

GSD should be considered in young adults with new lymphangiomas in the neck or other areas and associated focal or multifocal osteolysis who are negative for inflammatory, infectious, metabolic, and neoplastic conditions. The complexity of diagnosing Gorham-Stout disease should be emphasized. Currently, sirolimus has been shown to stabilize or reduce signs and symptoms of GSD and other complex lymphatic anomalies.

Abbreviations

GSD: Gorham-Stout disease
mTOR: Mammalian target of rapamycin
CXR: Chest X-ray
IV: Intravenous
CT: Computed tomography
ICU: Intensive care unit
MRI: Magnetic resonance imaging

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Case Report

OPEN ACCESS

Untreated pulmonary sequestration with recurrent superinfection supporting COPD development in a 42 year old male patient

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ABSTRACT

Background: Pulmonary sequestration is a congenital malformation in which nonfunctional lung tissue develops without connection to the bronchial system. The main complication is the occurrence of recurrent pneumonia.

Case presentation: We describe the case of a patient who was incidentally diagnosed with PS as part of the diagnostic algorithm for community-acquired pneumonia. Due to the relatively late diagnosis, the recurrent bronchopulmonary was conducive to the development of COPD and pulmonary emphysema. For prognostic reasons, surgical resection was performed by posterolateral thoracotomy.

Conclusions: Although cigarette smoking is the main risk factor for developing COPD, recurring lung infections may have a synergistic effect. Sometimes recurrent infections are caused by a congenital malformation. Especially in adults who have had recurrent pneumonia since childhood.

Key words: Pulmonary sequestration, congenital pulmonary malformation, COPD, pneumonia, surgical sequestrectomy

Background

Pulmonary sequestration (*lat.* sequestare = to separate) is a congenital pulmonary malformation in which lung tissue exists without communication with the bronchial tree. Since the segment is not ventilated, it remains non-functional [1]. It receives its blood supply not from the pulmonal artery, but from anomalous systemic arteries. Most commonly from the descending thoracic aorta (73%), less frequently from the abdominal aorta, celiac trunk, splenic artery or intercostal arteries [2].

They can appear as extralobar pulmonary sequestrations (ELS), which are covered with their own visceral pleura. With a proportion of 75-85%, the more common type is the intralobar sequestration (ILS), where the lesion lies within the pleural layer surrounded by a functioning lobe [3].

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The etiology remains unclear, but the most plausible hypothesis is the formation of an additional lung bud below the normal lung bud in organogenesis. Along with the normal bud, it moves caudally. If it ripens before the development of the pleura, an intralobar sequestestration results. Conversely, a later development of the bud leads to an extralobar sequestration [3].

In most cases, ILS get symptomatic with recurrent pneumonias of the surrounding pulmonary lobe. Since it is a congenital condition, issues start usually in childhood. In ELS, the sequester is separated from the functional lung tissue by pleura so that it is less likely to become infected [4].

The standard treatment for pulmonary sequestration is surgical removal. It is recommended to avoid progressive inflammation of the lung parenchyma due to recurrent infections. Endovascular embolization is a therapeutic alternative. It aims to reduce blood flow of the sequestered tissue, leading to progressive involution [3].

Case presentation

A 42-year-old male patient presented to the emergency department with fever and productive cough with a yellowish sputum and abdominal pain. The symptoms gradually developed over the past few days. For several months now, he has had an increasing amount of stress dyspnea and loss of weight.

The patient was born in Syria and came to Germany as a refugee in 2015. He reported recurrent bronchopulmonary infections since childhood occurring about twice a year, including multiple hospitalizations and antibiotic treatments. At the age of 25 he was treated against tuberculosis over six months. No preexisting diagnoses or regular medication intake could be determined. There was a continued cigarette abuse with 5-10 cigarettes daily and cumulatively 10 pack/years. Currently, he was working as a gardener in the public sector.

On initial examination he had a blood pressure of 94/73 mmHg with a heart rate of 89/min. The respiratory rate was 25/min with an oxygen saturation of 97% on room air. The tympanic body temperature was 37.7°C. The patient was awake and oriented to all qualities. Heart-sounds were normal. The lung examination revealed expiratory crackles on the basal lung-sections. The abdominal wall was slightly painful to pressure on the left upper quadrant.

After fluid substitution of 2L crystalloid, blood pressure returned to normal. Laboratory investigations revealed elevated inflammatory markers (CRP 111.2 mg/L, leukocytes 12.200/microliter). The chest x-ray showed bilateral atypical infiltrates and a cavernous process on the right basal lung-section.

For further specification, a CT-scan of chest and abdomen was performed. A pronounced paraseptal pulmonary emphysema could be shown. Small-spotted infiltrates on the left lower lobe were present. A consolidation, interspersed with partially secretion-filled caverns, was observed in the right lower lobe (Figure 1). No connection to the genuine bronchial system could be detected. The lesion was supplied from two large-caliber arterial branches, arising from the abdominal aorta. The accessory blood

Figure 1. CT scan indicates signs of lung damage known as pulmonary emphysema. Small-spotted pneumonic infiltrates found in the lower left lobe. Fluid-filled cavities observed within the lower right lobe.

vessel showed an aneurysmal dilation of 11 mm from which two separate branches arise, supplying the consolidation (Figure 2). These findings suggest a superinfected intralobar pulmonary sequestration (ILS).

Blood cultures were drawn and a calculated antibiotic therapy with Piperacillin/Tazobactam 4.5g three times a day was initiated. The patient was admitted to a normal care ward. Regarding the differential diagnosis of reactivated tuberculosis, the patient was isolated. An interferon-gamma-release-assay (IGRA) was performed, and sputum was sampled.

On the next day the examinations were supplemented by a flexible bronchoscopy. A significant quantity of purulent secretion was observed, primarily originating from the right bronchial system. Bronchoalveolar lavage fluid (BALF) was sampled from the right lower lobe.

After starting antibiotic treatment, the patient's condition improved, and the inflammation markers decreased (CRP: 55.1 mg/l on day 3; 29.6 mg/l on day 4). The IGRA test was positive, which can be attributed to a past tuberculous infection that occurred 19 years ago. But sputum, BALF and bronchial secretion all were negative by Auramine-fluorescence staining, PCR and cultural. However, BALF exhibited mixed colonization with *Staphylococcus aureus* (MSSA), *Streptococcus pneumoniae* and *Haemophilus influenzae*. Blood cultures stayed negative after seven days of incubation. After discharge, oral sequence therapy with Cotrimoxazol 960mg twice a day was given for additional 14 days.

Three months after discharge the patient was seen in the outpatient clinic. The cough had almost completely disappeared. Though, dyspnea persisted during physical effort. Body plethysmography revealed an obstructive ventilation disorder with a Tiffeneau index of 59,45% (LLN = 69,7%) without reversibility after salbutamol inhalation. FEV_1 was 3.0L accordingly 64,9% target value. The CT scan graphically confirmed structural emphysema and in a bodyplethysmography, the residual volume was increased (134% of target value).

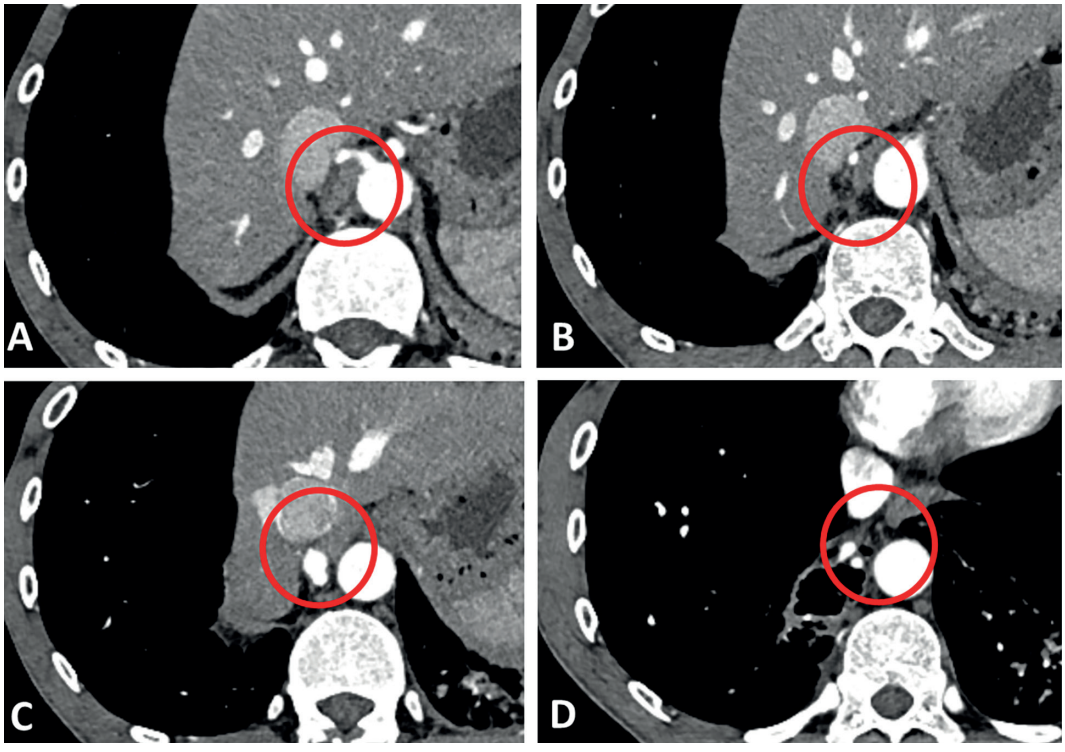

Figure 2. Vascular supply to the PS is through an accessory vessel that originates from the abdominal aorta (A), passes through the diaphragm (B), and ends in an aneurysmal dilation (C) before dividing into two supplying branches (D).

There was no evidence of bronchial asthma in the patient's medical history. The diagnosis COPD GOLD II stadium E was made, and a therapy with a dual bronchodilatator (Indacaterol and Glycopyrroniumbromid) was initiated. An evaluation was conducted for alpha-$_1$-antitrypsin deficiency due to the patient's young age and relatively low cigarette consumption (10 pack/years). The serum concentration of alpha-$_1$-antitrypsin was 179 mg/dL (normal range 90-200 mg/dL). An incorrectly high determination in acute inflammation could not be assumed because leukocyte count, CRP and fibrinogen were also within the normal range at the time.

CT-scan in elective interval exhibited a significant regress of the left sided infiltration. The basomedial sequestration within the right lower lobe had been detected again, but the fluid-levels within the cavities were reduced (Figure 3).

It could be concluded that the recurrent superinfections of the sequestration contributed to the development of COPD and lung emphysema at a relatively young age. For prognostic reasons, the case was discussed with the Department for thoracic surgery for an elective sequestrectomy.

Surgery was scheduled a few weeks after the outpatient presentation. The right hemithorax was opened via posterolateral thoracotomy. Pleural adhesions were carefully detached, the two supplying arterial branches were disconnected, and the sequestration was resected using a stapler. After insertion of two chest drains, the patient was extubated and transferred to an intermediate care unit.

On the second postoperative day, the patient could be transferred to a normal ward. Later on, he developed an acute exacerbation with increased amount of sputum, leading to an antibiotic therapy with Ampicillin/Sulbactam orally for seven days. Chest drains were removed at fourth and fifth postoperative day. On the sixth day after surgery, the patient was discharged home in a good condition.

Gross Pathology exhibited a triangular shaped, 8 x 6 x 5 cm measuring resected lung tissue, including two clipped blood vessels. An afferent bronchus could not be defined. On the cut surface, the tissue was of brownish colour and interspersed with numerous cavities. A viscous white liquid flowed out of the cavities after slicing (Figure 4). Histopathologically, the tissue presented with fibrosis and advanced

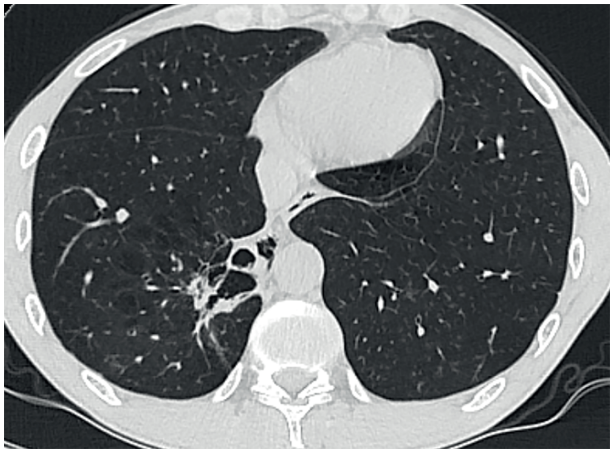

Figure 3. CT-scan in elective interval.

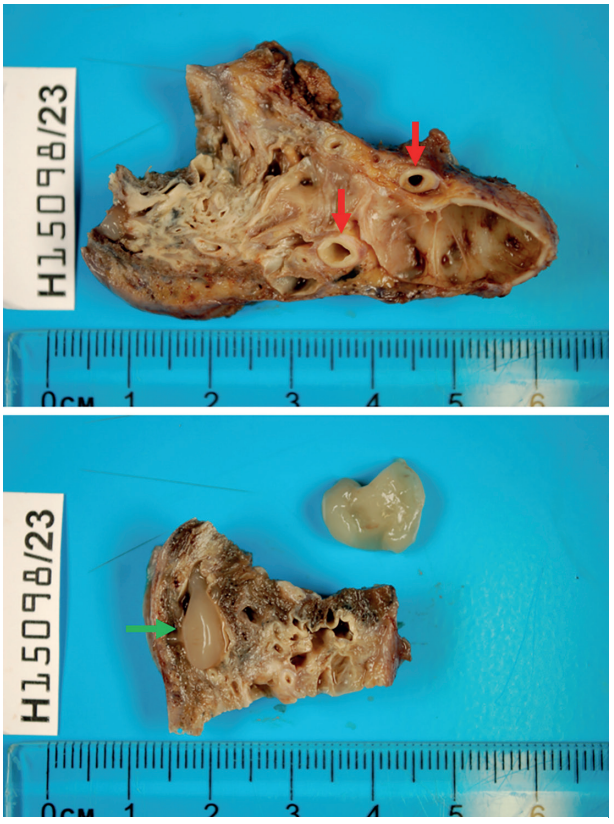

Figure 4. Resected, formalin fixed, pulmonary sequestration, revealing two supplying arterial branches (red arrows) and mucoid filled caverns (green arrow).

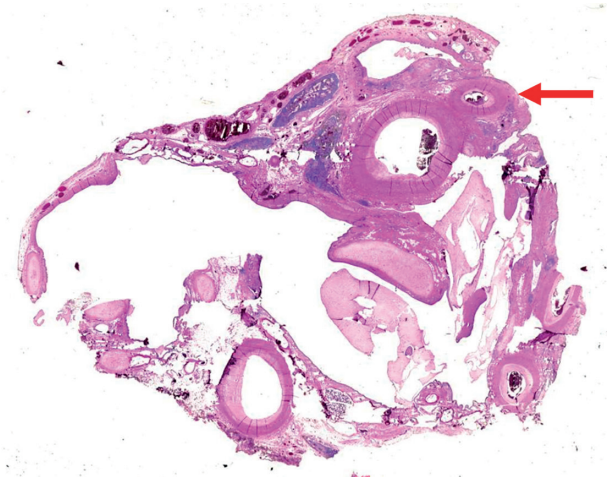

Figure 5. Examination of pulmonary sequestration stained with Hematoxylin and Eosin. The feeding vessel shows the characteristic wall structure of a systemic elastic artery (red arrow).

organized alteration. The feeding vessel exhibited the characteristic wall structure of an elastic systemic artery (Figure 5).

The patient was followed up two months after discharge and reported no new respiratory infections since then. Dyspnea and cough were no longer present. There was an allodynia in the area of the thoracotomy scar, which was treated with analgesics.

With a Tiffeneau index of 67.15% (LLN = 69.7%), body plethysmography continued to show a slightly improved bronchial obstruction. In contrast, residual volume increased to 154% of target value. In this stable phase of the disease, the total IgE level was 104 IU/ml and the eosinophil granulocyte count was 130,9/microliter, ruling out an asthma/COPD overlap. For this reason, the dual bronchodilator therapy was continued without any changes.

Discussion

The patient presented here was first diagnosed with PS in adult age, although he had reported numerous pneumonias since childhood. The late diagnosis is probably due to the fact that the patient grew up in a structurally less developed country, where CT scans are probably not as common as in Western countries.

In a case collection from Mayo Clinic databases, between 1997 and 2016, 32 patients were identified with PS first diagnosed as adults. 15 out of 32 adults with PS were asymptomatic, most common complaint was cough (34%), followed by dyspnea, chest pain, fever and, like in our case, recurrent respiratory infections (16% each) [3].

Historically, COPD has been described as a condition caused by years of cigarette smoke [5]. Thus COPD prevalence correlates with age and smoking duration [6,7]. Even in younger patients, smoking is the main risk factor for development of COPD [8].

Key aspect of COPD-pathogenesis is an imbalance between inflammation and anti-inflammation in lung parenchyma [5]. Therefore, recurrent infections, especially in early development, may also lead to chronic damage to the respiratory tract. A synergistic effect of smoking and frequent pulmonary infections can be assumed. Within smoker-stratified models, FEV_1 deficits among smokers associated with infant lower respiratory infections, compared to smokers without infections, were recently described [9].

The patient was a current smoker, which is indeed a factor for development of his pulmonary emphysema. However, the numerous cases of pneumonia in his history will have contributed significantly to his lung disease.

It is also worth mentioning tuberculosis at the age of 25. Tuberculosis infection is also a risk factor for developing COPD [6]. Unfortunately, tuberculosis treatment was based only on anamnestic reports, without written prescriptions. Except for the cavernous changes, which can be adequately explained by the sequestration, there were no other image morphological residues.

Following the initiation of inhalation therapy, the question arose of a specific therapy of the PS. The therapeutic indication consisted mainly of prognostic aspects. On the one hand, recurrent lower respiratory infections can promote the development of emphysema, on the other hand, chronic infections are also associated with more decline of lung function [10].

As mentioned earlier, treatment options for PS are surgical excision or interventional embolization of the

supplying artery. Embolization seems to be the gentler procedure, as no thoracotomy is necessary. But studies have shown that only some of the endovascular treated PS achieved complete remission. Another drawback is that there is no tissue obtained for pathologic examination [11]. In the case of our patient, there was also a risk that the caverns would melt down abscessing during ischemia conditions.

Surgical methods include thoracotomy and video-assisted thoracoscopy (VATS). VATS is considered a good choice in selected cases of simple PS without adhesions [12]. Due to numerous superinfections, our patient has developed major pleural adhesions in the area of the diaphragm and mediastinum (Figure 1), which is why we opted for an open thoracotomy.

A significant surgical pitfall is the systemic vascular supply of the sequester. Because the lesion is supplied by accessory arteries, accurate preoperative imaging is helpful. This allowed us to target the arteries and clip them before resection. In this way, a large perioperative blood loss could be avoided.

Conclusion

When pulmonary emphysema is diagnosed at a young age, cigarette smoke may not be the only cause. Recurrent respiratory infections can contribute synergistically to the development of COPD. In this case of recurrent lower respiratory tract infections, a predisposing factor may be present. In addition to an immune deficiency, a congenital malformation, like in our case pulmonary sequestration, might be a rare cause of COPD development.

In our patient, an intralobar pulmonary sequestration was diagnosed relatively late; recurring infections led to morphological lung damage. We decided to remove the lesion for prognostic reasons. Different treatment options were available. Due to the cavernous changes and the pleural adhesions, an open operation through posterolateral access, seemed appropriate.

List of abbreviations

BALF = Bronchoalveolar lavage fluid
COPD = Chronic obstructive pulmonary disease
CRP = C-reactive protein
CT = Computer tomography
ELS = Extralobar lung sequestration
FEV1 = Forced expiratory volume in one second
GOLD = Global initiative for chronic obstructive lung disease
IGRA = Interferon gamma release assay
ILS = Intralobar lung sequestration
LLN = Lower limit of normal
MSSA = Methicillin sensitive *Staphylococcus aureus*
PCR = Polymerase chain reaction
PS = Pulmonary sequestration
VATS = Video-assisted thoracoscopy

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Breve resoconto

a cura della Redazione

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Le nuove sfide in Medicina respiratoria

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Gli operatori sanitari di oggi si trovano a dover gestire non solo le diverse patologie acute e croniche dei pazienti, ma anche un Sistema Sanitario complesso e dinamico che si avvale di nuove tecnologie; essi devono pertanto avere capacità adeguate per affrontare le nuove sfide e tutti gli inerenti aspetti legislativi, politici, finanziari, organizzativi, professionali, tecnologici e di assistenza. Da ciò deriva la necessità crescente di un approccio multidisciplinare e strategico alle problematiche, che si basi su strumenti aziendali condivisi, integrati nel processo decisionale quotidiano della gestione del nostro Sistema Sanitario. Partendo da queste "nuove sfide", la tematica si è dibattuta dal 7 al 9 novembre scorso nel tradizionale Congresso autunnale "Pneumomeeting" di Taormina, giunto alla 17a edizione e contrassegnato, come sempre, da una vocazione clinica e interdisciplinare. Il programma articolato sotto la guida scientifica dei Chairmen: Dr. Salvatore Bellofiore, Dr. Riccardo Giuliano, Dr. Salvatore Privitera, Dr. Mario Schisano e Prof. Carlo Vancheri ha visto la partecipazione di una Faculty di ottimo livello scientifico.

Come è noto, la recente pandemia da Sars- COV-2, anche in ambito strettamente pneumologico ha messo in luce le lacune del nostro Sistema Sanitario, contribuendo ad accelerare un processo di revisione e di innovazione e riconoscendo una maggiore centralità alle Malattie Respiratorie.

In questo contesto di cambiamento Pneumomeeting 2024 ha voluto dare il suo contributo attraverso il confronto dialettico fra professionisti sanitari, in particolare pneumologi, alla luce della loro esperienza scientifica e professionale, mirando a fornire ai partecipanti e agli organismi sanitari competenti messaggi chiari, utili nell'esercizio quotidiano della professione medica ma anche nelle scelte organizzative da parte dei decisori politici.

L'edizione 2024, con un format articolato in Simposi di approfondimento, Letture e Workshop, ha proposto due sessioni monotematiche di aggiornamento, con un programma scientifico centrato su problematiche specifiche di frequente riscontro nella pratica clinica quotidiana sia ospedaliera che territoriale in un confronto dinamico fra evidenze scientifiche e di real-life. Tra i vari temi dibattuti utili per la pratica clinica quotidiana, ricordiamo a titolo d'esempio le malattie rare del polmone, le nuove strategie diagnostiche e terapeutiche nelle patologie polmonari ostruttive, oltre alle relazioni di elevato contenuto scientifico relative all'insufficienza respiratoria acuta e cronica, ad asma e BPCO, alle apnee ostruttive nel sonno e al loro trattamento sia ventilatorio che attraverso altri innovativi percorsi terapeutici.

Attenta partecipazione durante un momento dei lavori congressuali nella sala principale.

L'angolo della Cultura (non solo Medicina…)

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Se anche l'universitario ignora l'italiano

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"La scuola non deve insegnare un mestiere
ma deve insegnare come cambiare mestiere".
(Massime dalla saggezza confuciana).

"Quello è di un'ignoranza enciclopedica".
Stanislaw J. Lec

Nel 1948 frequentai la quinta elementare a 5 chilometri da casa nella scuola dove insegnavano i miei genitori: per eccesso, diciamo così, di "vivacità" le suore mi avevano "invitato" ad andare altrove per la licenza elementare. Pertanto, ogni santa mattina, assieme a papà e mamma, mi recavo con il tram alla mia nuova scuola. Un giorno feci notare a babbo che su un muro c'era scritto: "Il pescìe grande mangia sempre il pescìe piccolo"; il commento accomodante fu: "«Che vuoi fare, figlio mio, la guerra è appena finita, le scuole sono state chiuse per anni, perdoniamo quella "ì" di troppo».

Ma le cose - anche senza guerre in atto - sembra che oggi non siano cambiate granché, anzi. Ammesso che allora ci fossero delle attenuanti, oggi queste sono decisamente inammissibili. È stato accertato che su 100 alunni del secondo anno delle superiori, venti non sanno l'italiano. Eppure la nostra lingua è una parte essenziale del problema perché conoscere la propria lingua significa padronanza del ragionamento e delle risorse espressive più adeguate per illustrarlo. Un bambino italofono si affaccia alla scuola elementare con una dotazione di 2000 parole, che sono quelle che ti permettono di sopravvivere: il 90 per cento dei discorsi prodotti comunemente dagli adulti, invece di avere un patrimonio linguistico molto più ricco, usa lo stesso numero di parole. Questa sembra essere la situazione degli adolescenti italiani con una forbice che si allarga drammaticamente tra i licei del Nord-Est e gli istituti professionali del Mezzogiorno. In parole povere, non sapere l'italiano significa che, alla fine delle scuole superiori, un ragazzo non è in grado di capire un articolo di fondo. Inoltre, molti arretrano davanti alle prime parole astratte. Per molti sono incomprensibili parole come "esimere" o "desumere", che sono mattoni fondamentali per la costruzione di un discorso argomentativo. O parole meno usuali come "facezie", che possono dare alla frase una connotazione ironica. O, infine "deflagrante" e "propedeutico", per non dire di "pàupulo": si tratta del verso del pavone, ma ho dovuto consultare il vocabolario anche io. Per non parlare poi della tabella sul vaccino contro l'influenza: essa non richiede finezze interpretative, si tratta di un testo trasparente, con poche subordinate e nessuna parola desueta. Ebbene, è preoccupante che non l'abbiano capito tra il 33 e il 40 per cento dei quindicenni. Forse gioca anche il fattore dell'ansia, comprensibile in ragazzi alle prese con i test.

Secondo l'indagine PISA, in uno su cinque che non conosce l'italiano, il deficit principale non è l'ortografia, un problema ricorrente è la violazione della coerenza testuale, che è poi l'incapacità di argomentare gerarchizzando le questioni trattate. Anche nei temi di intonazione intimistica sorprendono le frasi prive di senso compiuto. Infatti è stato riportato da un docente un tema in cui l'alunna di 15 anni, scrive: «Noi ragazze siamo molto diverse dai maschi... perché noi cerchiamo sempre l'abbraccio, il bacetto che ci fa sentire al sicuro da tutte le cose che ci sembrano brutte. Al contrario i maschi...» e qui mi sarei aspettato: "sono insensibili", "pensano soprattutto al sesso". Niente di tutto questo. «Al contrario i maschi cercano di dare il meglio di loro, ma alla fine non ci riescono». La ricostruzione dello specifico maschile s'è perduta per strada... Questo perché a scuola si insiste troppo sulla teoria grammaticale, specie nella scuola media e nel biennio. Poi scrivere bene implica leggere bene. E leggere bene significa andare oltre il testo letterario. E allora più saggistica e meno Dante? No, Dante è fondamentale, ma nel triennio delle superiori bisognerebbe leggere anche una rivista come *Limes*, ossia articoli di geopolitica e sociologia, storia economica e storia della scienza. Brani che possano offrire modelli di organizzazione linguistica del pensiero complesso. Paradossalmente questa operazione è più facile negli istituti tecnici che non nei licei, in cui è tuttora centrale il percorso letterario, com'è giusto che sia. E allora qualcuno suggerisce di far cimentare gli alunni con esercizi più pedestri, come il riassunto, genere che prediligo e che verifica la comprensione, educa alla sintesi correggendo la tendenza alla verbosità e aiuta a selezionare le notizie più importanti. La sua pratica andrebbe estesa oltre la scuola media. Per la correzione, va bene il rosso e il blu (me li sogno ancora di notte sin dai tempi delle elementari dalle suore), ma oggi suggerirei ai professori anche la matita verde per evidenziare con questo colore la scrittura più espressiva e meno scontata. Anche per evitare di trasformare il compito in un camposanto pieno di croci; insomma, se c'è, diamo anche qualche premio! Non bisogna però avere pretese eccessive nel senso che si voglia vedere fiori di stile fiorire dalle tastiere di architetti, matematici, scienziati e medici, come accadeva per Leon Battista Alberti, Renato Caccioppoli, Enrico Fermi e Umberto Veronesi! Niente affatto: si chiede solo che studenti e laureati sappiano scrivere e parlare in italiano, possedere un buon bagaglio lessicale, conoscere grammatica e sintassi, in un cammino che parta dal ciclo di elementari e medie.

Chiediamo una cosa ovvia? Sì, ma fondata, purtroppo, su un'attività che assurdamente non è "alla moda", ritenuta dal coro supino dei nuovi analfabeti globali superata e poco moderna: l'attività della lettura. In Italia la lettura è una Cenerentola non solo senza scarpine, ma buttata nel fuoco e in fin di vita, come dicono le statistiche che rivelano cose aberranti: come il fatto che un'enorme percentuale di laureati non legge libri, un'altra legge solo libri per lavoro, un'altra ha in casa meno di cento libri: e si parla di architetti, medici, ingegneri, chimici, informatici, professori e così via. Tuttavia la lettura è la sola via che porta all'apprendimento di quella "grammatica e sintassi" e di quel "buon bagaglio lessicale" evocati: la lettura contiene implicitamente ciò che forma il linguaggio, le cui regole possono essere spiegate a un "leggente" in poco tempo, quando per spiegarle a un "non-leggente" non basterebbe una vita. Ma cosa dicono i laureati rispondendo a domande sulla lettura? Rispondono che è superata, che ci sono altri modi di apprendere, e che in sintesi a loro non gliene frega un accidente di saper leggere e scrivere: e poi se proprio vogliono fare i colti dicono "dirimere un dubbio", unendo in puro Italian style il burocratese all'ignoranza. Invece lettura e scrittura contribuiscono a formare una mente organizzata e duttile, dotata di connessioni molteplici, in grado di accostarsi ai digital media in maniera attiva e creativa, non usando uno strumento complesso alla maniera di un primitivo. La questione sembra semplice, ma non lo è: i seicento (dotti, medici e sapienti, direbbe Edoardo Bennato, *ndr*) che recentemente hanno scritto al

Ministro chiedono che a scuola si impari l'italiano, ma lo chiedono alla scuola dei quiz e dei quizzetti considerati a lungo come moderni o scientifici da fabbricanti di riforme provinciali.

È nostra convinzione che la lettera inviata al Ministero dell'Istruzione non sia sufficiente: ci vorrebbero centinaia di migliaia di lettere da parte del corpo docente intero e dei familiari degli alunni che riportasse al centro della società intera il problema della lettura e scrittura dell'italiano. Solo allora forse ci troveremmo di fronte a un vero cambiamento, perché saremmo costretti a parlare di lettura libera fin dalla scuola e poi nell'età adulta; non dovremmo giustificare chi dice, o pensa senza dirlo, che leggere è "una cosa vecchia"; viceversa, riscopriremmo che chi pensa male, cioè in maniera ottusa e violenta, lo fa perché parla male e legge male, imparando ciò che ben sanno psichiatri e neuro scienziati, e cioè che chi non ha parole per esprimersi indebolisce anche i sentimenti legati alle parole e crede che una vendetta sia un atto di giustizia, che farsi massacrare di botte dal fidanzato sia amore, che sputare sui deboli sia essere forti, che politica significhi arricchirsi e religione assassinio. La lettera dei seicento in difesa dell'italiano morente è solo un inizio: se si vuole davvero che esista un futuro, a questo inizio dovrà seguire una valanga. Una valanga metaforica, come si direbbe in un passabile italiano.

Non è possibile che gli alunni di un primo anno del liceo scientifico ignorino un verbo come "biasimare", oltre "beffardo" e "sardonico"; ma l'elenco potrebbe a questo punto comprendere molte altre parole, per es. "alacre, blandire, foriero, gaudio, laconico, mellifluo, risibile, sussiego, tralignare"... Alcuni esperti hanno sottolineato che il punto nodale della questione è che molti giovani «non sono in grado di argomentare, perché non padroneggiano la sintassi e la testualità». Sono come impacciati nel confronto con forme e categorie puntuali, sostituite da entità diffuse e capienti contenitori di riempimento eterogeneo di senso, fanno difficoltà a smarcarsi dalla sequenzialità; non riescono a sottrarsi alle insidie delle riprese "ingenue" del già detto (sembra dicano una cosa per la prima volta, in realtà ne hanno già parlato); non sanno procedere ordinatamente per punti e non riescono a riprendere il filo del discorso dal punto esatto in cui lo hanno interrotto; non distinguono tra elementi portanti ed elementi accessori di un testo; non sono in grado di intervenire sul flusso del pensiero tagliandovi capitoli e paragrafi; non sanno adoperare nel modo corretto i connettivi (dunque, infatti, tuttavia…).

E allora quale futuro? Come uscire da questa imbarazzante e dannosa situazione? Abbiamo, innanzitutto, bisogno di una scuola davvero esigente nel controllo degli apprendimenti, oltre che più efficace nella didattica, altrimenti né l'impegno degli insegnanti, né l'acquisizione di nuove metodologie saranno sufficienti. Un docente ha candidamente confessato: «Dedico ormai una buona parte della mia attività di docente a correggere l'italiano delle tesi di laurea». Intanto, i nostri tempi, caratterizzati da un'accensione quasi esclusivamente visiva (tv, pc, telefonini, film, foto, etc) potrebbe finire per annullare le qualità necessarie per affrontare una pagina scritta. Forse fra qualche decennio tracce e orientamenti di lingua e di scrittura prenderanno definitivamente il posto delle vecchie regole. Come dire un ritorno dunque a condizioni premoderne, non dissimili da quelle di diffuso analfabetismo

Dante Alighieri, padre della lingua italiana.

dell'Europa medievale. È indispensabile invece che, a far da traino, intervengano i fruitori attivi e colti dell'italiano; gli appassionati consapevoli dell'importanza del suo valore comunicativo come delle sue tante ambiguità e insidie; gli insegnanti e gli educatori animati da quel senso civico che li fa fortunatamente diffidare delle facili soluzioni, semplicistiche o ideologiche, a delicati o complessi problemi grammaticali; i veri "militanti" della lingua, sensibili alle responsabilità che ci si deve assumere ogni qualvolta, dalla propria tribuna di professionisti operanti in campi strategici (docenti, giornalisti, accademici, politici, anchorman...) si parla o si scrive perché altri realmente leggano o ascoltino.

È vero che nella scuola dell'obbligo il buonismo con cui gli insegnanti tendono a promuovere tutti, anche gli analfabeti, è dilagante, ma è altrettanto vero che i nostri ragazzi fanno oggi i conti con un disprezzo generalizzato della lingua italiana diffuso sia nei romanzi di certi autori contemporanei, pieni zeppi di parolacce, sia nei giornali e nella televisione, che fanno largo uso di un linguaggio sempre più sciatto, pieno di scorciatoie e strafalcioni. Con la speranza di non essere finiti anche noi con "il piede nel fosso" della sciatteria.

Meeting Calendar

WHEN	WHERE	WHAT	WHO TO CONTACT
		2024	
December 5-7	Astana (Kazakhstan)	Third National Congress of Respiratory Medicine	https://congressnorm.kz/
December 6-7	Mons (Belgium)	Belgian Pneumology Days 2024	https://belgianrespiratorysociety.be/
December 12-15	Athens (Greece)	33rd Panhellenic Pulmonology Congress 2025	https://www.33pneumonologiko2024.gr/
January 16-17	Odense (Denmark)	Thoracic ultrasound training programme	www.ersnet.org
March 1	Copenhagen (Denmark)	Thoracic ultrasound training programme	www.ersnet.org
March 6-8	Vienna (Austria)	Course: "Paediatric asthma"	www.ersnet.org
March 11-12	Heidelberg (Germany)	Course: "EBUS training programme – part one"	www.ersnet.org
March 17-19	Naples (Italy)	Skills course: "Paediatric bronchoscopy"	www.ersnet.org
April 10-12	Antwerp (Belgium)	Sleep and Breathing Conference 2025	www.ersnet.org
March 23-2	Estoril (Portugal)	ERS Lung Science Conference 2025	www.ersnet.org
June 5-7	Marseille (France)	Skills course: "Rigid bronchoscopy"	www.ersnet.org
September 27-October 1	Amsterdam (Netherlands)	ERS Congress 2025	www.ersnet.org
September 29-October 1	Naples (Italy)	Skills course: "Paediatric bronchoscopy"	www.ersnet.org
November 14-16	Verona (Italy)	XXVI Congresso della Pneumologia Italiana - XlVIII AIPO -ITS	segreteria@aiporicerche.it

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1. Troy NM, et al. J Allergy Clin Immunol 2022;S0091-6749(22)00040-9.
2. BRONCHO MUNAL, Riassunto delle caratteristiche del prodotto.

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