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ABOUT

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Thoracic Research and Practice is a bimonthly journal that is published in English in January, March, May, July, September, and November.

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Thoracic Research and Practice started its publication life following the merger of two journals which were published under the titles "Turkish Respiratory Journal" and "Toraks Journal" until 2008. From 2008 to 2022, the journal was published under the title "Turkish Thoracic Journal". Archives of the journals were transferred to Thoracic Research and Practice.

Abstracting and indexing

Thoracic Research and Practice is covered in the following abstracting and indexing databases; PubMed Central, Web of Science - Emerging Sources Citation Index, Scopus, EMBASE, EBSCO, CINAHL, Gale/Cengage Learning, ProQuest, DOAJ, CNKI, TUBITAK ULAKBIM TR Index.

Aims, Scope, and Audience

Thoracic Research and Practice aims to publish studies of the highest scientific and clinical value, and encourages the submission of high-quality research that advances the understanding and treatment of pulmonary diseases.

Thoracic Research and Practice covers a wide range of topics related to adult and pediatric pulmonary diseases, as well as thoracic imaging, environmental and occupational disorders, intensive care, sleep disorders and thoracic surgery, including diagnostic methods, treatment techniques, and prevention strategies. The journal is interested in publishing original research that addresses important clinical questions and advances the understanding and treatment of these conditions. This may include studies on the effectiveness of different treatments, new diagnostic tools or techniques, and novel approaches to preventing or managing pulmonary diseases.

Thoracic Research and Practice publishes clinical and basic research articles, reviews, statements of agreement or disagreement on controversial issues, national and international consensus reports, systematic reviews and meta-analyses, letters to the editor and editorials. Conference proceedings may also be considered for publication.

The target audience of the journal includes healthcare professionals and researchers who are interested in or working in the pulmonary diseases field, and related disciplines.

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Thorac Res Pract. 2025;26(3):88-96 DOI: 10.4274/ThoracResPract.2024.24079

Original Article

A Research on Healthcare Professionals' Stigma Towards Tuberculosis Patients

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Abstract

OBJECTIVE: Strong collaboration between healthcare professionals and patients is necessary for the control of tuberculosis (TB), a potentially fatal and contagious disease without treatment. Our research aims to evaluate whether healthcare professionals have stigmatizing attitudes and behaviours toward TB patients.

MATERIAL AND METHODS: A web-based survey of 19 questions covering clinical situations was designed. A total of 528 healthcare professionals working in different healthcare institutions across the country participated in the survey. Stigma scores were recorded on a 5-point Likert response scale ranging from -2 to +2: the extreme points were 'strongly disagree' and 'strongly agree'.

RESULTS: The highest stigma scores were observed in non-physician auxiliary healthcare personnel groups such as medical secretaries, social workers, dietitians, pharmacists, midwives, nurses, and nurse assistants, while the lowest scores were detected in specialist physicians and academic physicians. In demographic analyses, it was observed that healthcare workers (HCWs) who more often encounter TB cases have higher stigma scores. In addition, when evaluated according to the type of institution they work in, it was found that stigma levels were higher in pharmacies, clinics, individual medical practices, private and independent healthcare institutions, and workplaces.

CONCLUSION: This study can contribute to reducing the stigma levels of HCWs towards TB patients with effective training programs and appropriate health policies, thus improving the health services provided to patients.

KEYWORDS: Tuberculosis, stigmatization, healthcare workers, health policies

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INTRODUCTION

Tuberculosis (TB) control continues to maintain its importance in the 21st century. Some of the reasons behind this are the increasing global climate crisis, the effects of regional conflicts and wars, mass human migrations, and disrupted TB control mechanisms during the Coronavirus disease-2019 (COVID-19) pandemic. Immigrants and refugees are more likely to disrupt TB treatments and accelerate the spread of TB in societies.[1-4] At this point, the attitudes and behaviours of healthcare professionals towards TB cases gain importance. Studies showed that, 80% of TB cases in various societies were subjected to stigma. It has been demonstrated that TB cases who encounter stigma tend to exhibit behaviours that will disrupt TB control and to avoid seeking medical help. Their compliance with TB treatment decreases.[5,6] This has led the World Health Organization to emphasize that TB stigma is a major obstacle to ending TB by 2050 and that all forms of discrimination in health should be eliminated.[7]

Due to professional ethics, it is more difficult to reveal the stigmatising attitudes and behaviours of health professionals towards TB cases, than to investigate society-based stigma. In addition, the negative attitudes of health professionals towards TB cases have a more negative effect on TB patients than the stigmatising attitudes of society.[8,9] In this context, we aimed to elucidate the attitudes and behaviours of health professionals towards TB patients and to reveal the reasons for stigma, if any.

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MATERIAL AND METHODS

Ethics Approval

The survey was conducted between March and June 2024. All procedures adhered to the ethical standards of the responsible institutional and national committees on human experimentation, as well as the Helsinki Declaration of 1975, revised in 2008. Ethics committee approval was granted by University of Health Sciences Türkiye, Gazi Yaşargil Training and Research Hospital (protocol number: 920, date: 05.11.2021), and informed consent was obtained from all participants. The participants' identities were kept confidential, and the data obtained were used only within the scope of this research.

Research Design

This study involved 528 healthcare workers (HCWs) from various provinces and hospitals. A 19-question survey, designed based on clinical situations observed by the researchers in the work environment, was used to measure the participants' attitudes towards TB cases. Participants shared their opinions on TB-related clinical and work environments using a 5-point Likert scale. Only question 18 used a 3-point Likert-type scale with the options 'Yes,' 'No,' and 'No idea,' allowing participants to express opinions reflecting on their entire professional life. Responses were scored between "strongly disagree" and "strongly agree", with a stigma score of -2 and +2 at the extremes. Participants' demographic information such as age, gender, education level, specialty, institution type, and the number of patients seen annually was recorded (Table 1).

HCWs were recruited through a web-based approach. Invitations to participate in the survey were distributed via email and WhatsApp by the researchers, targeting healthcare professionals across various institutions in the country. Participation was voluntary, and all responses were anonymized to ensure confidentiality.

Study Participants

Participants were healthcare professionals from public, university, and private institutions, and individual healthcare facilities. They included midwives, nurses, nursing assistants, general practitioners (GPs), residents, specialist physicians, academic physicians, pharmacists, dietitians, dentists, laboratory technicians, social workers, and medical secretaries.

Main Points

- Healthcare workers' (HCWs) stigma levels towards tuberculosis (TB) patients were found to be high, especially among non-physician auxiliary health personnel and nurses.
- HCWs who encounter TB cases more frequently have higher stigma scores.
- Stigmatized attitudes towards TB patients were found to be higher among private and individual medical practitioners.

Data Collection and Processing Methods

Responses were scored from -2 to +2 stigma points, ranging from 'strongly disagree' to 'strongly agree'. The frequency of the responses in each question was multiplied by the coefficient of that response according to the Likert scale, and the weighted frequency (WF) of the questions was calculated. Then, the WF values were divided by the total number of participants and the Weighted Frequency Index (WFI) was obtained for each question. Since some WFI values were outside -1 and +1, WFI values were normalised by dividing them by the highest

Table 1. Survey statements

S1	If I had to examine a patient with tuberculosis, I would be putting my health at risk.
S2	After examining tuberculosis patients, I pay more attention than usual to hand disinfection.
S3	I unconsciously show bias against tuberculosis patients because they can infect me.
S4	In some cases, tuberculosis patients may try to infect healthcare workers deliberately, though this is not representative of all cases.
S5	Even though tuberculosis cases concern my specialty, I immediately refer them to the tuberculosis centre.
S6	Patients with tuberculosis are contagious even if they use a surgical mask.
S7	DOT is ineffective in controlling tuberculosis.
S8	Treatment of tuberculosis patients should be carried out only by pulmonologists.
S9	The entire treatment process of tuberculosis patients should be completed in 'Sanatorium Type' hospitals.
S10	Tuberculosis patients must first complete tuberculosis treatment before addressing health problems.
S11	In the centre where I work, tuberculosis patients cannot be hospitalised and treated because of their comorbidities.
S12	I feel pressure from the management of the institution where I work to refer tuberculosis patients to tuberculosis dispensaries or sanatoriums.
S13	Tuberculosis patients should benefit from private health services, for a fee.
S14	Physicians should pay attention to the socio-economic problems of tuberculosis patients.
S15	As a healthcare worker, if I were diagnosed with tuberculosis one day, I would not want other healthcare professionals to know about this. I am worried about not being able to receive qualified health care for my health problems at the health institution I apply to.
S16	I am uncomfortable interacting with tuberculosis patients in my work unit.
S17	I prefer to communicate with the relatives of tuberculosis patients rather than with the patients themselves.
S18	In the past, I treated a patient differently from usual when I knew he had tuberculosis.
S19	Healthcare professionals often stigmatise tuberculosis patients.

This table lists the statements used in the survey to assess attitudes and perceptions towards tuberculosis patients. Each statement reflects a different aspect of how healthcare professionals may view or interact with individuals diagnosed with tuberculosis.
DOT: Directly Observed Treatment

absolute value of WFI in our data set, thus obtaining the Normalized Weighted Frequency Index (NWFI) ranging from -1 to +1 (Table 2). WF, and NWFIs were calculated to assess stigma scores. These indices were determined by multiplying the frequency of each response by its corresponding stigma coefficient, summing the results, and then averaging them. The formulas and detailed calculations are provided in Appendix 1.

Statistical Analysis

The collected data were analyzed using Statistical Package for the Social Sciences 20.0 statistical software. Descriptive statistics were calculated for demographic data, and Mann-Whitney U and Kruskal-Wallis tests were applied for group comparisons. In the analysis of stigma scores, inverse values were used to ensure that higher scores represented higher stigmatisation. Post-hoc analyses were performed by applying Mann-Whitney U tests between subgroups. The results were considered statistically significant when the *P* value was less than 0.05.

RESULTS

A total of 528 participants were included in the study. The mean age of the participants was 42.75 years [standard deviation (SD): 9.681], and the ages ranged from 23 to 79. The age distribution was approximately normal, with a skewness value of 0.287 (SD: 0.106). 23.1% (n = 122) of the participants were under 35 years of age, 53.4% (n = 282) were between 35 and 49 years of age, and 23.5% (n = 124) were 50 years of age and older. The gender distribution was 44.3% (n = 234) male and 55.7% (n = 294) female. According to the level of education, 0.4% (n = 2) of the participants were high school graduates, 1.9% (n = 10) had an associate degree, 22.9% (n = 121) had a bachelor's degree, 50.8% (n = 268) had a master's degree, and 24.1% (n = 127) had a doctorate. In the distribution by type of healthcare professionals, 8.5% (n = 45) were midwives, nurses, and nurse assistants, 26.7% (n = 141) were other healthcare professionals, 9.7% (n = 51) were GPs, 10% (n = 53) were residents, 30.5% (n = 161) were specialist physicians, and 14.6% (n = 77) were academic physicians. In terms of branch distribution, 48.1% (n = 254) are chest diseases specialists, 13.1% (n = 69) are specialists in internal medicine and its subspecialties, 11.2% (n = 59) are GPs and dentists, 16.7% (n = 88) are non-physician health workers and 11% (n = 58) work in the surgical branch. In terms of distribution by health service level, 12.5% (n = 66) work in primary care, 18.9% (n = 100) in secondary care, and 68.6% (n = 362) in tertiary care (Table 3).

Table 2. Survey statements and responses with WF, WFI and NWFI

	-2 (n, %)	-1 (n, %)	0 (n, %)	+1 (n, %)	+2 (n, %)	WF	WFI	NWFI
S1	113 (8.4%)	135 (10.0%)	84 (6.2%)	121 (8.9%)	75 (5.5%)	-90	-0.170	-0.531
S2	204 (15.1%)	135 (10.0%)	51 (3.8%)	74 (5.5%)	64 (4.7%)	-341	-0.645	-1.000
S3	142 (10.5%)	131 (9.7%)	57 (4.2%)	87 (6.4%)	111 (8.2%)	-106	-0.200	-0.561
S4	60 (4.4%)	92 (6.8%)	57 (4.2%)	74 (5.5%)	245 (18.1%)	352	0.666	0.292
S5	150 (11.1%)	96 (7.1%)	63 (4.7%)	65 (4.8%)	154 (11.4%)	-23	-0.043	-0.406
S6	89 (6.6%)	111 (8.2%)	74 (5.5%)	119 (8.8%)	135 (10.0%)	100	0.189	-0.177
S7	11 (0.8%)	14 (1.0%)	76 (5.6%)	87 (6.4%)	340 (25.1%)	731	1.384	1.000
S8	64 (4.7%)	84 (6.2%)	44 (3.3%)	104 (7.7%)	232 (17.2%)	356	0.674	0.300
S9	110 (8.1%)	116 (8.6%)	59 (4.4%)	81 (6.0%)	162 (12.0%)	69	0.130	-0.235
S10	141 (10.4%)	121 (8.9%)	54 (4.0%)	73 (5.4%)	139 (10.3%)	-52	-0.098	-0.460
S11	95 (7.0%)	54 (4.0%)	113 (8.4%)	127 (9.4%)	138 (10.2%)	159	0.301	-0.067
S12	55 (4.1%)	89 (6.6%)	101 (7.5%)	92 (6.8%)	191 (14.1%)	275	0.520	0.149
S13	91 (6.7%)	70 (5.2%)	61 (4.5%)	70 (5.2%)	236 (17.5%)	290	0.549	0.177
S14	50 (3.7%)	82 (6.1%)	135 (10.0%)	124 (9.2%)	137 (10.1%)	216	0.409	0.039
S15	59 (4.4%)	109 (8.1%)	82 (6.1%)	104 (7.7%)	174 (12.9%)	225	0.426	0.055
S16	78 (5.8%)	121 (8.9%)	69 (5.1%)	107 (7.9%)	153 (11.3%)	136	0.257	-0.110
S17	111 (8.2%)	125 (9.2%)	87 (6.4%)	68 (5.0%)	137 (10.1%)	-5	-0.009	-0.373
S18	227 (16.8%)		109 (8.1%)		192 (14.2%)	-70	-0.132	-0.494
S19	50 (3.7%)	82 (6.1%)	139 (10.3%)	141 (10.4%)	116 (8.6%)	191	0.361	-0.007

This shows the frequencies (n) and percentages (%) of responses to survey statements, along with the WF and WFI. Responses are given on a scale from -2 (strongly disagree) to +2 (strongly agree). The WF is calculated by multiplying the frequency of each response by its corresponding weight on the Likert scale and summing these products. The WFI is obtained by dividing the WF by the number of participants. The NWFI scales the WFI values to a range between -1 and +1.

WF: Weighted Frequency, WFI: Weighted Frequency Index, NWFI: Normalized Weighted Frequency Index

Table 3. Summary of non-parametric test results for demographic variables

Variable	Group	N	Mean rank	Test statistic	*P*
Gender	Male	234	271.32	32567.000 (MWU)	0.324
	Female	293	258.15		
Age groups	<35	122	285.95	3.939 (KW)	0.140
	35-49	281	261.41		
	50+	124	248.29		
Degree	High school	2	279.25	6.637 (KW)	0.156
	Associate degree	9	266.56		
	Licence	121	294.30		
	Postgraduate	268	251.65		
	Doctorate	127	260.76		
HCWs type	Midwife and nurse	45	242.00	168.902 (KW)	0.001<
	General practitioner	51	266.58		
	Residant	53	284.16		
	Specialist physician	161	206.18		
	Academic physician	77	148.70		
	Other HCWs	140	392.41		
Branches	GPs and dentists	59	260.44	8.500 (KW)	0.075
	Internal medicine and sub-branches	69	229.60		
	Pulmonologist	254	270.51		
	Surgery	58	238.60		
	Non-physician HCWs	87	291.63		
HC step	First step	66	283.98	2.889 (KW)	0.236
	Second step	100	278.13		
	Third step	361	256.43		
Institution type	Public institution	257	202.36	120.515 (KW)	0.001<
	University institution	118	290.81		
	Private institution	59	263.81		
	Other	93	400.45		
Case numbers/year	1-30 cases	285	250.70	43.399 (KW)	0.001<
	31-100 cases	29	371.29		
	More than 100 cases	26	410.25		
	None	186	245.79		

Significant differences were found in the variables of type of HCWs, type of institution and annual number of cases ($P < 0.05$). No significant difference was found in other variables.
HCWs: healthcare workers

According to the type of institution, 48.9% (n = 258) of the participants work in a state institution, 22.3% (n = 118) in a university institution, 11.2% (n = 59) in a private institution, and 17.6% (n = 93) in other institutions or individually. In the distribution according to the number of cases seen annually, 54.1% (n = 285) see 1-30 cases, 5.5% (n = 29) see 31-100 cases, 4.9% (n = 26) see more than 100 cases, and 35.5% (n = 187) do not see any cases.

Non-parametric tests are conducted to examine the differences between demographic variables, including gender, age groups, education level, type of health worker, branches, health service level, type of institution, and annual number of cases.

No significant difference was found between genders (male and female) ($P = 0.324$). There was no significant difference between age groups (<35, 35-49, 50+), ($P = 0.140$). There was also no significant difference in the analyses conducted according to education levels (high school, associate degree, undergraduate degree, graduate degree, doctorate) ($P = 0.156$). Significant differences were found between types of HCWs ($P < 0.001$). The highest stigma score was found in the "other HCWs" group (mean rank 392.41), which included social workers, medical automation personnel, dietitians, and other non-physician HCWs. Similarly, significant differences were found between types of institutions ($P < 0.001$). "Other institutions" (mean rank 400.45), which included individual medical practice centres,

dental clinics, pharmacies and similar institutions, stood out as the group with the highest stigma score.

Significant differences in annual case numbers were also observed ($P < 0.001$). Those with more than 100 cases (mean rank 410.25) had the highest stigma scores. No significant differences were found among other demographic variables. These results highlight the variability in stigma levels across specific demographic groups and institution types, and they suggest the need for targeted interventions to address stigma in particular groups.

Stigma Scores by Type of Healthcare Professionals

Nurses had significantly higher stigma scores compared to other healthcare professionals ($P < 0.001$) and academicians ($P < 0.001$). Other healthcare professionals had substantially higher stigma scores compared to GPs ($P < 0.001$), residents ($P < 0.001$), specialist doctors ($P < 0.001$), and academicians ($P < 0.001$). In addition, GPs had higher stigma scores compared to specialist doctors ($P = 0.026$) and academicians ($P < 0.001$), and residents had higher stigma scores compared to specialist doctors ($P < 0.001$) and academicians ($P < 0.001$). Specialist doctors also had significantly higher stigma scores compared to academics ($P < 0.001$). There was no significant difference between nurses and GPs ($P = 0.458$), nurses and residents ($P = 0.124$), nurses and specialist doctors ($P = 0.079$), and GPs and residents ($P = 0.605$) (Table 4).

In summary, the highest stigma scores were observed among non-physician "Other Healthcare Professionals" (mean rank 392.41), including social workers, medical automation personnel, and dietitians. In contrast, the lowest stigma scores were observed among specialist doctors (mean rank 206.18) and academic doctors (mean rank 148.70).

The ranking by type of healthcare professionals from high to low stigma score was as follows:

- Other HCWs (392.41)
- Residant (284.16)
- GP (266.58)
- Nurse (242.00)
- Specialist (206.18)
- Academic (148.70)

Stigma Scores by Institution Type

The post-hoc analyses revealed significant differences in stigma scores between various types of institutions. Notably, public institutions showed significant differences when compared to university institutions ($P < 0.001$), private institutions ($P = 0.002$), and other institutions ($P < 0.001$). Similarly, university and private institutions exhibited significant differences when compared to other institutions ($P < 0.001$). However, no significant difference was found between university institutions and private institutions ($P = 0.210$) (Table 5).

Table 4. Post-hoc analysis results comparison of stigma scores among various HCW groups

Group 1	Group 2	Mean rank (group 1)	Mean rank (group 2)	MWU	Z	*P*
Nurse	Other HCWs	47.27	107.70	1092.000	-6.592	0.001<
Nurse	GP	46.26	50.48	1046.500	-0.742	0.458
Nurse	Residant	44.71	53.57	977.000	-1.537	0.124
Nurse	Specialist	117.30	99.64	3001.500	-1.758	0.079
Nurse	Academician	78.47	51.58	969.000	-4.053	0.001<
Other HCWs	GP	107.15	65.40	2009.500	-4.621	0.001<
Other HCWs	Residant	108.56	66.45	2091.000	-4.679	0.001<
Other HCWs	Specialist	209.13	100.45	3132.000	-10.810	0.001<
Other HCWs	Academician	141.87	49.23	788.000	-10.404	0.001<
GP	Residant	50.94	54.00	1272.000	-0.517	0.605
GP	Specialist	123.20	101.21	3254.000	-2.231	0.026
GP	Academician	80.56	53.86	1144.500	-3.988	0.001<
Residant	Specialist	132.31	99.33	2951.500	-3.365	0.001
Residant	Academician	85.83	51.51	963.000	-5.107	0.001<
Residant	Academician	129.54	98.51	4582.500	-3.254	0.001

In the ranking of stigma scores, the group with the highest stigma score was other HCWs with 392.41 points, and the group with the lowest stigma score was Academics with 148.70 points. These rankings reflect significant differences between the groups, with a *P* value <0.05.
HCWs: healthcare workers, GPs: general practitioners

The order of highest to lowest stigma scores was as follows:

- Other institutions (average rank 273.30)
- University institutions (average rank 228.96)
- Private institutions (average rank 190.93)
- Public institutions (average rank 169.19)

These findings underscore variability in stigma levels and highlight the need for tailored interventions. Notably, public sector workers demonstrated lower stigma scores (202.36), while private or individual HCWs exhibited the highest stigma scores (400.45) (KW: 120.515, $P < 0.001$).

Stigma Scores According to Annual Number of Cases

The analysis of stigma scores according to the annual number of cases revealed significant differences. Specifically, significant differences were found among the following groups: 1-30 cases and 31-100 cases ($P < 0.001$), 1-30 cases and 100+ cases ($P < 0.001$), 31-100 cases and no cases ($P < 0.001$), and 100+ cases and no cases ($P < 0.001$). However, no significant difference was found between the groups with 1-30 cases and no cases ($P = 0.838$) and the groups with 31-100 cases and 100+ cases ($P = 0.251$). These results indicate that the number of annual cases has a significant impact on stigma levels. HCWs who handle more cases have higher stigma scores (410.25), while those who handle no cases have lower stigma scores (245.79), (KW: 43.399, $P < 0.001$) (Table 6).

Most and Least Stigmatizing Expressions

The study identified the highest and lowest stigmatizing expressions based on NWFI values (Table 7).

Table 5. Post-hoc analysis results-institution type

Group 1	Group 2	Mean rank (group 1)	Mean rank (group 2)	MWU	Z	*P*
Public	University	169.19	228.96	10329.500	-4.960	0.001<
Public	Private	151.05	190.93	5668.000	-3.025	0.002
Public	Other	140.11	273.30	2855.500	-10.882	0.001<
University	Private	92.42	82.17	3078.000	-1.255	0.210
University	Other	88.43	128.29	3414.000	-4.711	0.001<
Private	Other	50.71	92.86	1222.000	-5.757	0.001<

There were significant differences among public, university, private, and other institutions ($P < 0.05$). The highest stigma scores were recorded as other institutions (273.30), university institutions (228.96), private institutions (190.93), and public institutions (169.19), respectively

Table 6. Post-hoc analysis results-case number/year

Group 1	Group 2	Mean rank (group 1)	Mean rank (group 2)	MWU	Z	*P*
1-30	31-100	151.15	219.90	2323.000	-3.886	0.001<
1-30	100 +	148.51	238.06	1571.500	-4.862	0.001<
1-30	None	237.04	234.41	26209.500	-0.205	0.838
31-100	100 +	25.66	30.62	309.000	-1.148	0.251
31-100	None	155.74	100.56	1312.500	-4.445	0.001<
100 +	None	168.58	97.82	804.000	-5.511	0.001<

There were significant differences between 1-30 cases and 31-100 cases ($P < 0.001$), 1-30 cases and 100+ cases ($P < 0.001$), 31-100 cases and no cases ($P < 0.001$), and 100+ cases and no cases ($P < 0.001$). However, there was no significant difference between the 1-30 cases and no cases ($P = 0.838$) and between the 31-100 cases and 100+ cases ($P = 0.251$) groups

Table 7. Most and least stigmatize statements with NWFI

Most stigmatize statements	NWFI	Least stigmatize statements	NWFI
After examining tuberculosis patients, I pay more attention than usual to hand disinfection.	-1.000	DOT is ineffective in controlling tuberculosis.	1.000
I unconsciously discriminate against tuberculosis patients because they can infect me.	-0.561	Treatment of tuberculosis patients should be carried out only by chest doctors.	0.300
If I had to examine a patient with tuberculosis, I would be putting my health at risk.	-0.531	Tuberculosis patients deliberately try to infect healthcare workers.	0.292
In the past, I treated a patient differently than usual when I knew he had tuberculosis.	-0.494	Tuberculosis patients should benefit from private health services for a fee.	0.177
Tuberculosis patients must first complete tuberculosis treatment to diagnose and treat other health problems.	-0.460	I feel pressure from the management of the institution where I work to refer tuberculosis patients to tuberculosis dispensaries or sanatorium-type hospitals.	0.149
Even though the health problems of tuberculosis cases concern my branch, I immediately refer the cases to the tuberculosis centre.	-0.406	As a healthcare worker, if I were diagnosed with tuberculosis one day, I would not want healthcare professionals to know about this. Because I am worried about not being able to receive qualified health care for my health problems at the health institution I apply to.	0.055
I prefer to communicate with the relatives of tuberculosis patients rather than with them.	-0.373	Physicians should pay attention to the socio-economic problems of tuberculosis patients.	0.039
The entire treatment process of tuberculosis patients should be completed in 'Sanatorium Type' hospitals.	-0.235		
Patients with tuberculosis are contagious even if they use a surgical mask.	-0.177		
I am uncomfortable encountering tuberculosis patients in my work unit.	-0.110		
In the centre where I work, tuberculosis patients cannot be hospitalised and treated due to their comorbidities.	-0.067		
Healthcare professionals stigmatise tuberculosis cases.	-0.007		

The highest and lowest stigmatizing expressions were determined according to NWFI values. According to NWFI values, the most stigmatizing expressions were determined as S2, S3, S1, S18, S10, S5, S17, S9, S6, S16, S11, and S19, respectively. The expression with the lowest NWFI value was S2, and the value was -1.000.
DOT: Directly Observed Treatment, NWFI: Normalized Weighted Frequency Index

DISCUSSION

Higher levels of stigmatisation were observed among non-physician health personnel, including social workers, medical automation personnel, laboratory technicians, and dietitians, as well as in workplaces such as individual medical offices, dental clinics, and pharmacies. Increased stigma levels were associated with a higher number of cases. In contrast, lower stigma scores were found among academicians and specialist physicians and in public or state institutions.

Similar findings were obtained in a study by Sima et al.[9] on 108 health workers in rural Ethiopia. The study assessed healthcare professionals' knowledge, attitudes, and stigmatizing behaviors regarding TB, indicating that a lack of knowledge and negative attitudes could negatively impact the quality of TB care. In a survey by Shrestha et al.[10] on 190 HCWs in Nepal, TB infection control knowledge, attitudes, and practices were assessed. The study found that while HCWs generally had a positive attitude towards TB, there were significant knowledge and practice gaps, particularly among non-medical personnel. It is expected that stigmatising attitudes and behaviours in non-physician auxiliary healthcare personnel will decrease with increasing levels of education and knowledge about the disease. Frequent and intensive patient contact among healthcare personnel working as midwives, nurses, and nursing assistants may explain their stigmatisinging attitudes and behaviors.

The stigma hindrance to TB patients' access to healthcare is well-documented. Chen et al.[4] noted that TB-related stigma often leads patients to neglect other health needs, thereby restricting access to general healthcare services. Bresenham et al.[5] highlighted that such stigma during TB care processes results in exclusion from essential medical services. This perpetuates health inequities and conflicts with the ethical principles of healthcare provision. Nyblade et al.[8] emphasized the discriminatory impact of stigmatizing attitudes on treatment processes, underscoring the need for interventions and awareness programs to address these challenges.[6,12]

Analyses based on the type of institution revealed that healthcare professionals working in public institutions have lower stigmatization scores, while those in private medical practices (e.g., private clinics, independent pharmacies, and dental treatment centers) have higher stigmatization scores. The World Health Organization's 'Ethics Guidance for the Implementation of the End TB Strategy' offers several key recommendations for private healthcare institutions. These include encouraging private healthcare providers to integrate with national TB programs, adhere to standard treatment protocols, and

participate in public health reporting. Additionally, private institutions are advised to engage in TB awareness campaigns and support patient-centered approaches.[11] While there is a scarcity of studies in the literature that specifically examine the stigmatizing behaviors and attitudes of healthcare professionals towards certain disease groups, research on TB and human immunodeficiency virus-related stigma generally highlights that working in public institutions is linked to higher participation in in-service training, which in turn enhances awareness of specific disease groups.[9,10,12] The perception among healthcare professionals that the diagnosis and treatment of TB is primarily the responsibility of public healthcare providers may contribute to the stigmatizing attitudes and behaviors observed in individual and private healthcare settings. The NWFI rankings of responses to our survey questions support this notion. For example, in Question 10, participants believed that TB cases should complete their TB treatment before addressing other health issues (NWFI -0.460); in Question 5, participants showed a tendency to refer TB cases to specialized TB centers even when these cases fell within their own specialty and scope of work (NWFI -0.406); in Question 9, participants indicated that TB cases should complete the entire treatment process in sanatorium-type hospitals (NWFI -0.235); in Question 16, participants expressed discomfort with encountering TB cases in the workplace (NWFI -0.110); and, finally, in Question 11, participants mentioned challenges in admitting TB patients for treatment of comorbidities in the hospitals where they work (NWFI -0.067).

Analyses based on the annual number of cases show that HCWs who see more cases have higher stigmatization scores. Notably, HCWs who handle more than 100 cases per year have the highest stigmatization scores. This finding suggests that the stigmatizing behaviors of HCWs increase with their intense workload and frequent patient contact. Supporting this, survey responses indicated: in Question 2, the need for more disinfection than usual after encountering a TB case (NWFI -1.00) was identified as the highest stigmatizing attitude; in Question 3, the unconscious tendency to treat TB cases differently due to the risk of infection (NWFI -0.561); in Question 1, concerns about risking health while examining a TB patient (NWFI -0.531); and in Question 17, a preference for communicating with the relatives of TB patients rather than the patients themselves (NWFI -0.373). In Question 6, the belief that TB cases are contagious, even when using surgical masks, (NWFI -0.177) was also highlighted as a stigmatizing attitude. This aligns with findings from a study by Vigenschow et al.[13], which examined knowledge, attitudes, and practices regarding TB among 103 HCWs in the Moyen-Ogooué region of Gabon. In their study, 72.8% of HCWs reported fearing TB infection, and 63.1% viewed TB as a stigmatizing disease. These results emphasize the importance of supporting and training HCWs in managing infectious diseases such as TB.

Due to the absence of studies in the literature investigating the stigma levels of healthcare professionals, a study design based on clinicians' observations was used instead of a standardized stigma scale.

CONCLUSION

HCWs have exhibited stigmatizing attitudes and behaviors towards TB cases, primarily due to concerns about infection transmission, lack of awareness that TB can be diagnosed and treated in public institutions, and the increased caseload that elevates the risk of transmission. Enhancing the TB knowledge of HCWs through formal education and in-service training programs, along with implementing measures that prioritize employee health and reduce infection transmission, can help mitigate these stigmatizing attitudes and behaviors.

Ethics

Ethics Committee Approval: The study protocol was approved by the University of Health Sciences Türkiye, Gazi Yaşargil Training and Research Hospital (protocol number: 920, date: 05.11.2021).

Informed Consent: Informed consent was obtained from all participants.

Footnotes

Authorship Contributions

Concept: M.S.B., Design: M.S.B., Data Collection or Processing: M.S.B., Analysis or Interpretation: M.S.B., Literature Search: M.S.B., B.Ç., Writing: B.Ç.

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Click the link to access Appendix 1: https://d2v96fxpocvxx.cloudfront.net/68ab204c-182b-49da-b227-bc7efe058632/content-images/3138d370-17e3-4dd1-9e6a-f7263283ed42.pdf

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Original Article

Etiologies and Treatment Outcomes of Chronic Cough Diagnosed with a Pathophysiological Diagnostic Procedure: A Single-center Retrospective Observational Cohort Study

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Abstract

OBJECTIVE: We developed a pathophysiological diagnostic procedure to identify etiologies of chronic cough (CC) like cough variant asthma (CVA), atopic cough (AC), cough predominant asthma, sinobronchial syndrome (SBS), and mucoid impaction of small bronchi. After identifying the etiologies of CC through an understanding of its pathophysiological processes, we determined the patient's management outcomes based on the pathophysiological diagnosis.

MATERIAL AND METHODS: In this retrospective observational cohort study, the medical records of CC patients from April 2013 to March 2018 was analyzed to assess the etiologies and treatments based on the pathophysiological diagnostic procedure. The capsaicin cough-reflex sensitivity test, methacholine-induced bronchoconstriction cough response test, bronchodilator reversibility test, bronchial responsiveness test, chest and sinus computed tomography, and sputum investigations were used for pathophysiological diagnosis.

RESULTS: CC etiologies were diagnosed in 289 of the 298 patients who underwent the diagnostic procedures. The remaining nine patients had normal diagnostic findings. The three most common causes of CC were CVA, AC and SBS. Cough disappeared completely in 278 of the 286 patients who completed treatment. The median time to complete symptom resolution was 5.8 weeks.

CONCLUSION: Pathophysiological evaluation may facilitate prompt and objective diagnosis of the etiologies of CC. Our results suggest that pathophysiological diagnosis is better than the conventional diagnostic method in treatment outcomes.

KEYWORDS: Capsaicin, chronic cough, diagnosis, methacholine chloride, pathophysiology

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INTRODUCTION

Chronic cough (CC), i.e., any cough occurring for more than eight weeks without any obvious clinical or radiological evidence of pulmonary disease is one of the most common reasons for referral to a chest physician. Cough variant asthma (CVA), atopic cough (AC), and sinobronchial syndrome (SBS) are the predominant causes of CC in Japan.[1] CVA and AC are associated with non-productive cough, whereas SBS is associated with a productive cough. CVA is primarily characterized by an increased cough response associated with bronchial smooth muscle contraction.[2] The fundamental features of AC include the presence of eosinophilic tracheobronchitis with cough-reflex hypersensitivity;[3] the absence of typical asthma precursors,[1] and the absence of chronic airflow limitation.[1] SBS is indicated by cough receptors stimulated by overproduction of lower respiratory tract secretions.[4]

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Currently, the diagnostic methods for the assessment of presumptive CC etiology are determined by observing improvements following the administration of specific treatments for the CC. There are many concerns regarding the effectiveness of CC therapeutic diagnostic processes.

1. Low specificity of specific treatment regimens leading to false-positive results.

2. Spontaneous cough relief leading to false positive results.

3. Insufficient treatment potency causing false negativity.

4. False negative results in the case of resistance to the therapeutic agents, for example in severe of difficult-to-treat cases.

5. False negative results arising from the occurrence of more than one cause of the CC.

6. Differences between studies in the criteria used to assess response to cough treatment.

7. It takes time to initiate appropriate treatment according to the true pathophysiology.

In addition, treatment is further hampered by drug doses that are often not designed to achieve antitussive effects.[5] Differences in evaluation criteria for cough treatment have also led to different classifications of cough etiologies.[6] Therefore, a new mechanism based on the pathophysiological processes involved in CVA, AC, and SBS may allow us to move from slow and ineffective treatment-based diagnosis to a faster and more reliable pathophysiological diagnosis.

In this study, we successfully developed a pathophysiological diagnostic procedure to determine CC etiologies from 289 CC patients. The diagnostic processes utilized include capsaicin cough-reflex sensitivity test (Cap-Cough test), methacholine-induced bronchoconstriction cough response test (Meth-Cough test), bronchodilator reversibility test, bronchial responsiveness test, chest and sinus computed tomography, and sputum investigations. This study evaluated the patients' clinical outcomes based on our diagnostic procedure.

MATERIAL AND METHODS

Study Subjects

In our institution, all patients presenting for treatment of CC undergo the following tests, after obtaining the patient's informed consent: Cap-Cough test, Meth-Cough test, bronchodilator reversibility test, bronchial responsiveness test, chest imaging, sinus imaging, blood test, and sputum examination. This retrospective observational cohort study included all patients who presented for CC diagnosis and treatment between April 2013 and March 2018. CC etiology was determined from patient records containing diagnostic procedures and treatments. The study was approved by the Ethical Review Board of the National Hospital Organization Nanao Hospital, and conducted in accordance with the revised version of the guidelines in the Declaration of Helsinki (UMIN ID: UMIN000018679, date: 05.11.2015). All patient details have been de-identified. The reporting of the study conforms to the STROBE guidelines.[7]

Main Points

- We developed a pathophysiological diagnostic procedure for identifying chronic cough (CC) etiologies.
- Pathophysiological evaluation may enable prompt diagnosis of the etiologies of CC, leading to better treatment outcomes.
- This procedure may meet the unmet medical needs in CC.

Study Protocol

Within 4 days of presentation, all patients completed the following investigations: spirometry, bronchodilator reversibility test, Cap-Cough test, Meth-Cough test, and bronchial responsiveness test. A dry wedge spirometer (Chestac 11, Chest Co., Ltd., Tokyo, Japan) was used to determine spirometric indices such as forced vital capacity and forced expiratory volume in the first second (FEV1). Spirometric tests and data interpretation were performed according to the recommendations of the ATS/ERS Task Group.[8] The bronchodilator reversibility test was conducted during the spirometry procedure and involved measurements both before inhalation and 30 minutes after inhalation of 50 μg of procaterol.

Measurements

Methacholine Inhalation Protocol

Methacholine inhalation was performed according to Takishima et al.,[9] using an Astograph (Jupiter 21; CHEST; Tokyo, Japan). Methacholine chloride (FUJIFILM Wako Pure Chemical Industries, Ltd., Osaka, Japan) was diluted in phosphate-buffered saline solution (PBS) to double the concentration (0.0195 to 160 mg/mL). The solutions of PBS and methacholine was inhaled for 1 min. Subjects were examined during quiet breathing while wearing a nose clip.

Assessment of Cough Response to Methacholine-induced Bronchoconstriction

The Meth-Cough test was evaluated as previously documented by Hara et al.[10] An observer counted coughs that occurred during the total time (α + 30 min), consisting of methacholine inhalation (α min, <1 min) and the 30 min after the methacholine inhalation. The cough response to methacholine-induced bronchoconstriction was considered as showing smooth muscle cough hypersensitivity when the Meth-Cough was ≥24 coughs/30+α min.[11]

Assessment of Capsaicin Cough-reflex Sensitivity

The Cap-Cough test was evaluated as previously described by Fujimura et al.[12] The lowest concentration of capsaicin that elicited at least 5 coughs (C5) was defined as the cough threshold. Inhaled capsaicin at a concentration of ≤0.98 μmol/L

for female subjects and ≤3.9 μmol/L for male subjects was used to determine epithelial cough hypersensitivity. The cut-off point was calculated as the geometric mean minus two geometric standard deviations.[13]

The following criteria were used to make the diagnosis: CVA, an increase in cough response to methacholine-induced airway smooth muscle contraction; AC, an increase in cough-reflex sensitivity to inhaled capsaicin; and a combination of CVA and AC, an increase in cough response due to both airway smooth muscle contraction and cough-reflex sensitivity.

Although typical asthma was excluded from CC, asthma patients having isolated CC were assessed in the present study when attending physicians could not identify key symptoms of asthma in patients, including wheeze, chest tightness, rhonchi, and airflow limitation measured by spirometry during the initial presentation. Patients in this study were classified as having cough predominant asthma (CPA) if they had one or more of the following distinctive signs of asthma: bronchial hyperresponsiveness, bronchial reversibility, and/or wheezes on auscultation during the clinical course.

The diagnostic criteria for CVA, AC, SBS, CPA, gastroesophageal reflux (GER), associated CC and mucoid impaction of small bronchi (MISB) syndrome are presented in Table 1. Although MISB syndrome has not been established as a clinical entity, a number of our patients met the diagnostic criteria and, when administered oral corticosteroids (OCS) and antifungal medications, had a successful treatment outcome. Diffuse panbronchiolitis was diagnosed based on the distinctive features observed in the chest X-ray and chest computed tomography. Bronchorrhea was defined as watery sputum production of more than 100 mL per day.

Statistical Analysis

No statistical sample size calculations were conducted. We analyzed all patients with a provisional diagnosis of CC presenting between September 2013 and August 2018. The capsaicin cough threshold was expressed as the geometric mean with geometric standard error of the mean. Statistical differences between the groups were analyzed using the Mann-Whitney U test, Kruskal-Wallis test with Dunn's post-hoc adjusted by Bonferroni, or Wilcoxon signed rank test, as appropriate. The count distributions for the two groups (<65 years and ≥65 years) were compared using Pearson's chi-square test. The relationship between cough threshold to inhaled capsaicin and cough response to bronchoconstriction was evaluated using Pearson's correlation coefficient. All comparisons were two-tailed, and *P* values of <0.05 were considered significant. All analyses were conducted with IBM Statistical Package for the Social Sciences statistics 23 (Japan IBM Co., Tokyo, Japan). Continuous variables were reported as mean±standard deviation.

RESULTS

Overall, 301 patients (121 men, 180 women, mean age 57.0±17.1 years) initially presented to the clinic during the 5-year study period. Three patients (two men and one woman) did not perform the complete diagnostic evaluation. The cause of CC was diagnosed in 289 patients, and the results indicated that the diagnostic values were within normal limits in 9 patients (Figure 1). The median duration of cough in patients was 260.0 weeks (range 10.4-3588.0 weeks). Of the cases analyzed, 83 patients were referred for refractory cough from other facilities, including respiratory clinics.

The number of coughs (Meth-Cough) induced in the first 15+α min and the second 15 min after methacholine inhalation is shown in Figure 2. The number of coughs in the first 15+α minutes was overwhelmingly higher than that in the second 15 minutes. This trend was also observed in previous studies in healthy subjects.[10] Twelve patients had a high number of coughs in the second 15 minutes. Details are given below: 4 patients with CVA+SBS (44 in the first; 51 in the second, 14 in the first; 20 in the second, 9 in the first; 30 in the second, 31 in the first; 36 in the second), 2 patients with AC+CVA+SBS (7 in the first; 18 in the second, 25 in the first; 33 in the second), 1 patient with CPA (0 in the first; 1 in the second), 1 patient with AC+CPA (0 in first; 7 in second), 1 patient with AC+SBS (2 in first; 5 in second), 1 CPA+GER (0 in first; 22 in second), 1 patient with CPA+SBS (3 in first; 7 in second), 1 patient with therapeutically diagnosed AC+CVA (0 in first; 11 in second).

The frequency of each CC etiology, demographic characteristics, clinical features, and pulmonary function test results is shown in Table 2. A total of 194/289 patients (67.1%) had two or more causes of CC. CVA (250/289), AC (103/289), and SBS (140/289) were the main etiologies for cough (Table 2). Elderly patients (≥65 years) had significantly more underlying conditions than non-elderly ones (*P* = 0.0484, data not shown). There was no significant relationship between C5 and the Meth-Cough (data not shown).

Of the 289 patients, 10 left our clinic before receiving adequate cough treatment. Also, 271/279 (97.1%) patients had complete symptomatic cough resolution whereas eight patients (2.9%) had incomplete resolution of the cough (Figure 1). The specific treatments of CC based on etiology and additional treatments required for complete cough resolution are shown in Table 3. Of the 279 patients, 49 (17.6%) required additional treatments. Thirty-eight patients required antifungal drugs, and ten patients required additional treatments for GER-related cough: proton-pump inhibitors, ten patients, gastrointestinal promotility drugs, nine patients, and rikkunshito, seven patients (Table 3). The diagnosis of GER-related cough was based entirely on a therapeutic diagnostic procedures.[6]

The median time required for cough resolution in 271 patients, whose cough completely resolved, was median 5.8 weeks [95% confidence interval (CI), 8.0-10.6 weeks]. The time required for cough resolution was significantly different based on the need for additional treatments (*P* = 0.0049, Figure 3).

Table 1. Diagnostic criteria for CVA, AC, sinobronchial syndrome, cough predominant asthma, and mucoid impaction of small bronchi syndrome

All criteria were met for each diagnosis.
CVA
1. Isolated chronic non-productive cough lasting ≥8 weeks
2. No history of wheezing or dyspnea and lack of adventitious lung sounds on physical examination
3. Increase in cough response to methacholine-induced bronchoconstriction
AC
1. Non-productive cough lasting ≥8 weeks
2. Presence of one or more findings indicative of an atopic predisposition, including a history and/or complications of allergic diseases (excluding asthma), peripheral blood eosinophilia (>6% or >400 cells/μL), increased total serum IgE level (>200 IU/mL), presence of IgE antibodies specific to aeroallergens, and positivity of allergen skin testing and/or presence of induced sputum eosinophilia (>2.0%)
3. Increase in cough-reflex sensitivity to inhaled capsaicin
SBS
1. Productive cough lasting ≥8 weeks.
2. One or more of the following:
(i) Symptoms such as postnasal drip and throat clearing
(ii) Signs such as mucous or mucopurulent secretions in the upper and middle pharynx and cobblestone appearance of the mucosa
(iii) Fluid retention and/or mucosal thickening on sinus CT scan
(iv) Increased neutrophil count in nasal secretions
(v) Increased neutrophil count in spontaneous sputum.
3. Cough relief upon treatment with 14-member macrolides. Treatment efficacy was evaluated at 2 months after initiation and was judged as effective when the productive cough diminished to half or less.
Cough predominant asthma (CPA)
1. Isolated chronic non-productive cough lasting ≥8 weeks
2. No history of wheezing or dyspnea and lack of adventitious lung sounds on physical examination and no airflow limitation assessed by spirometry
3. One or more of the following:
(i) Bronchial reversibility, defined as a percentage increase of ≥12% and an absolute volume increase of 200 mL in FEV1
(ii) Presence of bronchial hyperresponsiveness [provocative concentration of methacholine causing a 20% fall in FEV1 (PC20) <10 mg/mL]
(iii) Presence of wheezes on auscultation during clinical course
MISB
1. Productive cough lasting ≥8 weeks
2. Increased eosinophil count in spontaneous sputum
3. Impaction of small bronchi and remarkable thickening of bronchial walls on chest CT
Clinical features of MISB
(i) Cough was relieved upon short-term treatment with oral corticosteroids, but it relapsed soon after treatment termination (intractable).
(ii) Bacteria causing chronic airway infection were seldom detected in purulent sputum, and sputum eosinophil counts were increased.
(iii) Long-term low-dose macrolide therapy was not effective.
(iv) MISB was mostly identified in the lower lobes.
(v) Fungi were seldom culturable in clinically available fungal growth media.
(vi) A combination of oral corticosteroids and itraconazole was effective.
GER-related cough[6]
Characteristic medical history that suggests the cough is due to GER (pre-treatment diagnosis) and signs to consider to make a definitive diagnosis (post-treatment diagnosis) based on the therapeutic effects.
1. Suggestive findings
Suspect that the cough is due to GER when a chronic cough (especially dry cough) has the following characteristics:
(i) Accompanied by esophageal symptoms of GER, such as heartburn and acid reflux
(ii) Accompanied by laryngopharynx symptoms of GER, such as throat clearing, hoarse voice, and abnormal sensation of the laryngopharynx
(iii) Exacerbation of coughing during conversation, eating, immediately after moving the body/going to bed/waking up, while stooping, and with weight gain. Typically, there is none or less coughing during the night
(iv) Intense cough ending in vomiting
(v) Suspect GER disease if drugs that could cause a cough (e.g., angiotensin-converting-enzyme inhibitors) have not been prescribed, and treatment for CVA and SBS is ineffective, particularly if a nocturnal cough is improved by CVA treatment, but a daytime cough persists
2. Post-treatment diagnosis
If the cough is improved by GER treatment (proton pump inhibitor, gastrointestinal prokinetic agents, and obesity/diet improvement), the diagnosis can be confirmed.
Note:
(i) Proton pump inhibitors should be started at higher doses. However, monotherapy may be ineffective (consider adding a gastrointestinal prokinetic agent at an early stage).
(ii) In patients with other comorbidities (especially cough variant asthma), no improvement may be generally expected without sufficient treatment for both diseases.

CVA: cough variant asthma, AC: atopic cough, SBS: sinobronchial syndrome, FEV1: forced expiratory volume in the first second, IgE: immunoglobulin E, CT: computed tomography, MISB: mucoid impaction of small bronchi syndrome, GER: gastroesophageal reflux

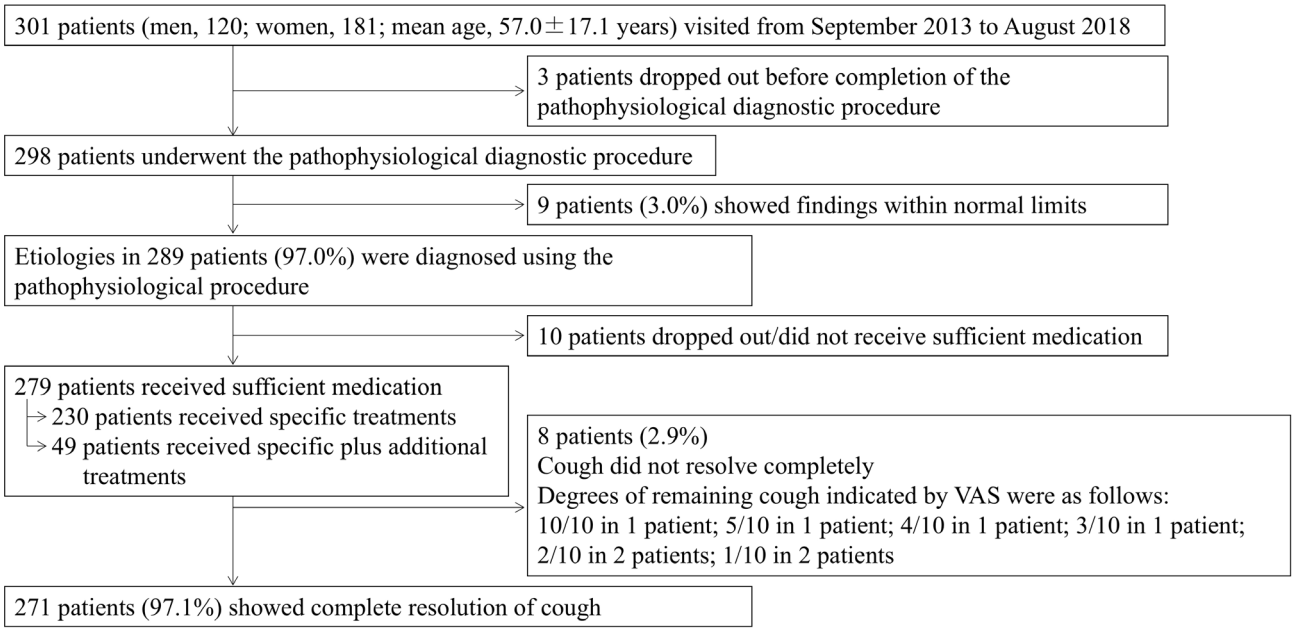

Figure 1. Details of patients who underwent the pathophysiological diagnostic procedure

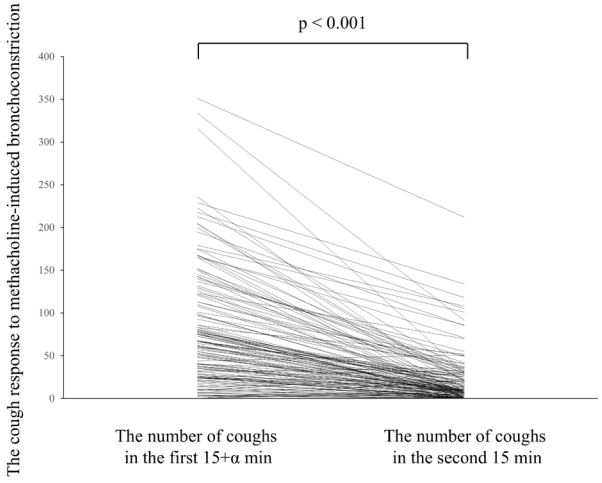

Figure 2. The number of coughs elicited in the first 15+α min and the second 15 min after methacholine inhalation

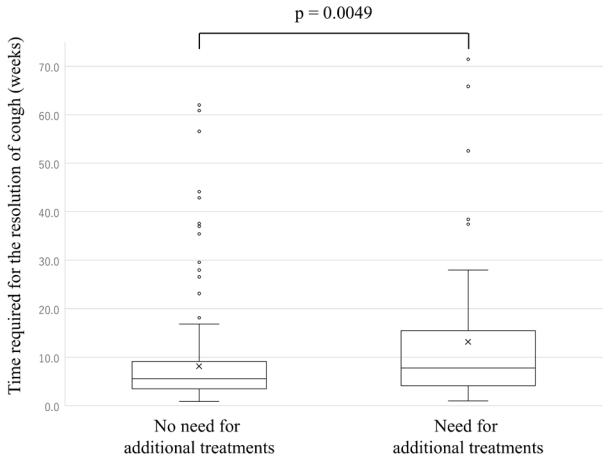

Figure 3. Comparison of cough resolution periods between patient groups with or without additional treatments

DISCUSSION

This study showed that our pathophysiological diagnostic process led to an increased diagnosis of CC and successful outcomes. The findings are unique because we were able to present not only diagnostic procedures and therapeutic measures but also complete CC treatment results.

We found that 97.1% of patients who were diagnosed using the pathophysiological procedures outlined above and who completed the treatment achieved complete cough elimination. The results are noteworthy given that previous studies typically evaluate the efficacy of cough therapy in terms of improvement, not cough elimination when making a diagnosis.[6,14,15] In addition, unexplained CC is found in about 46% of individuals referred to specialty pulmonology clinics.[16]

Because we did not use the therapeutic diagnostic procedures, except 9 patients who had pathophysiological diagnostic results within normal limits in this study, we could not directly compare these two diagnostic procedure outcomes regarding patients' characteristics or cough elimination. On the other hand, Hara et al.[17] have previously shown that complete cough elimination with a therapeutic diagnostic procedure was achieved in only 84.2% of a 36-patient cohort. In prospective studies, the usefulness of our pathophysiological diagnostic procedure should be compared with the conventional therapeutic diagnostic procedure.

Table 2. Etiologies of chronic cough in 298 patients, as determined using the pathophysiological diagnostic procedure and demographic characteristics, clinical features, and pulmonary function tests

	AC	CVA	CPA	SBS	Unknown	AC+CVA	AC+CPA
Number of pts (No. of Fem)	3 (3)	82 (56)	4 (3)	4 (1)	9 (5)	52 (21)	2 (1)
Age (years)	66±14	52±17	64±123	67±17	67±11	50±18	53±13
FVC (%pred.) (%)	124±4	107±15	105±18	106±11	110±14	102±17	90±16
FEV1 (%pred.) (%)	120±8	102±13	102±10	97±29	109±17	96±16	79±17
FEV1/FVC ratio (%)	76±2	80±8	79±7	72±17	80±6	81±9	73±6
Meth-C test	15±3	117±82	11±11	16±9	9±6	124±113	7
C5 (μM)	1±1	7±1	6±2	31±1	17±2	2±1	2±2
Sputum nut (%)	71±16	54±31	32±10	51±30	71±15	70±24	32±7
Sputum eos (%)	0±0	11±24	1±1	25±19	3±2	7±14	26±25
Blood eos (%)	3±2	3±5	2±1	4±3	3±3	3±2	5±1
Total IgE level (IU/mL)	183±31	251±562	26±7	2673±3258	283±577	281±542	173±168
Positive rate of specific IgE (%)	100	51	0	50	22	51	50
	AC+SBS	CPA+SBS	CVA+SBS	AC+CVA+SBS	CVA+MISB+SBS	CPA+MISB+SBS	AC+CVA+MISB+SBS
Number of pts (No. of Fem)	9 (3)	9 (6)	76 (54)	35 (17)	3 (3)	2 (2)	2 (1)
Age (years)	69±4	67±13	59±15	64±14	68±10	61±24	68±4
FVC (%pred.) (%)	91±21	109±12	101±16	105±18	78±7	97±9	100±6
FEV1 (%pred.) (%)	85±12	100±9	95±17	99±21	65±15	767±15	89±4
FEV1/FVC ratio (%)	77±9	74±5	78±8	77±9	66±15	63±11	72±1
Meth-C test	13±7	17±11	123±96	119±87	86±62	16±5	153±102
C5 (μM)	2±1	10±1	8±0	1±1	12±1	16±2	2±2
Sputum nut (%)	79±17	71±16	62±25	67±21	74±11	60±35	95±1
Sputum eos (%)	5±3	11±16	13±21	12±20	11±7	26±25	2.0±0
Blood eos (%)	2±1	3±2	4±4	3±3	2±1	5±5	2±1
Total IgE level (IU/mL)	291±575	107±100	268±687	147±254	104±47	64±33	399±391
Positive rate of specific IgE (%)	22	11	46	46	100	50	50
	Others						
Number of pts (No. of Fem)	6 (3)						
Age (years)	64±15						
FVC (%pred.) (%)	88±15						
FEV1 (%pred.) (%)	82±15						
FEV1/FVC ratio (%)	75±7						
Meth-C test	41±67						
C5 (μM)	14±2						
Sputum nut (%)	74±12						
Sputum eos (%)	3±1						
Blood eos (%)	4±3						
Total IgE level (IU/mL)	59±31						
Positive rate of specific IgE (%)	67						

Others including the following patients, DPB 1 patient, MISB 1 patient, CPA+MISB 1 patient, SBS+Bronchorrhea 1 patient, AC+CVA+DPB 1 patient, AC+CVA+MISB 1 patient.

AC: atopic cough, CPA: cough predominant asthma, CVA: cough variant asthma, DPB: diffuse panbronchiolitis, eos: eosinophils, Fem: female, FVC: forced vital capacity, FEV1: forced expiratory volume in 1 s, FeNO: fractional exhaled nitric oxide, MISB: mucoid impaction of small bronchi, nut: neutrophils, pts: patients, pred.: predicted, SBS: sinobronchial syndrome, IgE: immunoglobulin E

Table 3. Etiologies and treatments of 279 chronic cough patients. Diagnosis and treatment were based on pathophysiological diagnosis. Additional treatments for complete cough resolution are listed separately although there is some overlap with original treatment in some cases

Etiology	N	Specific treatments	Additional treatments (n = number of cases)
Single cause	86		
AC	3	H1-RA, ICS, OCS (n = 1)	
CVA	75	Beta-2, ICS, LTRA, LAMA, OCS (n = 24), seratrodast	Antifungal drug (n = 10) Gastrointestinal promotility drugs (n = 2) H1-RA (n = 1) PPI (n = 3) Rikkunshito (n = 2)
CPA	4	Beta-2, ICS, LTRA, OCS (n = 1), seratrodast	Gastrointestinal promotility drugs (n = 1) PPI (n = 1) Rikkunshito (n = 1)
SBS	4	Macrolides	Beta-2 (n = 4) ICS (n = 4) LTRA (n = 4)
Dual causes	145		
AC+CVA	51	Beta-2, ICS, LTRA, LAMA, OCS (n = 25), seratrodast	Antifungal drug (n = 7) Gastrointestinal promotility drugs (n = 3) PPI (n = 3) Rikkunshito (n = 3)
AC+CPA	2	Beta-2, H1 RA, ICS, LTRA, OCS (n = 1)	
AC+SBS	9	H1 RA, ICS, macrolides, OCS (n = 3)	Antifungal drug (n = 1) Beta-2 (n = 1)
CPA+SBS	9	Beta-2, ICS, LTRA, macrolides, OCS (n = 5)	Antifungal drugs (n = 1)
CVA+SBS	74	Beta-2, ICS, LAMA, LTRA, macrolides, OCS (n = 37), seratrodast	Antifungal drugs (n = 11)
Triple causes	40		
AC+CVA+SBS	35	Beta-2, H1-RA, ICS, LAMA, LTRA, macrolides, OCS (n = 12), seratrodast	Antifungal drugs (n = 8) Gastrointestinal promotility drugs (n = 3) PPI (n = 3) Rikkunshito (n = 1)
CVA+MISB+SBS	3	Antifungal drugs, beta-2, ICS, LTRA, OCS (n = 3)	
CPA+MISB+SBS	2	Beta-2, ICS, LTRA, macrolides, OCS (n = 1)	
Quad causes	2		
AC+CVA+MISB+SBS	2	Antifungal drugs, beta-2, H1-RA, ICS, LTRA, macrolides, OCS (n = 1)	
Others	6		
			Beta-2 (n = 2) ICS (n = 2) LTRA (n = 1)

Others including the following patients, DPB 1 patient, MISB 1 patient, CPA+MISB 1 patient, SBS+Bronchorrhea 1 patient, AC+CVA+DPB 1 patient, AC+CVA+MISB 1 patient.

AC: atopic cough, Beta-2: beta-2 agonists, CPA: cough-predominant asthma, CVA: cough-variant asthma, DPB: diffuse panbronchiolitis, GER: gastroesophageal reflux, H1-RA: histamine H1 antagonists, ICS: inhaled corticosteroids, LAMA: long-acting muscarinic antagonists, LTRA: leukotriene receptor antagonists, MISB: mucoid impaction of small bronchi, OCS: oral corticosteroids, PPI: proton-pump inhibitors, SBS: sinobronchial syndrome

An accurate pathophysiological investigative process may dramatically improve therapeutic efficacy for chronic cough (CC) because the initial treatment period for a suspected cough etiology can last between 1 and 8 weeks.[6,18,19] In addition, without rapid treatment, cough damaging the airway quickly becomes self-perpetuating, resulting in exacerbated airway inflammation and worsening cough.[20] Fujimura et al.[3] showed that therapeutic diagnosed AC resistant to H1 receptor antagonist had higher degree of eosinophil infiltration in the biopsied bronchi and this result implicated that pathological feature influenced the therapeutic effect of CC.

Ideally, the efficacy of our therapeutic regimens used in this study should be examined in a prospective clinical trial. However, the drugs used in this study are primarily described in the 2021 Japanese guidelines.[6] Therefore, we do not believe that our therapeutic regimens in this study deviate from general routine medical care. On the other hand, we consider the possibility that the administration of OCS may have affected the therapeutic efficacy should be considered. Doan et al.[21] reported that short-term oral prednisolone dramatically improved cough in CVA, and all cases were subsequently controlled primarily with inhaled corticosteroids (ICS).[21] The 2020 German guidelines stated that some CC patients respond only to systemic corticosteroids, because of the tussive effect of ICS, which also prevents proper deposition of medication in the airways.[22] Furthermore, Puente-Maestu et al.[23] showed that physicians were reluctant to prescribe OCS for patients with refractory or unexplained CC, probably because of the safety profile of OCS, even though they recognize their effectiveness.

In this study, the main additional treatment for cough was antifungal drugs which were used to eliminate cough that was resistant to specific cough treatments, including corticosteroids. Fungus-associated CC (FACC) is a relatively new clinical concept defined as CC with the following findings: the presence of environmental fungi in sputum, especially filamentous basidiomycetes (f-BM); and response to antifungal drugs. FACC may have been diagnosed with unexplained CC because FACC did not respond to the general cough medications[24] and specialized facilities to isolate f-BM were not available.[6]

We found that few patients needed additional treatment for GER-related cough. Kanemitsu et al.[25] reported that GER-related subacute cough CC were increasing in Japan also, and they recently reported that 11.9% (37/312) of subacute and CC patients had GER-related cough. Globally, the proportion of GER-related cough in CC is extremely variable, ranging from 2 to 86%.[26] In this study, only 10 out of the 279 CC patients (3.6%) were diagnosed with GER-related cough. We do not fully know the reasons for the discrepancy between the proportion of GER-related cough of the previous studies and those of the present study, but it is possible that adequate cough treatment based on pathophysiological diagnostic procedures suppresses further reflux induced by cough and the cough-reflux vicious cycle. It has been reported that the evidence for the diagnosis of GER-related cough is insufficient,[27] and that a powerful placebo effect influences the efficacy of treatment for cough,[28] including GER-related cough.[27]

This study diagnosed two or more etiologies in 67.1% of CC patients. In such cases, treatment-based diagnostic processes are challenging and time-consuming. Guidelines have indicated that the accuracy of treatment-based diagnostic processes for CC with multiple etiologies is limited.[6] Our findings indicate that cases with multiple etiologies accounted for a substantial proportion of the CC cases. This was because we could use a pathophysiological diagnostic procedure, and determine the final diagnosis at the point when the cough was completely resolved. We found that the elderly had a greater incidence of multiple etiologies compared to non-elderly individuals. On average, the participants of this study were over 5 years older than those from several past studies.[29]

The main causes of CC in our patients were AC, CVA, and SBS. According to a 2005 study, three leading causes of CC in Japan were AC, CVA, and SBS.[29] As a result, the etiologies of CC may have remained relatively the same over the past 15 years. During that time two guidelines for cough management were published in Japan,[1,6] and several advances in cough research and diagnostic procedures occurred.[19] In Western countries, increased bronchial hyperresponsiveness is considered important for the diagnosis of CVA, while Chinese and Japanese guidelines recommend confirming the efficacy of bronchodilators. It has long been known that the efficacy of bronchodilators does not always coincide with increased bronchial hyperresponsiveness. The studies from China reported that 23.6% to 37.5%[30] of patients with CC diagnosed with CVA based on increased bronchial hyperresponsiveness or diurnal variation in PEF greater than 20% were refractory to bronchodilators. Also, in Japan, when patients with chronic or subacute/CC were diagnosed with CVA based on increased bronchial hyperresponsiveness and response to bronchodilators, the prevalence of CVA was reported up to 67.0%,[25]. Considering these results, it is possible that the proportion of patients diagnosed with CVA increased with physiological or our pathophysiological diagnostic criteria compared to CVA based solely on the efficacy of bronchodilators. Furthermore, the findings of this study, in which 86.5% of CC, were diagnosed with CVA, were considered consistent with the results of the above-mentioned Japanese studies. It is necessary to validate the efficacy of bronchodilators in patients with pathophysiologically diagnosed CVA.

There are few reports analyzing the length of treatment needed to achieve complete resolution of cough. In 2017, a study in a tertiary care clinic reported that it took more than 14 weeks for the cough to improve (complete or partial resolution).[31] In that study, 65/155 (41.9%) patients attending a tertiary care clinic and 67/193 (34.7%) individuals attending a secondary care clinic had a complete resolution of their cough, and 76/155 (49.0%) patients in tertiary care clinics and 97/193 (50.3%) patients in secondary care clinics had at least 50% improvement in their cough. The longitudinal CC prognosis has been investigated in two retrospective cohort studies. Kang et al.[32] reported that 64/323 individuals with (19.8%) had persistent cough 4 years after evaluation and management in a Korean tertiary clinic, and Koskela et al.[33] reported that 31 of 68 CC patients (46%) still had persistent cough five years post-initial evaluation at a Finnish University. We found that the median time to complete symptomatic resolution of cough was 5.8 weeks (95% CI: 8.0-10.6) and that the number of etiologies did not affect the time to complete resolution of cough. Thus, our findings suggest that the assessment and management of CC based on pathophysiological investigative processes may help to improve prognosis.

The use of ICS to treat eosinophilic airway diseases, like CVA, AC, and CPA, is problematic. For example, CVA may lead to future airway remodeling and typical asthma, which requires long-course ICS treatment, whereas AC does not lead to these conditions, and ICS treatment can be stopped after the resolution of the cough. Therefore, differentiating CVA from AC before starting treatment is essential, even though it is not recommended by some guidelines due to specific reasons

that may need further explanation.[6,18,19] In addition, long-term use of ICS is known to increase the risk of pneumonia and mycobacterial infection among individuals with chronic obstructive pulmonary disease. Although there are currently no data on risks associated with the use of ICSs in CC patients, we suggest that the routine use of ICSs in individuals with cough is not recommended.

In the present study, we used C5, which indicated the cough threshold for cough-reflex sensitivity evaluation. Several studies have shown that this traditional index, C5, displayed overlaps between healthy subjects and patients with CC,[34] and there is also a need for standardization of the methodology regarding the equipment and protocols in assessing cough-reflex sensitivity to inhaled capsaicin. Hara et al.[10] previously found that the median Meth-Cough was 7 (range, 0-71/30+α min) in 41 healthy young subjects. Problems with this previous study include that only young, healthy subjects were included and that their number was too small to establish reference values. Therefore, the results of this previous study alone cannot be used to develop pathophysiological diagnostic criteria for CVA. Nor, can the overlap between the Meth-Cough in healthy subjects and in cough variant asthma (CVA) be assessed. The Clinical and Laboratory Standards Institute in the USA stipulates that a sample size of at least 120 persons is required for the establishment of reference values by the percentile method. We are currently reassessing the Meth-Cough in healthy subjects of various age groups. In the evaluation of Meth-Cough, we compared the number of coughs elicited in the first 15+α min and the second 15 min after Meth inhalation; the most of the cough symptoms occurred within 15+α min, suggesting that these were not spontaneous but induced by bronchoconstriction. This trend was also observed in previous studies in healthy subjects.[10]

This study had several limitations. First, it was a single-center retrospective study, while multicenter prospective studies are necessary to confirm our findings and develop the methods and endpoints as diagnostic tools. Second, most of the patients included in the study had CC that did not improve with cough treatment at other institutions. That is, CC improvements reported in the current study may be influenced by previous treatments.

CONCLUSION

In conclusion, more effective diagnoses and treatments are needed for CC patients. Poor treatment efficacy and unclear diagnosis are major challenges and unmet needs in CC management.[35] Pathophysiological CC diagnostic procedures only require 2 days, compared to more than 1 week for traditional CC diagnostic procedures.[18,19] Our diagnostic procedure included the Cap-Cough test, and the Meth-Cough test before the commencement of therapy. We found that the median treatment time required for complete resolution of cough based on our pathophysiological diagnosis, was only 5.8 weeks, compared to therapeutic diagnoses, which typically take multiple years for resolution.[6,32,33] Thus, a pathophysiology-based evaluation procedure may dramatically improve the management of CC.

Ethics

Ethics Committee Approval: The study was approved by the Ethical Review Board of the National Hospital Organization Nanao Hospital and conducted in accordance with the revised version of the guidelines in the Declaration of Helsinki (UMIN ID: UMIN000018679, date: 05.11.2015).

Informed Consent: Retrospective study.

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Footnotes

Authorship Contributions

Concept: J.H., M.F., Design: J.H., Data Collection or Processing: J.H., M.F., Analysis or Interpretation: J.H., Literature Search: J.H., M.F., M.Y., R.T., N.O., S.Y., Writing: J.H.

Conflict of Interest: No conflict of interest was declared by the authors.

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Original Article

Artificial Intelligence-guided Total Opacity Scores and Obstructive Sleep Apnea in Adults with COVID-19 Pneumonia

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Abstract

OBJECTIVE: We previously demonstrated that artificial intelligence (AI)-directed chest computed tomography (CT)-based total opacity scores (TOS) are associated with high-risk obstructive sleep apnea (OSA) based on the Berlin Questionnaire. In the current study, we examined the association between TOS severity and OSA severity based on polysomnography (PSG) recordings among participants with a history of Coronavirus disease-2019 (COVID-19) infection.

MATERIAL AND METHODS: This was a post-hoc analysis of 56 patients who underwent CT imaging after being diagnosed with COVID-19 pneumonia as well as overnight PSG for a validation study with a median of 406 days after the initial COVID-19 onset. The AI software quantified the overall opacity scores, which included consolidation and ground-glass opacity regions on CT scans. TOS was defined as the volume of high-opacity regions divided by the volume of the entire lung, and severe TOS was defined as the score ≥15. OSA was defined as an apnea-hypopnea index (AHI) of at least 15 events/h.

RESULTS: In total, 21 participants had OSA and 35 had no OSA. The median TOS was 10.5 [interquartile range (IQR) 1.6-21.2] in the OSA group and 2.8 (IQR 1.4-9.0) in the non-OSA group ($P = 0.047$). In a multivariate logistic regression analysis, OSA, AHI, and oxygen desaturation index were associated with severe TOS ($P < 0.05$ for all, respectively) adjusted for age, sex, body mass index, and hypertension.

CONCLUSION: AI-directed CT-based TOS severity in patients with COVID-19 pneumonia was associated with OSA severity based on PSG recordings. These results support our previous findings suggesting an association between questionnaire-based high-risk OSA and worse outcomes in COVID-19 pneumonia.

KEYWORDS: Obstructive sleep apnea, COVID-19, artificial intelligence, chest CT

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INTRODUCTION

Severe acute respiratory syndrome-Coronavirus-2 has led to a global epidemic, severely affecting the medical, economic, and service sectors since its outbreak in late December 2019.[1] As of September 19, 2024, there were 776.137,815 cases and 7.061,330 deaths worldwide.[2] Most individuals infected with Coronavirus disease-2019 (COVID-19) experience a range of symptoms, from undetectable to mild to severe, at the beginning of the pandemic. With appropriate medication and social distancing, many infected individuals have recovered at home. However, people with underlying medical conditions are at higher risk of hospitalization or more severe outcomes.

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Obstructive sleep apnea (OSA) is the most common sleep-related breathing disorder, affecting almost 1 billion people globally.[3,4] The condition is described as recurrent upper airway resistance that leads to decreases or interruptions in airflow, accompanied by increased respiratory attempts.[5] The prevalence of OSA increases with age and body mass index (BMI).[6] Individuals with diabetes, high blood pressure, smoking, and asthma are also more likely to develop OSA[7] and have an increased risk of severe COVID-19 outcomes.[8]

In the early stages of the COVID-19 outbreak, it has been reported that patients with OSA are more prone to COVID-19 infection and could be at higher risk of experiencing more severe symptoms compared to individuals not having OSA.[9-11] A retrospective analysis of medical records showed that around 10% to 12% of COVID-19 patients had been previously diagnosed with OSA.[12,13] The mortality rate of patients with COVID-19 diagnosed with OSA was higher than that of controls, as reported by Cade et al.[11]

Determining the actual occurrence of OSA in patients with COVID-19 is challenging because conducting polysomnography (PSG) during an active infection is not practical. In our previous study, we performed a longitudinal, questionnaire-based study among adults with COVID-19 pneumonia in 2020 and estimated the occurrence of high-risk OSA at 38% using the Berlin Questionnaire (BQ).[13] Because obesity and hypertension are known comorbidities that negatively impact the prognosis of COVID-19, we modified the BQ scoring system to exclude these diseases.[14] The modified BQ (mBQ) indicated that the prevalence of OSA was 22%. Our analysis proposed that patients identified as high-risk for OSA using the modified criteria experienced worse prognoses compared with those with low-risk OSA, regardless of sex, age, and other concomitant diseases.[14]

The primary engagement of the upper airway system and the lungs has made chest computed tomography (CT) imaging an essential tool for diagnosing, initially evaluating, and monitoring patients with COVID-19 throughout the pandemic.[15,16] During these demanding times, it is vital to quickly and accurately determine disease severity. Artificial intelligence (AI) systems enable the rapid assessment of large numbers of patients, evaluation of disease severity, prediction of prognosis, and assessment of treatment response.[17]

In our previous research, we investigated the relationship between AI-assisted CT-based severity scores (SS) and short-term sequels.[18] Through receiver operating characteristics curve analysis, we discovered a total opacity score (TOS) of 2.65 on CT scans that resulted in 81% sensitivity and 56% specificity regarding the requirement for supplemental oxygen. Moreover, a multivariate logistic regression analysis indicated that a TOS >2.65 was linked to a nearly fourfold increase in the need for extra oxygen support and a 2.4-fold increase in the risk of hospitalization.[18]

In a subsequent study, we found a significant relationship between TOS and high-risk OSA and adverse COVID-19 outcomes. We now address the association between TOS severity and OSA severity in terms of apnea-hypopnea index (AHI) based on PSG data.[19]

Main Points

- We previously demonstrated that artificial intelligence-guided chest computed tomography-based total opacity scores (TOS) are linked to high-risk obstructive sleep apnea (OSA) based on the Berlin Questionnaire.
- Our results suggest that the severity of TOS is associated with the severity of OSA based on objective polysomnography findings.
- These results further support the link between OSA and poor outcomes in patients with Coronavirus disease-2019 pneumonia.

MATERIAL AND METHODS

Study Design, Participants, and Ethics Approval

As illustrated in Figure 1, this study included 320 adults with COVID-19 infection in 2020 as the initial OSA COVID-19 study.[9] Patients were, then, randomly invited for an overnight PSG in-hospital study at a median of 406 days [interquartile range (IQR) 379-475 days] after the initial COVID-19 onset. Participants without PSG and eligible CT scans as well as the ones with primary and metastatic lung malignancies and history of tuberculosis were excluded with remaining 56 participants for the current study protocol (Figure 1).

The study protocol was approved by the Koç University Committee on Human Research (approval no: 2021.231.IRB2.049, date: 06.05.2021). Written informed consent was obtained from all participants. The initial OSA COVID-19 study was registered at ClinicalTrials.gov (NCT04363333).

Data Collection and Definitions

The diagnosis of COVID-19 was based on positive polymerase chain reaction analysis of nasopharyngeal samples, clinical symptoms, and radiological findings. All patients completed

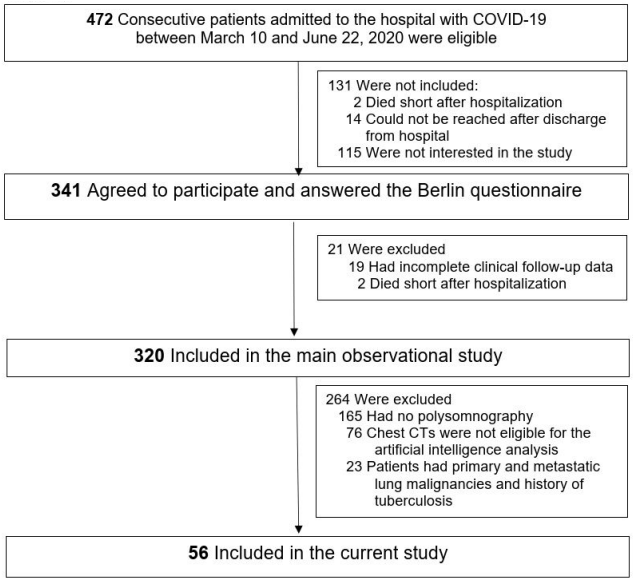

Figure 1. Flow of patients through the study

COVID-19: Coronavirus disease-2019, CT: computed tomography

a survey regarding sleep habits and sleep-related symptoms according to clinical routines. Demographics, concomitant diseases, and physical examination findings were documented. A BMI 30 kg/m^2 was defined as obesity.[20]

Chest Computed Tomography Protocol and Assessment

A 64-detector row CT scanner (Somatom® Definition AS; Siemens Healthineers, Forchheim, Germany) was used to scan each patient. After a full inspiratory breath-hold, a supine scan was performed, covering the lung apices to the costophrenic angles. Protocols for low radiation doses were used, and the scanner automatically selected X-ray tube parameters based on the size of the patient. No intravenous contrast agent was used.

Siemens Healthineers (Forchheim, Germany) supplied the automated lung opacity analysis application "CT Pneumonia Analysis," which was used to analyze images and determine the severity of pneumonia. High-opacity regions, like consolidations and ground glass opacities, which are frequently observed in lung infections, can be automatically identified and quantified using this technique. The technique computes the volumes of lobes, total lung volume, and areas with high opacity, including ground glass and consolidation, based on 3D segmentations of lesions, lungs, and lobes. The ratio of the volume of high opacity areas to the entire lung volume was used to estimate the degree of lung parenchyma involvement, which was defined as the percentage of total opacity. Figures 2A and 2B illustrate two examples of AI and CT images showing TOS values of 1.1 and 17.2, respectively.

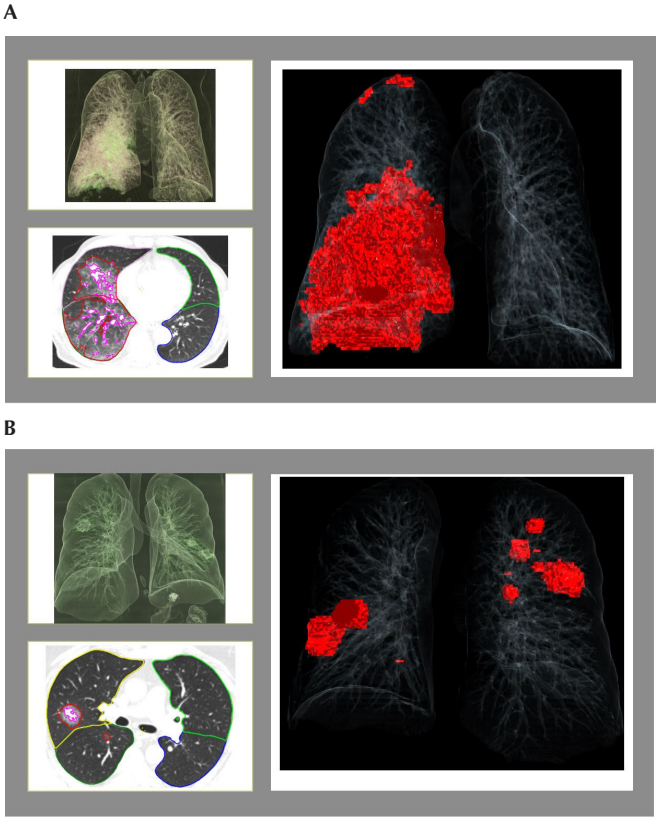

Figure 2. 360° volume rendering overview showing the affected areas and depiction of segmented lung lobes and high-density areas of a patient with (A) total opacity score of 19.3 and (B) total opacity score of 1

Sleep Studies

PSG (NOX-A1 system; Nox Medical Inc., Reykjavik, Iceland) was used in the Koç University Hospital sleep laboratory for this study. Electroencephalography, electrooculography, chin- and leg-electromyograms, nasal airflow, snoring intensity, thoracoabdominal and leg movements, body posture, heart rate (HR), oxygen saturation, and video recording were all measured as part of the PSG. According to the guidelines provided in The American Academy of Sleep Medicine Manual for the Scoring of Sleep and Associated Events 2.5,[21] sleep stages and arousals were evaluated using 30-s intervals. Hypopnea was defined as a decrease in nasal pressure amplitude of >30% and/or thoraco-abdominal movement of >30% for ≥10 seconds if there was significant oxygen desaturation (reduction by ≥3% from the immediately preceding baseline value) and/or an arousal. Apnea was defined as a nearly complete (>90%) cessation of airflow.[22] The oxygen desaturation index (ODI) was calculated as the number of major desaturations per hour of total sleep time, and the total number of significant desaturations was also recorded. The lowest SpO_2 and amount of time below 90% SpO_2 (TS90%) were recorded. According to the most recent International Classification of Sleep Disorders-3,[22] OSA was classified as an AHI ≥15 episodes per hour of total sleep time when OSA-related symptoms were missing. A professional sleep technician blind to the mBQ categorizations graded each PSG recording manually in a mixed order.

Statistical Analysis

For continuous variables, the mean with standard deviation or median with 25th and 75th percentiles was displayed, and for categorical categories, counts with percentages were used to represent the anthropometric traits and PSG results of the study population. The Shapiro-Wilk test was used to assess normalcy. The Student's t-test or Mann-Whitney rank-sum test was used to compare continuous variables between the OSA and no-OSA groups, and the χ^2 test or Fisher's exact test was used to compare categorical variables. All tests were conducted at the 5% significance level. IBM Statistical Package for the Social Sciences (SPSS) 26.0 for Windows (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses.

RESULTS

A total of 56 patients (mean age 56±11.5) years; 71.4% males were included (Figure 1). The median BMI was 29.3 (27.0-31.4) kg/m^2, and 35.7% of the entire population were obese and 39.2% were hypertensive. In total, 21 and 35 patients had OSA (AHI ≥15 events/h), and 35 had no OSA (AHI <15 events/h) (Table 1). The patients with OSA were older than the participants without OSA, but the other baseline characteristics, demographics, and comorbidities were similar, except for the need for supplemental oxygen, which was more common among the OSA patients, who also had significantly longer hospitalization duration during the initial period (Table 1).

As shown in Table 2, sleep efficiency and the proportion of slow-wave sleep were significantly lower in the OSA group than in the non-OSA group. The proportion of rapid eye movement sleep was similar in both groups. The AHI and oxygenation indices were more severe in the OSA group per definition.

Table 1. Baseline characteristics and demographics of COVID-19 patients with and without OSA

	OSA n = 21	No OSA n = 35	*P* value
Demographic characteristics			
Age, y	60.0 (56.5-66.0)	53.0 (45.0-60.0)	0.007
Age >65 years	4 (19.0)	4 (11.4)	0.456
Male sex	17 (81.0)	23 (65.7)	0.222
BMI, kg/m^2	30.4 (28.1-33.9)	28.1 (26.9-31.2)	0.135
Comorbidities			
Hypertension	10 (47.6)	12 (34.3)	0.323
Obesity	7 (33.3)	13 (37.1)	1.000
Diabetes mellitus	4 (19.0)	5 (14.3)	0.715
Coronary artery disease	1 (4.8)	3 (8.6)	1.000
COPD	0 (0.0)	0 (0.0)	1.000
Asthma	1 (4.8)	0 (0.0)	0.375
Current smoking	2 (9.5)	3 (8.8)	1.000
Hospitalization and intensive care unit			
Hospitalization	17 (81.0)	27 (77.1)	0.737
ICU ward	3 (14.3)	2 (5.7)	0.352
Supplemental oxygen	13 (61.9)	8 (22.9)	0.003
In-hospital days	13.0 (4.5-17.5)	6.0 (3.0-8.0)	0.005

COVID-19: Coronavirus disease-2019, OSA: obstructive sleep apnea, y: year, BMI: body mass index, COPD: chronic obstructive pulmonary disease, ICU: intensive care unit

Table 2. Polysomnographic characteristics of patients with COVID-19 with and without OSA

	OSA n = 21	No OSA n = 35	*P* value
TST, min	382 (340-422)	398 (347-418)	0.571
Sleep efficiency, %	80 (71-85)	87 (77-92)	0.036
Slow wave sleep, % TST	17.2 (14.2-22.9)	30.6 (22.5-34.1)	<0.001
REM sleep, % of TST	16.1 (11.8-20.2)	18.4 (15.2-20.0)	0.290
AHI, events/h	21.8 (17.8-33.0)	6.8 (3.0-8.8)	<0.001
ODI, events/h	18.2 (14.8-27.7)	4.9 (2.3-6.7)	<0.001
Mean SpO_2, %	92.4 (91.5-93.4)	94.2 (92.9-95.0)	<0.001
SpO_2 <90%, min	20.8 (8.9-61.0)	1.0 (0.2-5.7)	<0.001

COVID-19: Coronavirus disease-2019, OSA: obstructive sleep apnea, REM: rapid eye movement, AHI: apnea-hypopnea index, ODI: oxygen desaturation index, TST: total sleep time

As illustrated in Figure 3, the median TOS was 10.5 (IQR 1.6-21.2) in the OSA group and 2.8 (IQR 1.4-9.0) in the no-OSA group (P = 0.047) (Figure 3), and the TOS was significantly correlated with AHI (r = 0.33, P = 0.014) as well as with ODI (r = 0.31, P = 0.020) in the entire cohort (Figure 4).

As shown in Table 3, OSA, AHI, and ODI were significantly associated with severe TOS after adjusting for age, male sex, BMI, and hypertension.

DISCUSSION

The main finding of our study was that AI-guided CT-based TOS severity was significantly associated with OSA severity in terms of AHI and ODI.

To the best of our knowledge, this is the first study to investigate the association between radiological severity of COVID-19 infection and OSA severity based on PSG findings. Previous studies addressing the prevalence of OSA in patients with COVID-19 infection were retrospective in nature and based

on diagnostic codes because of the inability to perform PSG during the active infectious periods. A retrospective study reported that 9.5% of individuals with COVID-19 pneumonia had a documented OSA diagnosis.[23] Another study showed that COVID-19 patients, with confirmed OSA diagnoses had higher mortality rates (12.3%) than the control group.[11]

In our first study, we prospectively calculated the prevalence of OSA using the BQ among 320 patients with COVID-19 in the acute phase of infection.[13] We found that 38% of the study population had a high-likelihood of OSA based on the questionnaire, which was much higher than the anticipated 14% prevalence in a nationwide study involving 5.021 adults in Türkiye.[24] As previously discussed in detail elsewhere,[14] we modified the BQ scoring system by excluding obesity and

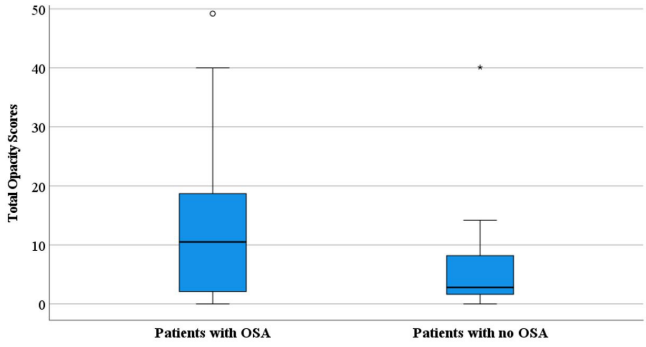

Figure 3. Comparison of total opacity scores among the study groups

OSA: obstructive sleep apnea

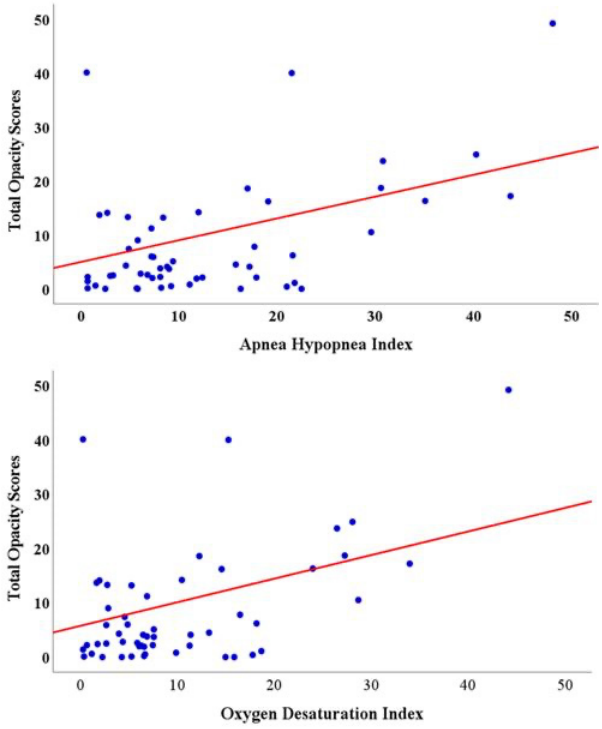

Figure 4. Linear association between total opacity scores and AHI and ODI

AHI: apnea-hypopnea index, ODI: oxygen desaturation index

Table 3. Regression analysis of variables associated with severe opacity score (TOS ≥15)

	Variables	Odds ratio	95% confidence interval		*P*
			Lower	Upper	
Model 1	Constant	0.016			0.256
	Age	0.978	0.885	1.082	0.669
	Male sex	2.030	0.251	16.396	0.669
	BMI	1.074	0.933	1.236	0.320
	Hypertension	1.743	0.277	10.960	0.554
	OSA	10.704	1.632	70.221	0.014
Model 2	Constant	0.050			0.428
	Age	0.964	0.868	1.070	0.491
	Male sex	0.904	0.107	7.663	0.926
	BMI	1.076	0.931	1.244	0.014
	Hypertension	1.401	0.213	9.200	0.725
	AHI	1.100	1.019	1.186	0.014
Model 3	Constant	0.013			0.243
	Age	0.982	0.889	1.085	0.724
	Male sex	1.197	0.150	9.579	0.866
	BMI	1.097	0.953	1.263	0.196
	Hypertension	1.299	0.219	7.718	0.774
	ODI	1.083	1.003	1.169	0.042

BMI: body mass index, OSA: obstructive sleep apnea, AHI: apnea-hypopnea index, ODI: oxygen desaturation index, TOS: total opacity scores

hypertension to better assess the prognosis of COVID-19 in individuals with high-risk OSA. The prevalence of high-risk OSA (22% in the study population) according to the mBQ.[13]

In the following validation study,[14] the participants completed the surveys again and attended the PSG. People were classified as having OSA if their AHI was 15 occurrences per hour. With a sensitivity of 89%, specificity of 93%, predictive value of 89%, and negative predictive value of 93%, the mBQ demonstrated an accuracy of 91%. With an area under the curve of 0.91, the mBQ was a reliable method for diagnosing OSA. The method showed excellent diagnostic accuracy, specificity, and sensitivity in patients with a history of COVID-19. After removing the confounding effects of obesity and hypertension, the mBQ may be used as a screening tool for high-risk OSA and as a predictive tool in clinical cohorts.[14]

Chest CT scans play an important role in hospital settings for various purposes, such as patient prioritization and diagnosis support. Additionally, it could help quantify the severity and progression of diseases as well as monitor the response to treatment. AI algorithms based on CT scans improve diagnostic accuracy by reducing false-negative results and predicting disease outcomes. They also enable the analysis of large image datasets quickly and at a faster speed for chest CT scans.[25-29]

In a research conducted by Kardos et al.[30] involving 1,259 patients it was found that 51.5% of the samples were positive for reverse transcription-polymerase chain reaction (RT-PCR). In the test group of patients evaluated using deep learning technology, CT severity scoring compared to RT-PCR results showed sensitivity at 68%, specificity at 55%, accuracy at 58%, and positive predictive value of 58.9%, respectively. This standardized scoring system for COVID-19 pneumonia helps in diagnosis and clinical decision-making. Furthermore, it is suggested that the deep learning-based CT SS can identify lung abnormalities linked to COVID-19 even before a positive result from RT-PCR testing.[30]

Chrzan et al.[31] suggested that AI-based automated assessment of CT scans in individuals with COVID-19 pneumonia might serve as a tool in COVID-19 pneumonia to evaluate clinical severity and determining the optimal treatment plan. In addition, AI analysis can eventually become a routine diagnostic imaging approach. They also verified that the possibility of being admitted to the intensive care unit or experiencing a fatal outcome was highly correlated with the number of lung abnormalities detected by AI on CT scans during COVID-19. A connection was also observed regarding the extent of inflammation measured in laboratory tests.[31]

The application of AI in analyzing chest CT scans has proven valuable for predicting results and evaluating the severity of illnesses. Following the research findings of Chrzan et al.[31] and Kardos et al.,[30] who highlighted the effectiveness of AI programs in examining extensive image datasets and connecting lung abnormalities with clinical outcomes, our research further supports the idea of combining AI-generated TOS with conventional clinical evaluation techniques. The AI-powered method enhances the precision of risk assessment, which can play a role in making clinical decisions easier by identifying patients at higher risk of needing intensive care or extra oxygen support.

SS calculated by AI might serve as a valuable indicator of the need for additional oxygen support or admission to a hospital in patients with COVID-19 pneumonia. Higher SS values indicate more severe symptoms and possible outcomes. These findings emphasize the ability of AI to improve risk evaluation and guide treatment decisions. The integration of AI-based SS with traditional clinical parameters can enhance patient medical evolution. The findings of this research emphasize the growing significance of AI in diagnosis and patient care practices. The proposed method also aligns with current diagnostic methods and has the potential to greatly improve patient treatment quality and healthcare delivery standards overall.[32,33]

In this context, we also applied the AI-guided scoring systems to the short-term outcomes described in our first study.[18] As previously reported, a TOS >2.65 was significantly associated with an increased risk of extra oxygen need and hospitalization.[18] Moreover, based on the severity of mBQ and TOR, we have also defined TOR thresholds [no or mild TOR (<5), moderate TOR (≥5 & <15), and severe TOR (≥15)] and showed a significant relationship between HR-OSA and TOR thresholds.[19] Our current findings support this relationship and suggest that the severity of TOR (with a TOR score of ≥15) is associated with OSA severity, as objectively determined by AHI values.

The link between the severity of COVID-19 and OSA could be connected to the diversity of factors. Our initial research findings showed that individuals with more intense snoring experience worse outcomes.[13] It is uncertain whether snoring is a direct manifestation of OSA or an indicator of OSA. We postulated that those who snore more loudly may be more vulnerable to COVID-19, most likely as a result of the strain placed on the upper airway muscles.[13] Furthermore, it is possible that COVID-19 infection could increase the collapsibility of the upper airway muscles, leading to the initiation or worsening of OSA symptoms. This suggests a two-way relationship between OSA and COVID-19. There may be other mechanisms linking OSA with an increased risk of COVID-19 infection and adverse outcomes.[9,10] In particular, OSA, when associated with obesity, might worsen hypoxemia and the cytokine storm observed in patients with COVID-19.[10] Additionally, OSA might trigger COVID-19 infection and worsen outcomes in patients with hypertension and diabetes.[34] Some studies have suggested a connection between the development of pulmonary fibrosis and an increased risk of future OSA development in patients with COVID-19.[34] The inflammation caused by OSA, especially when combined with obesity or other health conditions, can worsen the cytokine storm seen in severe cases of COVID-19. Our findings support this hypothesis and offer further evidence that the severity of OSA as measured by specific PSG parameters is significantly correlated with the radiological severity of COVID-19.

This study has several implications for patient care in the medical field regarding COVID-19 infection and OSA. It is crucial to monitor COVID-19 patients with OSA, especially when TOS severity indicates significant lung abnormalities

on CT. Incorporating AI-assisted imaging analysis and tools like the mBQ can provide a more comprehensive approach to managing COVID-19 patients efficiently and effectively.

We acknowledge a certain limitations to our research. First, the sample size was small, which might limit the generalizability of the findings. Second, the study population was derived from near central districts of İstanbul, which might have limited the generalizability of the results to urban districts. Third, AI-based CT analysis might not be appropriate for all situations, such as the occurrence of concomitant lung cancer, fibrosis, and tuberculosis. Furthermore, the association between acute COVID-19 severity and chronic OSA may be affected by the post hoc study design, specifically the interval between the COVID-19 diagnosis and PSG.

CONCLUSION

AI-guided CT-based TOS severity in patients with COVID-19 pneumonia was associated with OSA severity based on PSG recordings. Moreover, the need for supplemental oxygen was more common in the OSA group, who had a longer hospitalization duration during the initial period. These results further support the association between OSA and poor outcomes in COVID-19 pneumonia.

Ethics

Ethics Committee Approval: The study protocol was approved by the Koç University Committee on Human Research (approval no: 2021.231.IRB2.049, date: 06.05.2021).

Informed Consent: Written informed consent was obtained from all participants.

Footnotes

Authorship Contributions

Concept: Z.A., Y.Ç., Ç.A., Y.P., Design: Z.A., Y.Ç., Ç.A., Y.P., Data Collection or Processing: Z.A., Y.Ç., Analysis or Interpretation: Z.A., Y.Ç., Ç.A., Y.P., Literature Search: Z.A., Y.Ç., Ç.A., Y.P., Writing: Z.A., Y.Ç., Ç.A., Y.P.

Conflict of Interest: Yüksel Peker reports grants from ResMed Inc and ResMed Foundation outside the submitted work. Zeynep Atçeken, Yeliz Çelik and Çetin Atasoy have nothing to declare.

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Original Article

The Prognostic Significance of MELD-XI in Patients Admitted to the Intensive Care Unit for Respiratory Failure

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Abstract

OBJECTIVE: Composite Model for End-Stage Liver Disease (MELD), an adapted version of the model score excluding international normalised ratio (MELD-XI), was reported to predict outcomes in patients with organ failure. Aim of study was to evaluate the prognostic significance of the MELD-XI score and compare it with the Sequential Organ Failure Assessment (SOFA) and Acute Physiology and Chronic Health Evaluation 2 (APACHE 2) scores in patients admitted to the intensive care unit (ICU) for respiratory failure.

MATERIAL AND METHODS: Out of 822 patients with respiratory failure between September 2020 and June 2023, a total of 727 patients with etiologies of chronic obstructive pulmonary disease exacerbation, cardiogenic pulmonary edema, pulmonary thromboembolism, pneumonia, bronchiectasis, kyphoscoliosis, neuromuscular diseases, obesity hypoventilation syndrome, and diffuse parenchymal lung disease were included.

RESULTS: A statistically significant correlation was found between MELD-XI, SOFA, and APACHE 2 scores. The cutoff value of the MELD-XI score was 11 on receiver operating characteristic analysis, indicating a higher risk of mortality in patients with a score of 11 or above. The APACHE 2 and SOFA scores of the MELD-XI ≥11 group were found to be higher and the Glasgow Coma Scale were lower than the MELD-XI <11 group. MELD-XI ≥11 was associated with an increased risk of mortality in overall [Hazard ratio (HR): 4.1, 95% confidence interval (CI): 2-6.4, $P < 0.001$] and subgroups with different etiologies in Cox regression analysis. In the multivariate analysis, MELD-XI was the most important independent variable indicating an increased risk of mortality, regardless of etiology (HR: 2.4, 95% CI: 2.0-2.5, $P < 0.001$).

CONCLUSION: MELD-XI is an important marker of ICU mortality in patients with respiratory failure due to different etiologies and is as effective as the SOFA and APACHE 2 in predicting mortality.

KEYWORDS: COPD, pulmonary vascular diseases, interstitial lung disease, bronchiectasis, cystic fibrosis, respiratory intensive care

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INTRODUCTION

Patients admitted to an intensive care unit (ICU) constitute a markedly diverse group in terms of age, clinical condition, disease origin, hemodynamic parameters, therapeutic response, and prognosis. Risk stratification systems, including Acute Physiology and Chronic Health Evaluation 2 (APACHE 2) and Sequential Organ Failure Assessment (SOFA), have been introduced to classify these patients more effectively and predict their outcomes. The Model for End-Stage Liver Disease (MELD) score is a prognostic model that incorporates the logarithmic evaluation of hepatic and renal function, two vital organ systems critical for determining prognosis. For individuals on oral anticoagulant therapy, the international normalised ratio (INR) component was excluded (-XI) due to potential inaccuracies in calculation.[1]

Pathologies that cause decreased organ perfusion decrease blood flow to the liver, leading to ischemic parenchymal changes and hepatocellular necrosis, especially in cases of acute decompensation. An increase in right atrial pressure and right heart dysfunction cause hepatic venous congestion. Cholestasis, in which liver enzymes and bilirubin are elevated, develops as a result of congestive hepatopathy.[2,3]

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The composite MELD score is an easy and effective tool for assessing liver dysfunction based on creatinine and serum total bilirubin. The aim of this study was to determine the risk of mortality in patients undergoing transjugular intrahepatic portosystemic shunt procedures. The MELD score was then used to evaluate post-operative mortality in patients with cirrhosis undergoing major gastrointestinal, orthopedic, and cardiovascular operations.[4,5] It can function as an indicator of multiorgan dysfunction. To obtain accurate results in the patient group using anti-coagulants, INR was excluded from the scoring.[1]

Patients admitted to the ICU for the management of respiratory failure may present with diverse underlying etiologies and preexisting health conditions. Currently, accepted indices are used for the risk and prognosis assessment of patients with respiratory failure.

Patients admitted to the ICU for the management of respiratory failure may present with diverse underlying causes and preexisting health conditions. Currently, established metrics are employed to evaluate the risk and predict the prognosis of patients with respiratory failure.

Newly devised organ failure assessment tools, such as the SOFA score, can aid in the continual evaluation of organ malfunction or breakdown and are beneficial for assessing morbidity. Despite their primary purpose being the description and quantification of organ dysfunction and prognosis prediction, numerous studies have substantiated the conspicuous correlation between organ dysfunction and fatality.[6] The foremost determinant of a patient's mortality risk in the ICU is the patient's physiological resilience.

With APACHE 2, in addition to physiological changes, chronological age and chronic health status are also evaluated, and the mortality risk is calculated.[7]

Respiratory failure can result from multiple organ dysfunctions and may also lead to complications in other organ systems, such as the cardiovascular, gastrointestinal, and renal systems. These additional comorbidities can significantly worsen the prognosis, often leading to more severe overall outcomes than initially expected.

Main Points

- The MELD-XI score is a reliable tool for predicting intensive care unit (ICU) mortality among patients with respiratory failure.
- MELD-XI scores ≥11 are associated with higher Acute Physiology and Chronic Health Evaluation 2 (APACHE 2) and Sequential Organ Failure Assessment (SOFA) scores, lower Glasgow Coma Scale score, and increased mortality risk.
- The multivariate analysis suggested that MELD-XI was an important independent predictor of mortality in ICU patients.
- The MELD-XI score may be as effective as the APACHE 2 and SOFA scores for assessing mortality risk across various clinical conditions.

The MELD-XI score was applied with the hypothesis that it could provide an accurate and straightforward method for predicting the prognosis of patients with respiratory failure in the ICU, and its relationship with the APACHE 2 and SOFA scores was subsequently evaluated.

MATERIAL AND METHODS

Study Design

Patients with acute hypoxemic and hypercapnic respiratory failure admitted to the ICU of a tertiary hospital between September 2020 and June 2023 were enrolled in this single-center, prospective study.

Settings

Hypoxemic respiratory failure was characterized by an arterial oxygen pressure (PaO_2) lower than 60 mmHg, and hypercapnic respiratory failure was defined by an arterial carbon dioxide pressure ($PaCO_2$) higher than 50 mmHg. Chronic obstructive pulmonary disease (COPD) and COPD exacerbation (COPDE) were identified in accordance with the guidelines set by the global initiative for COPD (GOLD).[8] Acute cardiogenic pulmonary edema (ACPE) was defined according to clinical and radiological findings.[9] The diagnosis of acute pulmonary thromboembolism (PTE) was made based on lung computed tomography angiography evaluation.[10] Pneumonia was defined as the radiological presence of infiltrate with symptoms of acute-onset lower respiratory tract infection.[11] The diagnosis of bronchiectasis was based on a combination of clinical examination and computed tomography scans.[12] Obesity-hyperventilation syndrome (OHS) was determined by the presence of obesity (body mass index >30 kg/m^2), awake alveolar hypoventilation as evidenced by a partial arterial pressure of carbon dioxide >45 mmHg, and other potential causes of hypercapnia and hypoventilation have been ruled out.[13] The diagnosis of diffuse parenchymal lung disease (DPLD) was based on clinical and radiological findings.[14]

Participants

Patients with unidentified etiologies of respiratory failure and multiple etiologies were excluded from the study. Morover, patients with lung carcinoma and extrathoracic malignancy were not included in the study. COPDE, ACPE, acute PTE, pneumonia, bronchiectasis, kyphoscoliosis, neuromusculer disease (NMD), OHS, and DPLD patients with respiratory failure were included in this study.

All patients received the necessary empirical anti-microbial therapy in accordance with their etiology, and patients with COPD received bronchodilators and systemic corticosteroid therapy. Patients with DPLD received the necessary immunomodulatory or anti-fibrotic treatment. All patients received prophylaxis against stress ulcers and deep vein thrombosis.

Ethical approval for this study was obtained from the Ankara University Faculty of Medicine Institutional Review Board (decision no: İ2-80-20, date: 13.02.2020). All included patients provided written informed consent for study participation. All subjects provided written informed consent for study participation.

Data Sources/Measurements

A detailed medical history of the cases was obtained. Demographic data, clinical findings, vital signs, laboratory tests, arterial blood gas results, and PaO_2/FiO_2 ratio were recorded by the intensive care physicians, who were also the authors of the study at ICU admission. Glasgow Coma Scale (GCS) scores, APACHE 2, and MELD-XI scores were measured within 12 hours after admission by the physician in charge of the ICU.

Diabetes mellitus, hypertension, coronary artery disease, arrhythmia, valvular heart disease, kidney failure, liver failure, cerebrovascular disease, and pulmonary hypertension (PHT) comorbidities were recorded.

Quantitative Variables

Adequate oxygenation and, when deemed necessary, non-invasive and invasive mechanical ventilation treatments were administered according to the severity of respiratory distress.[15-18]

The MELD-XI score was calculated using the following formula: MELD-XI = 5.11 x ln (serum bilirubin in mg/dL) ± 11.76 x ln (serum creatinine in mg/dL) ± 9.44 on the day of admission.[5]

SOFA score was measured using the mean arterial pressure or administration of vasopressor, PaO_2/FiO_2 ratio, platelets, bilirubin, creatinine levels.[6]

The APACHE 2 score was calculated based on vital signs, oxygenation, arterial PHT, laboratory tests, GCS, chronological age, and diagnosis of ICU admission.[7]

Statistical Analysis

For the statistical analysis in this study, we utilized Statistical Package for the Social Sciences (SPSS), version 20.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics were employed to present data with a normal distribution, expressed as numbers (percentage) and mean±standard deviation or median interquartile range.

Histograms, variation coefficients, Skewness and Kurtosis plots, and normality tests (if n < 50 Shapiro and if n > 50 Kolmogorov-Smirnov test) were used to determine the distribution characteristics of the variables. Group comparisons were made using Student's t-test, the chi-square test, and Mann-Whitney U test based on data distribution. The Student's t-test was used to evaluate the means, homogeneity of variances, and standard deviations of independent groups with normal distribution, and for cases with a sample size greater than 30. Independent groups segregated according to the MELD-XI cutoff value were compared using Student's t-test. The Student's t-test was also utilized to compare the means of normally distributed MELD-XI-SOFA and MELD-XI-APACHE 2 scores based on disease etiology. In some dependent groups, the sample size was <30, but the distribution of differences was normal.

The MELD-XI score cutoff value according to Youdan's index, sensitivity, specificity, area under curve, and lower and upper bound values were determined via receiver operating characteristic curve analysis.

Survival analysis of MELD-XI ≥11 and <11 groups were compared using the Log-Rank test.

Linear regression analysis revealed that MELD-XI ≥11 and etiologies of disease were significant variables affecting mortality. The Cox regression analysis was selected from the survival analysis. The time variable chosen was the duration of ICU stay, with mortality as the dependent variable (status) and MELD-XI ≥11 and etiologies of respiratory failure as independent variables. In the univariate analysis, length of stay in the ICU was the time variable, and mortality status was the dependent variable. Factors considered to be associated with survival during ICU stay were determined through clinical observation. The assumption of normality for the variables was made, and a linear relationship was observed among the normally distributed variables. Variables found to be statistically significant and clinically significant in the univariate analysis were subjected to Cox regression analysis with multiple independent variables. When identifying individual factors influencing ICU mortality by univariate analysis, independent variables associated with mortality were determined by multivariate Cox regression analysis. The significance level was set at $P < 0.05$.

RESULTS

Nine hundred eighty-five patients admitted to the ICU of a tertiary hospital between September 2020 and June 2023 were enrolled in this single-center, prospective study. A total of 822 patients had diagnosis of acute respiratory failure. Of these, 30 patients with lung cancer and extrathoracic malignancy, 65 patients with unidentified respiratory failure etiology and multiple etiological diseases were excluded from the study. Seven hundred twenty-seven patients admitted to the ICU with respiratory failure, including COPDE (n = 240), ACPE (n = 157), acute PTE (n = 91), pneumonia (n = 89), bronchiectasis (n = 40), kyphoscoliosis (n = 27), NMD (n = 24), OHS (n = 26), and DPLD patients (n = 33), were enrolled in this study (Figure 1).

The mean age of patients was 69.6±28.2 years and 66% (n = 480) were male. The mean MELD-XI score of the overall study population was calculated as 8.8±5.4, the mean SOFA score was 9.8±4.1, APACHE 2 score was 18.6±6.5 and GCS was 9.8±5.2. MELD-XI was significantly correlated with SOFA and APACHE 2 scores in the whole group and subgroups of different etiologies ($P < 0.001$) (Table 1).

At a cutoff point of 11 according to Youdan's index, MELD-XI had the best discriminatory power for prognosis and mortality [area under the curve (95%): 0.822 (0.791-0.853), sensitivity 78.4%, specificity 87.3%, $P < 0.001$] (Figure 2).

MELD-XI ≥11 was calculated in 297 cases, and MELD-XI <11 in 430 cases. There was no difference between the age and sex of these two groups. The APACHE 2 (26.7±8.6 vs. 17.7±5.3) and SOFA (15.4±5.3 vs. 7.9±4.6) scores of the MELD-XI ≥11 group were found to be significantly higher and the GCS (7.3±3.5 vs. 11.4±3.9) were lower than the MELD-XI <11 group ($P < 0.001$). While the PaO_2/FiO_2 ratio (257.5±100.6 vs. 360.7±85.4), pH (7.35±0.19 vs. 7.37±0.21) of the MELD-XI ≥11 group were lower, but lactate level (2.9±2.4 vs. 1.7±1.8) was higher, and the $PaCO_2$ values (57.8±18.6 vs. 56.6±15.4) of

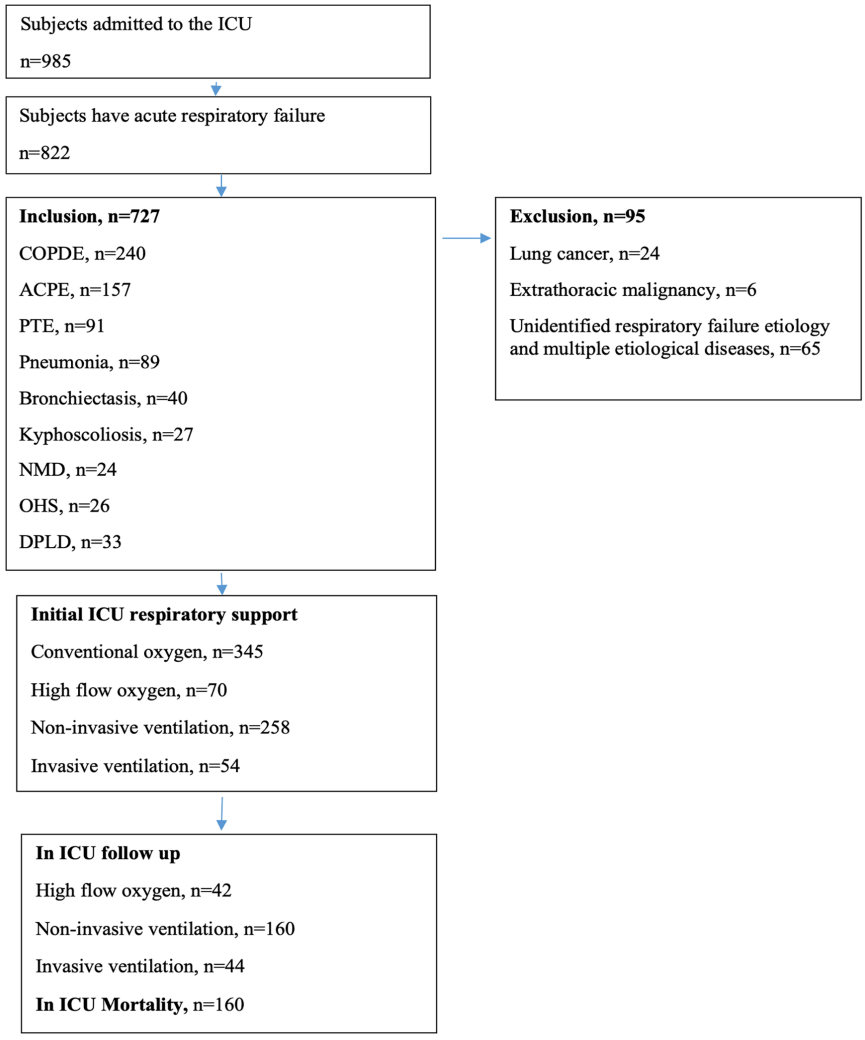

Figure 1. Flowchart showing the inclusion and exclusion characteristics of patients with respiratory failure admitted to the ICU

ICU: intensive care unit, COPDE: chronic obstructive pulmonary disease exacerbation, ACPE: acute cardiogenic pulmonary edema, PTE: pulmonary thromboembolic, NMD: neuromusculer disease, OHS: obesity hypoventilation syndrome, DPLD: diffuse parenchymal lung disease

the two groups were similar ($P < 0.001$, $P < 0.01$, $P < 0.001$, $P = 0.124$ respectively). When the laboratory tests of the two groups were compared, the serum creatinine (2.4±1.8 vs. 1.5±0.9, $P < 0.001$), urea (54.2±19.3 vs. 48.4±16.7, $P = 0.01$), bilirubin (2.7±2.6 vs. 0.9±0.8, $P < 0.001$), INR (1.3±1.1 vs. 0.9±0.7, $P = 0.001$), alanine aminotransferase (ALT) (58.5±12.4 vs. 34.3±8.4, $P < 0.001$) and aspartate aminotransferase (AST) (51.3±13.7 vs. 32.5±7.5 $P < 0.001$) values of the group with MELD-XI ≥11 were found to be significantly higher, but glomerular filtration rate (36.7±13.4 vs. 64.5±21.5, $P < 0.001$) and albumin (33.6±1.8 vs. 38.5±2.6, $P = 0.001$) measurements were lower than those of the other group (Table 2).

When the high-MELD-XI group was compared with the low-MELD-XI group, the rates of diabetes mellitus (35% vs. 22.1%, $P = 0.004$), kidney failure (26.9% vs. 8.8%, $P < 0.001$), liver failure (21.9% vs. 5.3%, $P < 0.001$), and PHT (31.3% vs. 17.9%, $P = 0.01$) were found to be higher. There were no significant differences between the two groups in the rates of hypertension, coronary artery disease, and cerebrovascular disease.

Of the patients included in the study, 160 (22%) died during the ICU follow-up. The mean MELD-XI value of the deceased patient group (13.6±5.4) was significantly higher than those who survived (7.8±6.9) ($P < 0.001$). The mortality rate of the group with MELD-XI score ≥11 (37.7%) was higher than that of the group with MELD-XI <11 (11.2%) ($P < 0.001$). When evaluated separately according to the etiologies of the diseases causing respiratory failure, it was found that the mortality rates of patients with COPD, ACPE, PTE, and pneumonia with MELD-XI score ≥11 were higher than those with low scores ($P < 0.001$, $P < 0.001$, $P < 0.004$, $P < 0.01$) (Table 3).

When the initial oxygen support and mechanical ventilation treatments in the ICU were compared, patients with high MELD-XI scores had higher rates of conventional oxygen and invasive mechanical ventilation treatments. In the ICU setting once more, patients with higher MELD-XI scores had elevated rates of high-flow oxygen administration, non-invasive mechanical ventilation, and invasive mechanical ventilation during follow-up (Table 4).

Table 1. MELD-XI, SOFA, and APACHE 2 scores according to respiratory failure etiology

	n	MELD-XI	SOFA	Q^{2*}	df*	*P**	APACHE 2	$Q^{2\theta}$	df^{θ}	P^{θ}
Overall	727	8.8±5.4	9.8±4.1	0.450	727	<0.001	18.6±6.5	0.401	727	<0.001
COPDE	240	10.4±6.2	15.4±5.4	0.363	240	<0.001	24.3±7.4	0.243	240	<0.001
ACPE	157	8.2±4.5	9.5±6.2	0.371	157	<0.001	19.7±8.6	0.361	157	<0.001
PTE	91	14.3±7.7	16.7±3.5	0.448	91	<0.001	25.5±6.4	0.418	91	<0.001
Pneumonia	89	12.5±6.3	10.6±8.4	0.426	89	<0.001	20.2±7.2	0.325	89	<0.001
Bronchiectasis	40	7.6±3.2	8.4±2.7	0.366	40	<0.001	16.8±3.5	0.368	40	<0.001
Kyphoscoliosis	27	5.3±4.3	6.7±6.3	0.378	27	<0.001	14.1±5.6	0.379	27	<0.001
NMD	24	6.5±5.2	7.5±4.5	0.359	24	<0.001	10.4±7.4	0.231	24	<0.001
OHS	26	6.2±4.4	8.3±5.8	0.326	26	<0.001	11.4±4.3	0.334	26	<0.001
DPLD	33	9.4±3.6	12.2±7.4	0.387	33	<0.001	15.6±8.7	0.396	33	<0.001

The Student's t-test was used to compare means between two groups.
Q^2: Homogenity of variance, df: degrees of freedom.
*: Statistical comparison of MELD-XI and SOFA scores.
$^{\theta}$: Statistical comparison of MELD-XI and APACHE 2 scores.
Results were given as mean±SD.
COPDE: chronic obstructive pulmonary disease exacerbation, ACPE: acute cardiogenic pulmonary edema, PTE: pulmonary thromboembolic, NMD: neuromusculer disease, OHS: obesity hypoventilation syndrome, DPLD: diffuse parenchymal lung disease, SD: standard deviation, APACHE 2: Acute Physiology and Chronic Health Evaluation 2, SOFA: Sequential Organ Failure Assessment

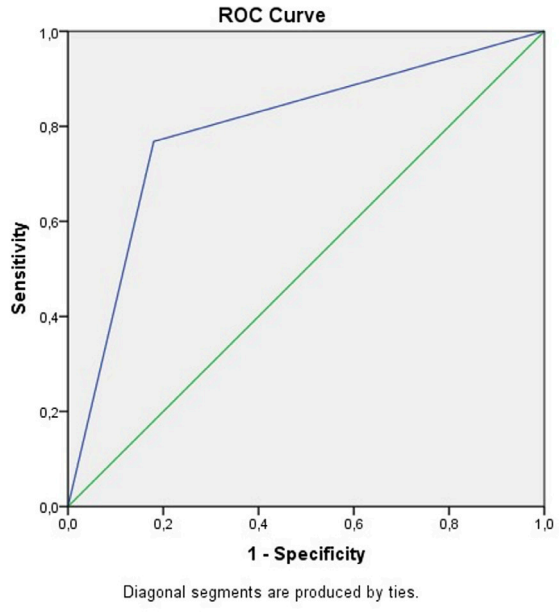

Figure 2. The cutoff value of the MELD-XI score was found to be 11 by ROC analysis

ROC: receiver operating characteristic

A MELD-XI ≥11 was associated with an increased risk of mortality in overall [Hazard ratio (HR): 4.1, 95% 2-6.4, $P < 0.001$] and subgroups with different etiologies in Cox regression analysis. [COPDE HR: 3.9, 95% confidence interval (CI): 2.4-5.8, $P < 0.001$, ACPE HR: 4.8, 95% CI: 3.2-6.7, $P < 0.001$, PTE HR: 6.3, 95% CI: 4.5-8.2, $P < 0.001$, pneumonia HR: 5.2, 95% CI: 3.9-7.1, $P < 0.01$, bronchiectasis HR: 2.5, 95% CI: 2.0-4.5, $P < 0.01$, kyphoscoliosis HR: 2.4, 95% CI: 1.8-2.9, $P < 0.01$, NMD HR: 2.6, 95% CI: 1.9-3.2, $P < 0.01$, OHS HR: 2.7, 95% CI: 1.5-3.6, $P < 0.01$, DPLD HR: 3.3, 95% CI: 2.4-4.3, $P < 0.01$] (Table 5).

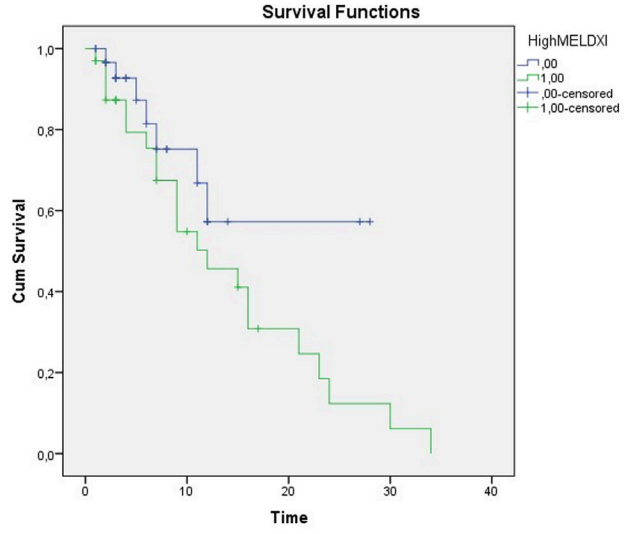

Figure 3. A comparison of survival between groups with MELD-XI ≥11 and MELD-XI <11 was conducted using the Log-Rank test

In the univariate analysis, MELD-XI was associated with a statistically significant increase in mortality risk (HR: 4.1, 95% CI: 2-6.9, $P < 0.001$). Moreover, univariate analysis demonstrated that PaO_2/FiO_2 (HR: 1.9, 95% CI: 1.5-2.1, $P < 0.001$), lactate (HR: 1.7, 95% CI: 1.3-1.8, $P < 0.001$), creatinine (HR: 1.9, 95% CI: 1.7-2.2, $P < 0.001$), urea (HR: 1.6, 95% CI: 1.3-1.7, $P < 0.001$) bilirubin (HR: 1.3, 95% CI: 1.0-1.6, $P < 0.001$, ALT (HR: 1.0, 95% CI: 0.9-1.2, $P < 0.001$ and AST (HR: 1.0, 95% CI: 0.9-1.1, $P < 0.001$) were risk factors for ICU mortality in patients with acute respiratory failure with MELD-XI ≥11 (Table 6).

Multivariate analysis demonstrated MELD-XI (HR: 2.6, 95% CI: 2.4-2.9, $P < 0.001$), PaO_2/FiO_2 (HR: 1.6, 95% CI: 0.7-2.1, $P < 0.01$), lactate (HR: 1.5, 95% CI: 0.9-1.6, $P < 0.01$), creatinine

Table 2. Comparison of groups according to MELD-XI cutoff values

	MELD-XI ≥11 n = 297	MELD-XI <11 n = 430	Q^2	df	*P*
Age, y	71.6±20.3	69.4±22.6	0.180	726	NS
Sex, M	258 (86.9)	222 (51.6)	19.36*	1	NS*
SOFA score	15.4±5.3	7.9±4.6	0.436	726	<0.001
GCS	7.3±3.5	11.4±3.9	0.290	726	<0.001
APACHE 2	26.7±8.6	17.7±5.3	0.385	726	<0.001
PaO_2/FiO_2	257.5±100.6	360.7±85.4	0.571	726	<0.001
$PaCO_2$, mmHg	57.8±18.6	56.6±15.4	0.243	726	NS
pH	7.35±0.19	7.37±0.21	0.422	726	<0.01
Lactate, mMol/L	2.9±2.4	1.7±1.8	0.536	726	<0.001
Htc, mg/dL	31.7±12.5	33.8±16.3	0.350	726	NS
WBC,	12.3±10.5	10.6±9.4	0.264	726	NS
PLT	273±180	255±162	0.371	726	NS
CRP, mg/L	64.4±53.2	38.6±25.2	0.248	726	0.01
Procalcitonin	0.08±0.05	0.06±0.06	0.326	726	NS
Cre	2.4±1.8	1.5±0.9	0.467	726	<0.001
GFR	36.7±13.4	64.5±21.5	0.475	726	<0.001
Urea	54.2±19.3	48.4±16.7	0.354	726	0.01
Bilirubin	2.7±2.6	0.9±0.8	0.523	726	<0.001
Na	140±9.8	138±7.5	0.198	726	NS
K	4.0±1.9	3.8±1.7	0.087	726	NS
Alb	33.6±1.8	38.5±2.6	0.479	726	0.001
INR	1.3±1.1	0.9±0.7	0.486	726	0.001
ALT	58.5±12.4	34.3±8.4	0.543	726	<0.001
AST	51.3±13.7	32.5±7.5	0.555	726	<0.001
BNP	565 (150.5)	420 (136)	0.224$^{\theta}$	726	NS$^{\theta}$

The Student's t-test was used to compare means between two groups.

Q^2: Homogenity of variance, df: degrees of freedom.

: The chi-square test was used to compare sex (= χ^2 value).

$^{\theta}$: Mann-Whitney U test was used to compare BNP ($^{\theta}$ = Z value).

Results were given as mean±SD or n (%).

SOFA: Sequential Organ Failure Assessment, GCS: Glasgow Coma Scale, APACHE 2: Acute Physiology and Chronic Health Evaluation 2, BE: base excess, Htc: hematocrit, WBC: white blood cells, PLT: platelets, CRP: C-reactive protein, Cre: creatinine, GFR: glomerular filtration rate, Bil: bilirubin, Na: sodium, K: potassium, Alb: albumin, INR: international normalized ratio, ALT: alanine aminotransferase, AST: aspartate aminotransferase, BNP: brain natriuretic peptide, SD: standard deviation, NS: not significant, M: male

(HR: 1.7, 95% CI: 1.0-1.8, *P* = 0.01), urea (HR: 1.4, 95% CI: 0.8-1.5, *P* = 0.01), and bilirubin (HR: 1.0, 95% CI: 0.7-1.3, *P* = 0.01) as risk factors for ICU mortality in acute respiratory failure patients with MELD-XI ≥11 (Table 6).

In the survival analysis comparing groups with MELD-XI scores ≥11 and <11 using the Log-Rank test, a log-rank chi-square value of x^2: 139.36 was found with *P* < 0.001. The survival time for the group with MELD-XI scores ≥11 was determined to be 13.32±0.67 (95% CI: 12.00-14.65) and for the group with MELD-XI scores <11 was 27.14±0.83 (95% CI: 25.51-28.76).

DISCUSSION

In this study, the MELD-XI score was found to have significant prognostic value in predicting ICU mortality among patients with respiratory failure from various etiologies, demonstrating comparable effectiveness to SOFA and APACHE 2 scores. It is known that patients with acute respiratory failure have a high ICU mortality. Hypoxia, hypoperfusion, and inflammation due to respiratory failure cause liver and kidney dysfunction, leading to poor prognosis. In these cases, in addition to the respiratory system, insufficiency or dysfunction of organ systems, such as the kidney and liver, increases morbidity and mortality. As soon as patients with respiratory failure are admitted to the ICU, an easy way to quickly determine the risk will increase the chance of successful treatment. Scoring systems such as the SOFA score and APACHE 2 are used to determine prognosis in critically ill patients.[6,7]

APACHE 2 is a multi-parameter scoring system that has long been used to assess the severity of illness and predict outcomes

Table 3. Comparison of mortality rates in patients with MELD-XI ≥11 and MELD-XI <11 according to respiratory failure etiology

Mortality	n	MELD-XI ≥11 n = 297	MELD-XI <11 n = 430	χ^2	df	*P*
Overall	160	112 (37.7)	48 (11.2)	44.83	1	<0.001
COPDE	61	45 (15.2)	16 (3.7)	24.82	1	<0.001
ACPE	38	26 (8.7)	12 (2.8)	11.25	1	<0.001
PTE	19	14 (4.7)	5 (1.2)	8.210	1	0.004
Pneumonia	15	11 (3.7)	4 (0.9)	6.386	1	0.01
Bronchiectasis	4	2 (0.7)	2 (0.5)	0.138	1	NS*
Kyphoscoliosis	4	3 (1.0)	1 (0.2)	0.750	1	NS*
NMD	3	2 (0.7)	1 (0.2)	0.823	1	NS*
OHS	7	4 (1.3)	3 (0.7)	0.761	1	NS*
DPLD	9	6 (2.0)	3 (0.7)	2.446	1	NS*

The chi-square test was used to compare two independent groups.
χ^2: Chi-square value, df: degrees of freedom.
*: Statistically significant results could not be obtained due to the small sample size and the fact that fewer than 20% of the expected frequencies were less than 5.
Results are presented as n (%).
COPDE: chronic obstructive pulmonary disease exacerbation, ACPE: acute cardiogenic pulmonary edema, PTE: pulmonary thromboembolic, NMD: neuromusculer disease, OHS: obesity hypoventilation syndrome, DPLD: diffuse parenchymal lung disease, NS: not significant

Table 4. Evaluation of respiratory support therapies according to the MELD-XI cutoff value

	MELD-XI ≥11 n = 297	MELD-XI <11 n = 430	χ^2	df	*P*
Initial ICU respiratory support					
Conventional oxygen	116 (39.1)	229 (53.2)	5.164	1	0.02
High-flow oxygen	36 (12.1)	34 (7.9)	2.936	1	NS
Non-invasive ventilation	110 (37.0)	148 (34.4)	0.250		NS
Invasive ventilation	35 (11.8)	19 (4.4)	11.81	1	<0.001
In ICU follow-up					
High-flow oxygen	24 (8.1)	18 (4.2)	4.330	1	0.04
Non-invasive ventilation	85 (28.6)	75 (17.4)	8.055	1	0.006
Invasive ventilation	28 (9.4)	16 (3.7)	8.832	1	0.003
In patients with ICU mortality	112 (37.7)	48 (11.2)	44.83	1	<0.001
Duration of ICU stay	21.7±12.5	13.4±8.6	*0.568	726	<0.01

Results were given as mean±SD or n (%).
The chi-square test was used to compare two independent groups.
χ^2: Chi-square value, df: degrees of freedom.
*: Q^2 value, Student's t-test was used to compare mean duration of ICU stay.
SD: standard deviation, ICU: intensive care unit, NS: not significant

within the initial 24 hours of patient admission to the ICU. The SOFA score has recently gained widespread recognition for diagnosing sepsis and ascertaining treatment results in patients with sepsis. Furthermore, the SOFA score has been applied to evaluate the gravity of illness and predict prognosis in individuals with cancer, acute pancreatitis, acute liver failure, and acute respiratory distress syndrome.[6,19]

However, to find an easier and more effective scoring system, we applied the MELD-XI score to these patients and tried to determine its effectiveness in determining the risk of mortality and compared it with other scoring systems.

The MELD score was found to be effective in the prognostic assessment of patients with advanced liver disease. For the evaluation independent of the oral anti-coagulant effect, the MELD-XI score was established by excluding the INR value from the measurement.[20]

Significant results were obtained when the MELD-XI score was studied in various heart failure, arrhythmia, cardiovascular diseases, pulmonary embolism, and transplantation cases.[21]

To the best of our knowledge, this is the first study conducted in this patient group, and we found that the MELD-XI, SOFA, and

Table 5. A MELD-XI ≥11 predicted increased intra-ICU mortality in patients with COPDE, ACPE, PTE, and pneumonia

	LL	χ^2	df	HR	CI	*P*
COPDE	421.45	25.34	2	3.9	2.4-5.8	<0.001
ACPE	389.33	10.47	2	4.8	3.2-6.7	<0.001
PTE	235.42	32.19	2	6.3	4.5-8.2	<0.001
Pneumonia	346.74	27.51	2	5.2	3.9-7.1	<0.001

Cox regression analysis tests were employed for statistical evaluation.
LL: -2Log Likelyhood, χ^2: Chi-square, df: degrees of freedom, HR: Hazard ratio, CI: confidence interval, COPDE: chronic obstructive pulmonary disease exacerbation, ACPE: acute cardiogenic pulmonary edema, PTE: pulmonary thromboembolic

Table 6. Univariate and multivariate Cox regression analyses of mortality in the acute respiratory failure cohort

Variable	Univariate					Multivariate					
	LL	χ^2	HR	95% CI	*P*	B	SE	β	HR	95% CI	*P*
MELD-XI	168.63	36.24	2.6	2.4-2.9	<0.001	1.36	0.32	0.76	2.4	2.0-2.5	<0.001
PaO_2/FiO_2	247.91	15.42	1.9	1.5-2.1	<0.001	1.24	0.27	0.59	1.6	0.7-2.1	<0.01
Lactate, mmol/L	321.75	10.36	1.7	1.3-1.8	<0.001	1.20	0.33	0.47	1.5	0.9-1.6	<0.01
Cre	280.44	17.25	1.9	1.7-2.2	<0.001	1.32	0.41	0.72	1.7	1.0-1.8	0.01
Urea	352.65	8.42	1.6	1.3-1.7	<0.001	1.19	0.29	0.63	1.4	0.8-1.5	0.01
Bil	454.42	5.34	1.3	1.0-1.6	<0.001	1.05	0.21	0.39	1.0	0.7-1.3	0.01
ALT	545.80	4.25	1.0	0.9-1.2	<0.001	0.89	0.34	0.12	0.7	0.5-0.8	NS
AST	550.71	4.17	1.0	0.9-1.1	<0.001	0.53	0.13	0.09	0.8	0.6-0.8	NS

Univariate and multivariate Cox regression analysis tests were employed for statistical evaluation.
Multivariate Cox regression analysis: -2 LL: 782.279, χ^2: 18.186, df: 8, $P < 0.001$, R: 0.947, R^2: 0.897, f: 247.637, Durbin-Watson: 1.953.
LL: 2Log Likelyhood, χ^2: Chi-square, HR: Hazard ratio, CI: confidence interval, B: constant, SE: standart error, β: beta, SOFA: Sequential Organ Failure Assessment, GCS: Glasgow Coma Scale, Cre: creatinine, Bil: bilirubin, ALT: alanine aminotransferase, AST: aspartate aminotransferase, NS: not significant

APACHE 2 scores were correlated with the overall incidence of acute respiratory failure and different etiologies causing respiratory insufficiency. We believe that the cutoff value of the MELD-XI score may vary according to the diagnosis. By determining the cutoff value for the MELD-XI score, as in previous studies, we found 11 as the cutoff value. The SOFA and APACHE scores of the group with high MELD-XI scores were also significantly higher. The MELD-XI cutoff value was manifested by low oxygenation, worse laboratory findings, higher comorbidities, and higher mortality. The MELD-XI score was independent of age and gender. The MELD-XI score was found to be a valuable score independent of demographic characteristics associated with organ dysfunction.[22] In this large retrospective study involving 4,381 patients, unlike our study, all ICU patients were included, not just those with respiratory failure. Additionally, in this larger cohort, a MELD-XI score >12 was associated with more severe hypoxemic respiratory insufficiency.[22]

Patients with a high MELD-XI score received high-flow oxygen therapy instead of conventional oxygen therapy in the ICU because their oxygenation was more impaired. In addition, patients who started invasive mechanical ventilation treatment when they came to the ICU were more common in the high MELD-XI group. The group with higher MELD-XI scores remained in the ICU. The reason for this was explained by the fact that disease and the respiratory failure was more severe, and the need for invasive mechanical ventilation was much more.

In a study of patients with PTE, arterial saturation (SaO_2 <90%) was one of the components of simplified pulmonary embolism severity index (sPESI). In this study, the sPESI score was found to be significantly associated with MELD-XI. Additionally, MELD-XI >10.2 and sPESI ≥1.5 were associated with significantly worse in-hospital survival.[23] Those with high MELD-XI scores in the whole group and in subgroups with different etiologies have a higher mortality risk. This result led us to believe that mortality is higher in cases with multiorgan dysfunction independent of respiratory failure etiology. The risk was higher in PTE, pneumonia, and ACPE patients. The reason for this may be cardiovascular derangement, resulting in low output, congestive state, tissue oxygenization deterioration, and tissue hypoxia in these three diseases.[23]

The PaO_2/FiO_2 ratio, which indicated impaired oxygenation, increased lactate level suggestive of sepsis, increased creatinine level reflecting renal dysfunction, urea level, and bilirubin increase with impaired liver function test were independent risk factors for in ICU mortality with MELD-XI.[22]

The use of MELD-XI in the ICU could provide a more accurate and individualized approach to assessing patient prognosis and help clinicians prioritize interventions and tailor treatment

strategies. The early identification of high-risk patients has the potential to improve resource allocation and ultimately enhance patient outcomes.

The strength of this study lies in its prospective design and emphasis on highlighting the prognostic significance of MELD-XI for the first time in respiratory failure cases.

A limitation of this study was the inability to perform advanced comparisons due to the scarcity of patients with different etiologies of respiratory failure. The single-center study, the results may not be sufficiently generalizable. However, in future multicenter studies with a larger number of cases, the inclusion of diverse etiological disease groups will likely enhance the statistical significance of the results.

CONCLUSION

The MELD-XI score, which can be applied at the bedside and has advantages such as simplicity, speed, and affordability, can be used to determine the prognosis and mortality risk of patients with acute respiratory failure in the ICU. The MELD-XI score is just as efficient as more sophisticated testing. Future researchcould involve multi-center trials with varied patient populations to confirm the prognostic value of MELD-XI across different ICU environments.

Ethics

Ethics Committee Approval: This study was approved by Ankara University Faculty of Medicine, Clinical Research Ethics Committee (registration number: İ2-80-20, date: 13.02.2020).

Informed Consent: Verbal and written informed consent was obtained from the participants.

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Footnotes

Authorship Contributions

Surgical and Medical Practices - Concept - Design - Data Collection or Processing - Analysis or Interpretation - Literature Search - Writing: All authors contributed equally to all contribution sections.

Conflict of Interest: No conflict of interest was declared by the authors.

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Original Article

Scoring Pulmonary Fibrosis Following COVID-19 Pneumonia with Quantitative HRCT: Relationship with Clinical Parameters, Mean Platelet Volume and Lymphocyte/Monocyte Ratio

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Abstract

OBJECTIVE: Our study aims to quantify post-Coronavirus disease-2019 (COVID-19) pneumonia-related pulmonary fibrosis using high resolution computed tomography (HRCT) scoring and assess its correlation with clinical parameters, lymphocytes, mean platelet volume (MPV), and lymphocyte/monocyte ratio (LMR). Early detection and understanding of fibrosis progression in patient subsets are essential for enhancing post-COVID-19 patient outcomes.

MATERIAL AND METHODS: This retrospective, single-center study aims to quantify post-COVID-19 pneumonia pulmonary fibrosis using HRCT scoring and explore its associations with clinical parameters, lymphocytes, MPV, and LMR. From March 1, 2020, to December 31, 2021, HRCT reports of patients diagnosed with COVID-19 within 14 days of symptom onset were reviewed. Those with COVID-19 pneumonia were identified, and subsequent HRCTs performed 2 months or later post-infection were analyzed for fibrosis. Data on demographics, hospitalization details, and laboratory findings were collected. Fibrosis scores were determined using quantitative HRCT.

RESULTS: A total of 133 patients (60.2% male, mean age 57.3) were included. Of these patients, 50.4% were hospitalized. Quantitative HRCT analysis indicated average fibrosis of 2.7% (range: 0.9-28.7%). Lower lymphocyte counts correlated significantly with increased fibrosis ($P = 0.002$). No significant correlations were found between fibrosis development and hospitalization duration, age, or gender.

CONCLUSION: This study underscores the importance of monitoring lymphocyte counts in COVID-19 patients for early detection of pulmonary fibrosis. The findings suggest a need for screening and prompt diagnosis of fibrosis post-COVID-19, particularly in patients with lymphopenia. Further research using quantitative HRCT could enhance understanding and management of progressive interstitial lung diseases, especially in the context of future pandemics.

KEYWORDS: COVID-19, pulmonary fibrosis, quantitative HRCT, inflammation

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INTRODUCTION

There is currently insufficient evidence regarding the development of progressive irreversible pulmonary fibrosis characterized by widespread fibrotic involvement on high resolution computed tomography (HRCT), decreased quality of life, and increased mortality in patients who have recovered from Coronavirus disease-2019 (COVID-19) pneumonia in the long term. Early detection of pulmonary fibrosis, determining which patient groups are experiencing progression, and early initiation of treatment are crucial for improving the quality of life of patients in the post-COVID-19 period.

The most common initial tomographic findings are bilateral subpleural ground-glass opacities and consolidation in the lower zones when the radiological course of the disease is followed in the acute phase of COVID-19 pneumonia.[1] It

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often takes time for the tomographic images to improve in most patients. Ground-glass opacities may develop into consolidations approximately 4-14 days after the onset of symptoms, and after two weeks, the findings gradually disappear.[1] However, in some patients, even in early tomographies, fibrotic streaks and bronchiectasis may be examined.[2] There is little research on the progression of fibrosis in these patients during subsequent follow-ups, as well as on the clinical manifestations it causes and the treatments that should be applied. Additionally, there are limited studies on the use of quantitative HRCT, an objective scoring system, in the evaluation of fibrosis in progressive fibrotic interstitial lung diseases, when radiologists compare HRCT images for reporting.

It has been demonstrated in several studies that idiopathic pulmonary fibrosis (IPF) is associated with thrombotic events. In one study, patients with IPF showed higher mean platelet volume (MPV) values and lower platelet counts.[3] Another study in patients with pulmonary fibrosis investigated the role of monocyte count and lymphocyte/monocyte ratio (LMR). A negative correlation was found between monocyte count and forced vital capacity, and in newly diagnosed IPF patients, an LMR <4.18 was significantly associated with shorter survival as an independent risk factor.[4] In another study, a high monocyte count in IPF patients was associated with increased IPF progression, hospitalization, and mortality risks.[5] However, the relationship of these parameters with fibrosis developing after COVID-19 has not been investigated.

MPV has also been associated with several diseases, excluding pulmonary. MPV has been suggested as an inflammatory marker in various inflammatory diseases, includingrheumatoidarthritis,[6] obesity,[7] type 2 diabetes mellitus,[8] infections.[9]

MPV is related to inflammation in the intensive care unit (ICU) population; in one study, elevated MPV levels in ICU patients should alert clinicians to worse outcomes.[10] If we consider gastrointestinal diseases, red cell distribution width (RDW) and MPV values were found to be significantly higher in patients with hepatosteatosis.[11] RDW and MPV have been shown to be increased in subjects with irritable bowel syndrome, a condition that is associated with low-grade inflammation compared to the healthy population.[12] On the other hand, a MPV/lymphocyte ratio (MPVLR) level greater than 3.41% has 71% sensitivity and 51% specificity in predicting frailty in diabetic patients. MPVLR may be useful in predicting frailty in the type 2 diabetes population, study suggests.[13]

The aim of our study is to score pulmonary fibrosis developing after COVID-19 pneumonia using quantitative HRCT and to examine its relationship with clinical parameters, MPV, and LMR.

Main Points

- Our study examines the effects of the Coronavirus disease-2019 (COVID-19) pandemic.
- It is one of the rare studies that conducts a quantitative evaluation of post-COVID-19 fibrosis.
- In our study, the importance of the use of quantitative high resolution computed tomography were mentioned.

MATERIAL AND METHODS

This was a retrospective, single-center study. As our study was retrospective, no informed consent was obtained from patients. HRCT images taken within the first 14 days of patients diagnosed with COVID-19 in the hospital system were examined.Those with COVID-19 pneumonia (with or without ground-glass opacities, consolidations with or without air bronchograms) were identified, and among them, those who had HRCTs taken two months or later after COVID-19 infection were noted. Additionally, findings of fibrosis (honeycombing, traction bronchiectasis, interlobular septal thickening, reticular pattern) were recorded from follow-up HRCTs.[14]

The reason for setting the lower limit at two months is that in an immunocompetent individual, if there is less than 50% radiological improvement at two weeks despite effective treatment of pneumonia, or if there is no complete resolution at 4 weeks, delayed or unresolved pneumonia is considered.[15] Therefore, individuals with persistent radiological findings associated with COVID-19 on HRCT for at least two months were included in the study. Most patients had HRCTs available at 6 or 8 months, and those eligible for were included in the study.

Determining a clear fibrosis value in IPF is difficult, similar to the challenges faced with emphysema.[16] Various CT density thresholds have been proposed for evaluating the spectrum of interstitial lung diseases, including >-700 Hounsfield units (HU) and a range between -750 HU and -300 HU for specific detection of ground-glass opacities.[17,18] Based on studies, an optimal range for post-COVID-19 fibrosis has been suggested to be between -250 and -500 HU.[16,19]

In the follow-up of these patients, fibrosis scores were determined using quantitative HRCT. Patient age, gender, comorbidities, if any, length of hospital stay, duration of ICU, platelet count, MPV, and LMR were noted. Data analysis was conducted to examine correlations.

Inclusion criteria;

- Over 18 years of age,

- Patients who were diagnosed with COVID-19 and who were diagnosed with COVID-19 pneumonia during the active disease period at Ankara Atatürk Sanatorium Training and Research Hospital Hospital, who were COVID-19 polymerase chain reaction (PCR) positive, who were found to have COVID-19 pneumonia on HRCT imaging taken within the first 14 days, and who had follow-up HRCTs.

Patients excluded from the study;

- Those with diagnosed interstitial lung disease with fibrosis,

- Those with interstitial lung disease not associated with COVID-19 pneumonia,

- COVID-19 PCR (-) are those considered to have radiological COVID-19 disease.

Ethical approval of the study was obtained from the Ankara Atatürk Sanatorium Training and Research Hospital Clinical

Research Ethics Committee (project number: E-53610172-799, date: 09.08.2022).

Statistical Analysis

The data were evaluated using the IBM Statistical Package for the Social Sciences statistics 25.0. Descriptive statistics were provided as unit count (n), percentage (%), mean±standard deviation, and median (Q1-Q3) values. Pearson's chi-square and Fisher's exact test were used to evaluate categorical variables. A *P* value <0.05 was considered statistically significant. Multiple linear regression analysis was conducted to consider the effect of follow-up lymphocyte percentage and confounders.

RESULTS

Tomography data of patients were accessed within the specified dates (Table 1). Due to incomplete data, 65 patients were excluded from the study. Data analysis was conducted on a total of 133 patients (Figure 1). Of these, 60.2% (n = 80) were male, and 39.8% (n = 53) were female. Approximately half of the patients were hospitalized (50.4%, n = 67). The mean age of the patients was 57.3. The average length of hospital stay was 0 (0-65) days for ward admission and 0 (0-45) days for ICU admission. The initial lymphocyte count was 1.66 µL (0.2-4.26), platelet count was 252 µL (37-682), monocyte count was 6.75 µL ±2.62, MPV was 9.4 fL ±0.98, and LMR was 3.51 (0.2-11.67); while the follow-up lymphocyte count was 4.73 (0.5-19.83), follow-up platelet count was 274.03 µL ±80.66, follow-up monocyte count was 6.3 µL (0.8-12.3), MPV was 9.3 fL (7.4-12.3), and LMR was 4.73 (0.5-19.83). Quantitative HRCT analysis revealed an average of 2.7% (minimum: 0.9, maximum: 28.7) fibrosis development (Table 1). No significant relationship was found among hospitalization duration, age, gender, and fibrosis development (Table 2). Additionally, no significant relationship was found between MPV and the development of fibrosis.

When a more detailed examination was conducted on the relationship between laboratory parameters and the development of fibrosis, it was found that patients with lower lymphocyte counts were more likely to develop pulmonary fibrosis. The statistical significance of this finding was quite strong ($P = 0.002$), suggesting a robust association between low lymphocyte levels and increased fibrosis (Table 2). However, no other laboratory parameter showed a statistically significant

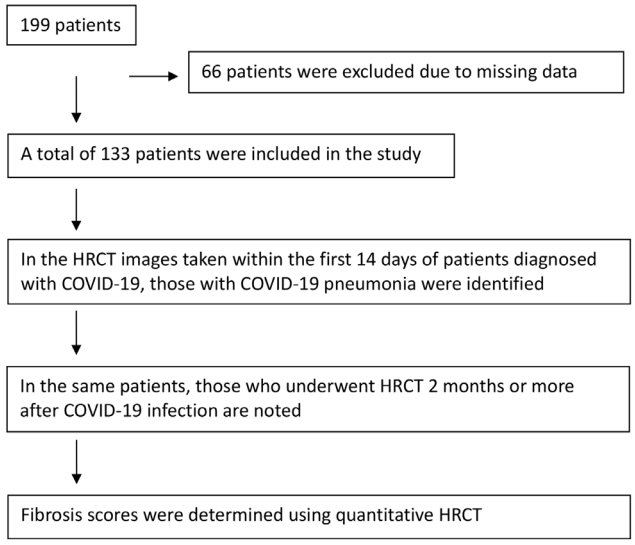

Figure 1. Selection of the study population

COVID-19: Coronavirus disease-2019, HRCT: high resolution computed tomography

Table 1. Laboratory parameters and fibrosis percentages

Variables Clinical/laboratory/radiological features	Descriptive statistics: n (%)*	
Gender, n = 133 (100%)	Male, n = 80 (60.2%) Female, n = 53 (39.8%)	
Quantitative BT score -250 HU	99 (92-99.8)	
Quantitative BT score -500 HU	96.3 (63.3-98.6)	
Fibrosis %	2.7 (0.9-28.7)	
Hospitalization duration (day)	0 (0-65)	
	Initial values	**Follow-up values**
Lymphocyte (10^3/µL)	1.66 (0.2-4.26)	2.49±0.99
Lymphocyte %	23.81±9.38	29.95±11.47
Monocytes (10^3/µL)	0.48 (0.08-7)	0.53 (0.06-2.12)
Monocytes %	6.75±2.62	6.3 (0.8-12.3)
Platelet (10^3/µL)	252 (37-682)	274.03±80.66
Mean platelet volume (fL)	9.4±0.98	9.3 (7.4-12.3)
Lymphocyte monocytes ratio	3.51 (0.2-11.67)	4.73 (0.5-17.63)
Lymphocyte % monocytes % ratio	3.49 (0.27-23)	4.73 (0.5-19.83)

*Mean±standard deviation is given for normally distributed variables, median (minimum-maximum) is given for non-normally distributed variables.
HU: hounsfield unit, BT: bleeding time

Table 2. Correlation analysis between fibrosis development and the study parameters

		Fibrosis %	Hospitalization duration	Onset lymphocyte	Onset lymphocyte %	Onset monocytes	Onset monocytes %	Onset platelet	Onset MPV	ICU duration	Follow-up lymphocyte	Follow-up lymphocyte %	Follow-up monocytes	Follow-up monocytes %	Follow-up platelet	Follow-up MPV
Fibrosis %	**Correlation coefficient**	1.00	0.015	0.086	-0.063	-0.006	-0.162	0.051	-0.081	0.132	-0.165	**-0.264**	0.017	-0.036	-0.065	-0.069
	P		0.084	0.324	0.469	0.941	0.063	0.0557	0.352	0.129	0.058	**0.002**	0.843	0.677	0.459	0.428
	n	133	133	133	133	133	133	133	133	133	133	**133**	133	133	133	133

ICU: intensive care unit, MPV: mean platelet volume

relationship with fibrosis development. This means that aside from lymphocyte counts, other measured values in the lab tests did not significantly affect the likelihood of the patients studied developing fibrosis. Furthermore, when considering the percentage of fibrosis development, no significant relationships were found with gender ($P = 0.207$) or hospitalization duration ($P = 0.151$) (Table 2). This suggests that neither the patient's gender nor the length of their hospital stay significantly influenced the extent of fibrosis development.

Box-Cox transformation was applied to the dependent variable, fibrosis %, to satisfy linear regression assumptions such as normality of residuals. Age, gender, and hospitalization duration variables, in addition to the follow-up lymphocyte %, were added to the model as confounders. The results of the model are provided in Table 3. According to the table, follow-up lymphocyte percentage still significantly affects fibrosis percentage after controlling for confounders ($P = 0.004$).

DISCUSSION

The effects of the COVID-19 pandemic continue worldwide, although the pandemic appears to be over, and we have not yet discovered other unknown side effects and long-term systemic effects. Pulmonary effects significantly affect human life and quality of life, and there is a need for new studies on diseases with pathogenesis and treatments that are not yet fully understood, such as fibrosisIn our study, we gathered valuable insights into the development of pulmonary fibrosis, a condition that significantly impacts long-term survival and quality of life. We observed that patients with a decrease in lymphocyte count, as measured by routine blood tests, experienced a notably higher rate of fibrosis progression. This finding has been instrumental in allowing us to monitor these patients more closely. When found in low numbers, lymphocytes, vital components of the immune system, may signal a weakened immune response, which could, in turn, accelerate the development of fibrosis. Our study highlights a clear link between low lymphocyte counts and increased fibrosis progression, underscoring the critical role of lymphocytes in understanding and managing this condition. These findings underscore the need for further research to understand the underlying mechanisms and to identify other potential factors that may influence fibrosis progression.

Humphries et al.[20] conducted a study examining the relationship between quantitative HRCT scores, pulmonary function tests, and the six-minute walk test in 141 patients diagnosed with IPF. It was shown that the measurement of lung fibrosis degree in quantitative HRCT is reliable and sensitive. A 3.4% increase in fibrosis score leads to a clinically significant decrease in patient performance. In our study, an average fibrosis development of 2.7% was detected, and without a pandemic period, a similar correlation could have been observed if these patients had undergone serial pulmonary function tests.

In a study on the quantitative HRCT detection of honeycombing areas in IPF, the honeycombing area measured by computer-aided methods showed a correlation with that estimated by expert radiologists and with parameters of pulmonary function tests. This study demonstrated that quantitative HRCT analysis

Table 3. Evaluation of the effect of follow-up lymphocyte percentage and confounders using multiple linear regression analysis

	β	SE (β)	Beta	t	*P* value	95% confidence interval for β	
						Lower bound	Upper bound
(Constant)	-0.499	0.467		-1.067	0.288	-1.423	0.426
Age	0.019	0.006	0.244	3.015	0.003	0.006	0.031
Gender	-0.163	0.162	-0.080	-1.004	0.317	-0.484	0.158
Hospitalization duration	0.025	0.009	0.226	2.813	0.006	0.007	0.042
Follow-up lymphocyte %	-0.021	0.007	-0.235	-2.898	0.004	-0.035	-0.007

F=7.622, $P < 0.001$, adjusted R^2: 0.17.
SE: standard error

of honeycombing areas may be useful and reliable in patients with IPF.[21]

In another study evaluating mortality in IPF patients using quantitative HRCT, correlation with pulmonary function tests was examined, and it was emphasized that quantitative scoring of HRCT can provide accurate predictions for survival.[22] Mortality data were not examined in our study because attributing the cause of death in patients with pulmonary fibrosis was not possible, as long-term follow-up was not performed.

In a study investigating the relationship between platelet count and MPV with IPF, it was found that MPV was higher in IPF patients and associated with both high and low platelet counts. This finding suggests that MPV could be used as an initial biomarker in IPF patients, but more comprehensive studies are needed.[3] However, in our study, no relationship was found between MPV and platelet count, and fibrosis developing after COVID-19.

In a study by Yu et al.[23] aimed at predicting the development of fibrosis following COVID-19 pneumonia, it was shown that fibrosis was more likely to develop in patients with high inflammatory markers (interleukin-6) and severe clinical conditions. Predictors of pulmonary fibrosis, such as interstitial thickening, irregular interfaces, coarse reticular pattern, and parenchymal bands, were identified as emerging during the disease process. It was indicated that irregular interfaces and parenchymal bands could be used to predict the early onset of pulmonary fibrosis.

In a recent investigation into the relationship between various laboratory parameters and the development of fibrosis, researchers focused specifically on lymphocyte counts. Fibrosis, which is the excessive accumulation of extracellular matrix components leading to tissue scarring, can significantly impact organ function and is associated with various chronic diseases.[24] For example, increased monocyte-to-lymphocyte ratio (MLR) levels are reliable markers of disease activity in ulcerative colitis and have been linked to active inflammation in inflammatory bowel disease.[25]

Numerous studies have demonstrated that lung cancer can develop from pulmonary fibrosis.[26-28] Also, a multicenter retrospective study of 345 patients with IPF found that those receiving antifibrotic therapy had a significantly lower incidence and prevalence of lung cancer compared to those not receiving treatment.[29] Additionally, lung cancer-related mortality was significantly lower in patients on antifibrotic therapy.[29] These findings suggest that antifibrotic therapy may be associated with a reduced risk of lung cancer development in IPF patients, potentially contributing to improved survival.

In a study of 113 patients with small cell lung cancer, survival was significantly longer in patients with MLR <0.367 than in those with MLR ≥0.367.[30] The development of fibrosis can also lead to malignancy in extrapulmonary organs, and studies have explored the role of MLR in predicting this. In particular, in gastrointestinal cancers, a high MLR predicts survival in gastric cancer and is associated with tumour response to neoadjuvant chemoradiotherapy in rectal cancer.[31] In hepatocellular carcinoma, high MLR is associated with poor outcomes and shorter progression intervals.[32] In gastrointestinal cancers, the majority of studies support that a high MLR indicates a poor prognosis, although there are few studies to the contrary.[33]

The study found that patients with lower lymphocyte counts tended to exhibit a greater propensity for fibrosis development. Lymphocytes are a crucial component of the immune system, playing vital roles in immune response and inflammation regulation. Their reduction may indicate an impaired immune response, which can facilitate the fibrotic process.

This discovery may have important clinical implications, as it highlights the potential role of lymphocyte levels as a biomarker for fibrosis risk. Understanding this relationship could lead to improved monitoring and therapeutic strategies for patients at risk of fibrotic diseases, allowing for earlier intervention and potentially better outcomes. Further research is needed to explore the underlying mechanisms that connect lymphocyte counts with fibrosis development, which may involve complex interactions between the immune system and fibrogenic pathways.

One of the limitations of the study was the inclusion of a small number of patients and its single-center design. Also, the patient group included in the study was not homogeneous; the number of male and female patients was not equally distributed, and baseline comorbidities were not recorded. The only people excluded were those with a previous diagnosis of interstitial lung disease, which was an important part of our study. However, when considering the strengths of the study, its importance lies in being the first study in the literature on quantitative HRCT and post-COVID-19 pulmonary fibrosis.

CONCLUSION

In conclusion, the assessment of IPF using HRCT requires considerable expertise, and there may be differences in interpretation even between experienced radiologists. Screening and early detection of pulmonary fibrosis will allow early initiation of treatment, and slowing fibrosis can improve patients' quality of life. Considering the possibility of new outbreaks unrelated to COVID-19, the importance of the widespread use of quantitative HRCT, paired with an objective scoring system for the assessment of fibrosis in progressive fibrotic interstitial lung disease, is emphasised. We believe that our study is valuable in this regard and provides important data for future research.

Ethics

Ethics Committee Approval: Ethical approval of the study was obtained from Ankara Atatürk Sanatorium Training and Research Hospital Clinical Research Ethics Committee (project number: E-53610172-799, date: 09.08.2022).

Informed Consent: Written informed consent was obtained from all patients during the time they were hospitalized for their clinical data to be registered in the database and used anonymously for scientific purposes.

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Footnotes

Authorship Contributions

Concept: C.D., P.E., G.Ş.K., H.E., Design: C.D., P.E., G.Ş.K., H.E., Data Collection or Processing: C.D., G.Ş.K., H.E., Analysis or Interpretation: C.D., P.E., G.Ş.K., H.E., Literature Search: C.D., P.E., G.Ş.K., H.E., Writing: C.D., P.E., G.Ş.K, H.E.

Conflict of Interest: The authors have no conflict of interest to declare.

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Original Article

Assessment of PAP Device Usage and COVID-19 Related Anxiety in Patients with OSAS During COVID-19 Pandemics

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Abstract

OBJECTIVE: In this study, we aimed to determine the positive airway pressure (PAP) device usage and pandemic-related anxiety in obstructive sleep apnea syndrome (OSAS) patients during the pandemic.

MATERIAL AND METHODS: Five hundred twenty-seven OSAS patients were recruited into the study. A questionnaire consisting of 7 questions was filled to find out their Coronavirus disease-2019 (COVID-19)-related anxiety levels and PAP device usage.

RESULTS: The mean age of the patients was 53.3 years (±11.9). One hundred forty-one 141 (27%) of the participants were female and 382 (73%) were male. Two hundred sixteen (41%) patients reported using the PAP device regularly [PAP (+) group); 307 (59%) patients reported not using it at all or using it irregularly (PAP (-) group]. Forty-nine (23%) PAP (+) patients and 91 (29%) PAP (-) patients had COVID-19. The use of a PAP device was not significantly associated with an increased risk of COVID-19 infection ($P = 0.077$). The most common symptom was myalgia without a between-group difference, ($P = 0.967$). There was no significant difference between the PAP (+) and PAP (-) groups in the hospitalization rates for COVID-19 ($P = 0.252$). The presence of apnea was not considered as a cause of a higher level of COVID-19-related anxiety in patients with the PAP (+) group compared to the PAP (-) group ($P = 0.095$).

CONCLUSION: There was no evidence that the use of PAP devices in OSAS patients influenced the risk of getting COVID-19 and the clinical course of the disease. PAP device usage did not affect the level of anxiety associated with the pandemic in patients.

KEYWORDS: Obstructive sleep apnea syndrome, COVID-19, positive airway pressure, sleep disorder, anxiety

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INTRODUCTION

Coronavirus disease-2019 (COVID-19) is a disease caused by Severe acute respiratory syndrome-Coronavirus-2 that presents with shortness of breath, headache, fever, loss of smell and taste, cough, myalgia, and sore throat.[1] The initial instances of COVID-19-related pneumonia emerged in Türkiye during March 2020. Obstructive sleep apnea syndrome (OSAS) is characterized by disrupted breathing patterns and cessation of breathing during sleep, particularly prevalent in obese individuals; it is clinically identified through a polysomnography-detected apnea-hypopnea index of ≥5 and has an average prevalence of 22% among men and 17% among women.[2,3] Elderly individuals who are diagnosed with hypertension, diabetes, cardiac conditions, and obesity encounter an increased susceptibility to mortality upon contracting COVID-19; these are also recognized as established risk factors for OSAS.[4,5] Amidst the global COVID-19 pandemic, patients' non-emergency access to medical facilities, including hospitals, was notably curtailed. This trend encompassed the closure of sleep laboratories and outpatient clinics specializing in sleep disorders within Türkiye as well as on a global scale, as part of comprehensive quarantine directives.

Several risk factors have been identified as potentially contributing to increased morbidity from COVID-19 in adults, including advanced age, male gender, and pre-existing comorbidities.[6] A potential association between the presence of OSAS and heightened susceptibility to COVID-19 infection is suspected and it is suggested that individuals with

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OSAS who contract COVID-19 may encounter exacerbated respiratory complications, potentially leading to increased mortality rates and the management of these patients poses distinctive challenges amid the pandemic and finally, the impact of pandemic conditions on the utilization of positive airway pressure (PAP) devices, recognized as the gold standard therapeutic modality for OSAS, remains uncertain.[7-9]

This study aims (1) to elucidate the frequency and clinical progression of COVID-19 in OSAS patients during the pandemic period, (2) to discern whether the adoption of PAP therapy has undergone alterations since the pandemic's start and (3) to ascertain the potential heightened vulnerability of individuals with sleep apnea to COVID-19 contraction, as well as (4) to explore their apprehensions regarding potential exacerbation of complications upon COVID-19 infection.

MATERIAL AND METHODS

Study Design

The study was conducted between 13 December 2020 and 29 May 2021. Patients diagnosed with OSAS according to the International Classification of Sleep Disorders-3 diagnostic criteria and followed up in the sleep outpatient clinic at the Neurology Department of the Marmara University Faculty of Medicine were identified. They were telephoned and informed about the study. Five hundred fifty-eight patients who underwent titration procedures at the sleep laboratory of Marmara University Faculty of Medicine, were called. Five hundred twenty-three patients who gave verbal consent to participate in this study were included, and the remaining 35 patients could not be reached. Using a telephone-based method, patients were contacted and administered a 12-question survey (Table 1). The survey focused on PAP device usage during the pandemic, concerns about the potential worsening of COVID-19 due to OSAS (Question 9), and levels of anxiety (Question 11) (Table 1). Drawing inspiration from the research conducted by Thorpy et al.[10] in the context of patients afflicted with OSAS, this inquiry encompassed the assessment of pandemic-related anxiety and the utilization status of PAP devices. The study included all individuals aged 18 or above, diagnosed with OSAS, who provided informed consent for their participation. Exclusion criteria encompassed patients unable to respond to the complete questionnaire. Patients who reported consistent use of the PAP device were categorized into the PAP (+) group, while those who reported no use or irregular use were placed in the PAP (-) group.

Main Points

- Obstructive sleep apnea syndrome (OSAS) patients were largely non-compliant with the treatment in terms of device use, regardless of the pandemic period.
- The use of positive airway pressure (PAP) devices in OSAS patients had no effect on the risk of getting Coronavirus disease-2019 and the clinical course of the disease.
- PAP device usage did not affect the level of anxiety associated with the pandemic in patients.

This study was approved on 03.12.2021 by Marmara University Faculty of Medicine's Clinical Research Ethics Committee with the protocol code of 03.12.2021.1399.

Statistical Analysis

All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) 26.0 for Windows (SPSS Inc., Chicago, IL, USA). The normality assumptions for all variables were tested using the Shapiro-Wilk test. Continuous variables were reported as means with standard deviations, or medians with interquartile ranges, and categorical variables were reported as percentages. Categorical variables were compared with Pearson's chi-square test or, when appropriate, Fisher's exact test. The Mann-Whitney U test was used when evaluating non-normally distributed (non-parametric) variables between two groups. The Spearman's correlation test was used to analyze the relationships between measurement datasets. All statistical tests were two-sided, and a P value <0.05 was considered significant.

RESULTS

Patients diagnosed with OSAS based on the International Classification of Sleep Disorders-3 diagnostic criteria and followed in the sleep outpatient clinic of the neurology department at Marmara University Faculty of Medicine, were identified. A total of 523 patients were included in the study, comprising 141 females (27%) and 382 males (73%), with a mean age of 53.3 years (standard deviation: 11.9, range: 23-90). Among these, 216 patients (41%) reported regular use of the PAP device, while 307 (59%) either did not use the device or used it irregularly.

Among regular PAP users, 49 patients (23%) contracted COVID-19 (Table 2), with myalgia being the most common symptom (76%, n = 37). Other symptoms frequently reported in this subgroup included fatigue (71%, n = 35), headache (51%, n = 25), fever (47%, n = 23), loss of smell (43%, n = 21), loss of taste (41%, n = 20), cough (39%, n = 19), and sore throat (8%, n = 4). In contrast, among the 307 non-users or irregular users of PAP devices, 91 patients (29%) were diagnosed with COVID-19 (P = 0.08) (Table 2). Symptom frequencies between COVID-19-positive PAP users and non-users were similar, with no statistically significant differences observed.

Hospitalization rates among COVID-19-positive patients also showed no significant differences based on PAP device usage, with 25 PAP users (12%) and 46 non-users (15%) requiring hospitalization (P = 0.25) (Table 2).

In the PAP user group, 31% (n = 67) were smokers, compared to 30% (n = 95) in the non-user group. Comorbidities such as diabetes (37%, n = 79), hypertension (44%, n = 96), and cardiovascular disease (8%, n = 18) were similarly distributed between the two groups, with no significant differences.

The analysis showed that concerns about COVID-19 exacerbation due to OSAS (Question 9) and levels of anxiety (Question 11) were comparable between PAP users and non-users who contracted COVID-19, with no statistically significant differences in either concern (P = 0.1 for both) (Table 2).

Of the COVID-19-positive PAP users, 45% (n = 22) discontinued PAP device usage during their illness (Question 7), while 19% (n = 27) of the 140 COVID-19-positive patients continued using the device throughout their illness (Question 12).

DISCUSSION

Obstructive sleep apnea is reported to have an average prevalence as high as 22% among men and 17% among women.[2,3] Patients who do not receive appropriate treatment for OSAS, such as PAP, face a greater risk for serious diseases such as hypertension, increased insulin resistance, ischemic cerebrovascular events, pulmonary hypertension, and metabolic syndrome.[11] With the emergence of the COVID-19 pandemic, the admission of non-urgent cases to medical facilities underwent stringent limitations. Consequently, the operations of sleep laboratories and sleep outpatient clinics

Table 1. COVID-19 and sleep apnea survey

1. Have you had COVID-19 disease?	Yes	No
2. What symptoms did you have?		
Headache		
Cough		
Sputum		
Fatigue		
Loss of smell		
Loss of taste		
Sore throat		
Muscle pain		
Fever		
3. Were you hospitalized?	Yes	No
4. Do you have any additional disease?		
Cardiovascular disease		
Obesity		
Hypertension		
Cardiac arrhythmia		
Kidney failure		
Diabetes mellitus	Yes	No
Asthma		
Chronic obstructive pulmonary disease		
Coronary artery disease		
Congenital heart disease		
Liver failure		
5. Do you smoke?	Yes	No
6. Are you using a PAP device?	Yes	No
7. Have you stopped using PAP due to COVID-19?	Yes	No
8. Do you use it more often after the COVID-19 pandemic?	Yes	No
9. Are you more worried about COVID-19 because you have apnea?	Yes	No
10. Do you think the main risk of contracting COVID-19 is apnea?	Yes	No
11. If you get COVID-19, do you think you will have a worse disease course because you have apnea?	Yes	No
12. Did you feel the need to use a PAP device when you got sick with COVID-19?	Yes	No

COVID-19: Coronavirus disease-2019, PAP: positive airway pressure, OSAS: obstructive sleep apnea syndrome

Table 2. COVID-19 infection incidence and related data according to PAP device use

	PAP (+) (n, %)	**PAP (-) (n, %)**	***P***
COVID-19 (+)	49 (23%)	91 (29%)	0.08
Hospitalization	25 (12%)	46 (15%)	0.25
Concerns about COVID-19 exacerbation (Question 9)	134 (62%)	212 (70%)	0.1
Level of anxiety (Question 11)	132 (61%)	209 (69%)	0.1

n: number, COVID-19: Coronavirus disease-2019, PAP: positive airway pressure, PAP (+): using the PAP device regularly, PAP (-): using the PAP device irregularly

were similarly curtailed, stemming from a combination of quarantine directives and the reassignment of clinical staff to COVID-19-related patient care. Given the restricted access of OSAS patients to medical services and the existing studies indicating an elevated risk of mortality and morbidity for OSAS patients in the context of COVID-19 infection, an imperative emerged to assess patients' adherence to PAP therapy.[7] Guided by the research conducted by Thorpy et al.,[10] we undertook this study.

While some studies advise OSAS patients to discontinue PAP device usage at home during the COVID-19 pandemic, other studies suggest the continuation of PAP treatment.[7,13] In a study investigating the changes of behavior in PAP device users during the COVID-19 pandemic, it was indicated that an increase in the viral load spreading to the environment with the use of PAP devices in patients infected with COVID-19 and the higher risk of transmission to people sharing the same environment are believed to increase.[14] In our study, it was observed that 45% of OSAS patients who were regular users of PAP and had a COVID-19 infection stopped using the device once infected. This behavior be attributed to the patients' perceptions of an augmented risk of virus transmission, heightened discomfort, issues with compliance, and amplified side effects, which may have been more clearly by the patients during infection. Additionally, patients may have faced increased challenges in addressing these concerns during the pandemic, because of restricted access or inability to access healthcare professionals or institutions.

The examination into the impact of the COVID-19 pandemic on PAP device usage in New York city revealed that 21% of participants increased their device usage, while 11% discontinued usage.[10] Additionally, an assertion was made suggesting that extended utilization of the PAP device is clinically safe.[10] 59% of the participants in our study reported that they used a PAP device irregularly or not at all. Regardless of the pandemic period, patients were found to be non-compliant with treatment, in terms of device use. Despite OSAS patients being categorized within the high-risk group due to comorbidities such as hypertension, obesity, and diabetes mellitus in relation to COVID-19 infection, their adherence to treatment was observed to be low. Additionally, there was a notable level of anxiety.

Previous investigations indicated that the prevalence of OSAS among COVID-19 cases requiring intensive care unit monitoring ranges from 8% to 28%, with OSAS potentially acting as a facilitator for COVID-19 infection, and linked to unfavorable outcomes in infected individuals.[15] Moreover, sleep deprivation has been proposed to contribute to the intensification of the pulmonary inflammatory process in COVID-19.[16] However, our study yielded results indicating no significant disparities in terms of disease contraction rates, symptoms, or hospitalization frequencies when comparing patients who used the PAP device with those who did not when infected with COVID-19. This could be attributed to the methodology involving telephone-based interactions with patients. Notably, data could not be gathered from individuals affected by COVID-19 with severe clinical courses, thus potentially introducing a bias. Moreover, patients' perceptions and recollections of the disease could have introduced variability in the results.

Thorpy et al.[10] reported that their patients were adherent to treatment and concerned about COVID-19-related complications even though they did not think they were subject to increased susceptibility to the infection. A French study showed that 33% of their study population discontinued PAP treatment without medical advice due to fear of increased virus transmission.[14] In our study population, differing from the previously mentioned studies, no notable distinction was found in the perception of susceptibility to severe infection due to OSAS between patients who had COVID-19 and utilized PAP devices and those who did not. This might be because of cultural and educational differences. Furthermore, it was ascertained that PAP device utilization did not influence the level of anxiety experienced during the pandemic in both our study group, and the study group of Thorpy et al.[10]

The main limitations of this study include its patient-centered assessment approach, the potential influence of sociocultural factors on responses to the anxiety scale, and its single-center design. Furthermore, the lack of evaluation of PAP device use and compliance in the pre-COVID-19 period for the same participant groups, as well as the assessment of anxiety levels using only a single question, represents additional constraints.

We investigated the impact of the COVID-19 pandemic and the infection on PAP device user behaviors through telemonitoring, and showed low device usage rates. This emphasizes the importance of creating health management plans and coordinating patient education in terms of possible health crises. Telehealth can be considered an effective way of facilitating patient care and avoiding unnecessary patient visits, especially for people at higher risk of contracting airborne diseases such as COVID-19 due to underlying health conditions or for those facing challenges in accessing physical sleep laboratory and outpatient clinic services due to geographic constraints or health-related limitations.

CONCLUSION

In conclusion, in this study, it was determined that during the COVID-19 pandemic, patients were largely non-compliant with the treatment in terms of device use. Even though OSAS patients were in the risk group for COVID-19, their anxiety levels were not high, and PAP device use did not affect the anxiety level during the pandemic period.

Ethics

Ethics Committee Approval: This study was approved by Ankara University Faculty of Medicine, Clinical Research Ethics Committee (registration number: İ2-80-20, date: 13.02.2020).

Informed Consent: Participants and their relatives were given clear information about the study and asked to read and sign the informed consent.

Footnotes

Authorship Contributions

Concept: G.S., Design: G.S., Data Collection or Processing: H.I., B.A., Analysis or Interpretation: H.I., B.A., E.V., Literature Search: H.I., B.A., E.V., B.B., K.A., Writing: E.V.

Conflict of Interest: No conflict of interest was declared by the authors.

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Original Article

Nationwide Assessment of Pulmonary Function Testing Practices and Safety Compliance During the COVID-19 Pandemic

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Abstract

OBJECTIVE: Coronavirus disease-2019 (COVID-19) presented considerable challenges to health services, particularly for a routine assessment method, the pulmonary function tests (PFTs), which can generate aerosols and require sharing common surfaces. Despite these risks, there is a need to continue testing, especially for vulnerable patient groups.

MATERIAL AND METHODS: An online survey was conducted from June 1 to June 26, 2020, to assess pulmonologists' practices regarding PFTs before and during the pandemic's first peak in Türkiye (March 11-May 20, 2020). The survey included 30 anonymized questions and received ethical committee approval. Statistical analysis was performed using the IBM Statistical Package for the Social Sciences statistical package.

RESULTS: Two hundred and forty-three respondents across 59 cities participated in the study. 93% were pulmonologists. 77.4% of PFT labs have adequate ventilation by having a window enabling room direct air exchange. 27.2% of the PFT labs continued testing during the first peak of the pandemic. 83.3% of the responding centers applied triage before testing. Ongoing tests included spirometry (100%), bronchodilator reversibility testing (62.1%), and carbon-monoxide diffusion testing (16.7%). 49% of the PFT labs conducted fewer than four tests daily, while 21.2% performed more than eight. PFT technicians used personal protective equipment, with 67.7% using eye protection and 75.3 % wearing FFP3 or FFP2 masks.

CONCLUSION: The survey found that pulmonologists have acted quickly and made moderate success in making preparations in PFT labs for the COVID-19 pandemic. Nevertheless, safer practice in PFT units still needs to be implemented.

KEYWORDS: Pulmonary function testing, COVID-19, occupational safety

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INTRODUCTION

The Coronavirus disease-2019 (COVID-19) pandemic has affected global healthcare systems, necessitating rapid adaptations to clinical practices to mitigate transmission risks. The primary transmission routes of Severe acute respiratory syndrome-Coronavirus-2 (SARS-CoV-2), the virus responsible for COVID-19, include respiratory droplets and contact with contaminated surfaces.

Pulmonary function tests (PFTs) are essential non-invasive procedures for assessing respiratory function and diagnosing various pulmonary conditions. However, the execution of PFTs poses unique challenges during the COVID-19 pandemic. The testing process can generate aerosols, potentially facilitating airborne transmission of the virus. Additionally, the PFT environment often involves shared equipment and close interaction between patients and healthcare providers, increasing the risk of contact transmission.[1,2]

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Despite these challenges, the need to continue PFTs remains, particularly for vulnerable populations requiring ongoing respiratory assessment and management. Balancing the continuation of these essential services with the imperative to protect healthcare workers and patients from infection is a significant concern.[3] Implementing stringent infection control measures, such as adequate ventilation, personal protective equipment (PPE), and thorough disinfection protocols, is crucial to minimize transmission risks during PFTs.[4,5]

This study aims to obtain information about the practice patterns of pulmonologists in PFT labs before the pandemic in Türkiye and to evaluate the compliance of pulmonologists in Türkiye with safety practice recommendations for PFTs during the COVID-19 pandemic. The findings can inform the development of clear and comprehensive guidelines by analyzing current practices and identifying potential gaps in adherence to safety protocols. Such guidelines are essential to ensure the continuation of PFT, safeguarding healthcare providers and patients amid ongoing and future public health crises.[6]

MATERIAL AND METHODS

This cross-sectional survey was conducted following approval from the Clinical Research Ethics Board of Başkent University Faculty of Medicine (approval number: KA20/201, date: 01.06.2020). Members of the Turkish Thoracic Society, a nationwide pulmonologist society, who consented to participate, were enrolled between June 1, 2020, and June 26, 2020. Reminders were sent every week.

A 30-item online questionnaire, developed by the authors using Google Docs, was administered to participants. The survey consisted of three sections: (1) demographics of the participants and information about pulmonary function test practices before the pandemic period, (2) PFT practices during the first peak of the COVID-19 pandemic, and (3) organizational plans for PFTs in the post-peak phase. The participants' workplaces were categorized as primary, secondary, and tertiary health-care centers.

The physical characteristics and operational details of the PFT laboratories, including ventilation, staffing, procedural volume, and available equipment, were also surveyed. The study evaluated PFT practices during the first peak of the pandemic (March 11-May 20, 2020), including the type and frequency of procedures, cleaning and disinfection methods, and the use of PPE. Respondents also reported their plans for implementing triage, PPE usage, and disinfection methods in the post-peak phase.

Data collection adhered to ethical principles and the Declaration of Helsinki, with voluntary participation and informed consent obtained before survey initiation.

Statistical Analysis

IBM Statistical Package for the Social Sciences statistics for Windows (21.0. Armonk, NY: IBM Corp.) software was used for statistical analysis. We primarily conducted categorical data analysis, reporting percentages and frequencies for categorical variables.

RESULTS

A total of 280 participants completed the survey. After excluding duplicate cases, 243 respondents' responses from 159 different health centers were evaluated for the final analysis. Of the respondents, 58.4% (142) were female. The majority of the participants were pulmonologists (93.0%), followed by pediatricians (2.0%), allergists (1.6%), thoracic surgeons (0.8%), other specialties (2.1%) and PFT technicians (0.4%). Participants represented seven regions of Türkiye, with at least one respondent from 59 of the 81 cities in Türkiye. The largest number of participants were from İstanbul (n=45), followed by Ankara (n=30), İzmir (n=22), and Bursa (n=11). Most participants worked in tertiary care centers (62.5%), with others from secondary and primary care centers, 33.5% and 1.3%, respectively.

Physical Conditions and PFT Practices Before the Pandemic

Details of the participants' PFT practices are presented in Table 1. Adequate room ventilation by having a window enabling room direct air exchange was reported in 77.4% of the PFT labs, while 22.6% lacked windows. Most PFT labs were relatively small, with 40.3% having a surface area larger than 10 m^2, ~35% measuring between 5-10 m^2, and approximately 15% less than 5 m^2. Of those centers, 153 (63.0) had a separate waiting room.

PFTs were most commonly performed by a trained technician in 50.6%, or trained nurses in 44.9%, and by the physician in 4.5% of the enrolled participants' workplaces. Most labs reported one (41.1%) or two (36.2%) staff members, while 22.6% had three or more. The number of PFTs performed daily varied, with 44.2% performing more than 40 tests daily, 26.7% performing 20-40 tests daily, and 30% performing less than 20 daily tests. Spirometry (100%) and bronchodilator responsiveness testing (92.6%) were the most commonly performed procedures in PFT labs, followed by carbon monoxide diffusion testing (47.3%), the 6-minute walking test (43.6%), and body plethysmography or other advanced lung volume measurements (32.1%). Other procedures included bronchoprovocation testing (36.2%) and cardiopulmonary exercise testing (8.5%).

PFT Practices During the First Peak of the Pandemic

During the first peak of the COVID-19 pandemic, 66 (27.2%) of the PFT labs in the participants' healthcare facilities continued testing, primarily in tertiary-care centers (55.4%), followed by secondary (40%) and primary-care centers (4.6%). Specific practices during this period are presented in Table 2.

The number of PFT tests performed daily was reduced, with most labs performing fewer than eight daily tests. Spirometry remained the most frequently performed procedure, while advanced tests, such as plethysmography and bronchoprovocation, were rarely conducted (Table 2). The types of PFT procedures stratified by the grade of the medical service in those PFT labs during the first phase of the pandemic period are summarized in Figure 1.

The use and type of PPE by the staff performing the procedures are presented in Table 3. Appropriate PPE was worn by 45.4% of the staff, with variations across healthcare levels [primary: 66.7%, secondary: 42.3%, and tertiary: 66.7%; (P = 0.151, data

not shown)]. During the first peak, 67.7% used eye protection by goggles or face shields. 75.3% of the technicians used FFP3 or FFP2 masks, whereas 12.2% used FFP3 or FFP2 masks with gown and gloves (Table 3).

Forty-seven (71.2%) respondents reported a reduction in the total number of staff working in the PFT laboratories. Routine COVID-19 triage, before entering the PFT unit, was implemented in 83.3% of the labs, but cleaning and disinfection practices varied. Only 48.5% of respondents reported having clear information about cleaning methods (Table 2). A total of 17 (25.8%) of the included centers used ultraviolet (UV) lamps in the PFT laboratories (primary, secondary, and tertiary levels,(n = 17, 26.2%); (n = 0, 0%); (n = 4, 15.4%). We observed that tertiary healthcare settings used UV lamps more than secondary healthcare facilities (76.5% vs. 23.5%, p<0.0001). 81.8% of the respondents reported flexibility in scheduling work hours, whereas 66.7% reduced the staff available in their PFT units.

Five labs (7.6%) performed PFTs on COVID-19 patients. The reported indications were the evaluation of dyspnea in the post-COVID phase in three patients, pulmonary fibrosis in one patient, and evaluation of disability in one patient in the post-COVID phase. Of those centers that continued performing PFTs in the pandemic phase, one PFT staff was diagnosed with COVID-19 during the first phase of the pandemic among the total respondents.

Survey Participants' Organizational Plans for Pulmonary Function Tests in the Post-peak Phase

All respondents (100%) planned to resume PFT in the post-peak phase using PPE. Table 3 presents participants' PPE preferences for the post-peak phase, showing a similar distribution with the first peak period. A total of 160 respondents (65.8%) were planning to apply triage screening, and 72 respondents (29.6%) were planning to use UV lamps in their PFT units in the post-peak phase (data not shown).

Main Points

- The pandemic created challenges for pulmonary function tests (PFTs) due to their potential for aerosol generation and increased transmission risks. This study aimed to evaluate the pre-pandemic and pandemic-era PFT practices among pulmonologists in Türkiye, focusing on adherence to safety recommendations and identifying gaps for guideline improvement.
- Two hundred and forty-three responses were analyzed from 59 different cities in Türkiye, with participants predominantly pulmonologists (93%) and most working in tertiary care centers (62.5%).
- PFT labs had varied ventilation, staffing, and space configurations, with only 40.3% meeting recommended size standards and 22.6% lacking adequate ventilation.
- During the pandemic's first peak, only 27.2% of PFT labs continued operations, primarily in tertiary care centers. Spirometry remained the most performed test, while significant reductions were noted in complex procedures like plethysmography and bronchoprovocation testing.
- Infection control measures varied, with only 45.4% of staff using full PPE consistently and 83.3% implementing routine Coronavirus disease-2019 triage.

DISCUSSION

This study provides a detailed analysis of PFT lab practices in Türkiye before and during the COVID-19 pandemic. To the best of our knowledge, this study is the first nationwide assessment; it captures the infrastructure, operational procedures, staff characteristics, and pandemic adaptations of PFT labs across a diverse range of healthcare facilities and geographic regions in Türkiye. The results reveal critical insights into the status of

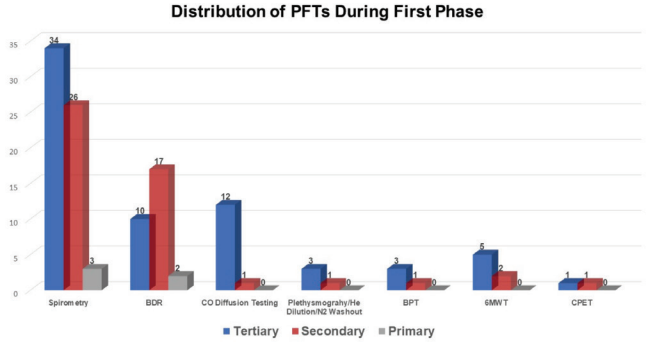

Figure 1. Distribution of pulmonary function tests during the first peak of the pandemic stratified by healthcare center levels

PFTs: pulmonary function tests

Table 1. Pulmonary function test practices of the pulmonary functions test labs before the pandemic period in Türkiye

	n (%)
Number of technicians/nurses working in the PFT lab	
1	100 (41.1)
2	88 (36.2)
≥3	55 (22.6)
Number of PFT tests performed per day	
<10	26 (10.7)
10-20	47 (19.3)
20-40	65 (26.7)
>40	105 (44.2)
Performed procedures in the PFT lab	
Spirometry	
Bronchodilator response testing	243 (100)
Carbon monoxide diffusion testing	225 (92.6)
Body plethysmography/helium dilution/nitrogen washout tests	115 (47.3)
Bronchoprovocation test	78 (32.1)
6-minute walking test	88 (36.2)
Cardiopulmonary exercise testing	106 (43.6)
The total surface area of the PFT lab	45 (8.5)
<5 m^2	36 (14.8)
5-10 m^2	109 (34.9)
>10 m^2	98 (40.3)
A separate waiting room is available for the PFT lab	153 (63.0)

PFT: pulmonary function tests

PFT labs and highlight areas requiring improvement to enhance safety and efficiency during overwhelming conditions such as the pandemic.

In our study, before the pandemic, PFTs were primarily conducted by trained technicians (50.6%) or nurses (44.9%), with test volumes often exceeding 40 tests daily. Spirometry and bronchodilator response testing were the most commonly performed procedures, reflecting their central role in pulmonary diagnostics globally.[7-10] The COVID-19 pandemic has significantly impacted PFT services worldwide, necessitating adaptations to minimize infection risk while maintaining essential diagnostic services.[11,12]

Table 2. Pulmonary function test practices of the pulmonary functions test labs during the first peak of the pandemic phase

	n (%)
Number of PFT tests performed per day	
<2	14 (21.2)
2-4	19 (28.8)
4-8	19 (28.8)
8-16	11 (16.7)
>16	3 (4.5)
Performed procedures in the PFT lab	
Spirometry	
Bronchodilator reversibility testing	66 (100.0)
Carbon monoxide diffusion testing	41 (62.1)
Body plethysmography/helium dilution/nitrogen washout tests	11 (16.7)
Bronchoprovocation test	3 (4.5)
6-minute walking test	4 (6.0)
Cardiopulmonary exercise testing	8 (12.1)
Triage performed	2 (3.0)
Cleaning/disinfection method	55 (83.3)
No information about the method used	
Ethanol >70%	32 (48.5)
Sodium hypochlorite at 0.1-0.5% in 1:10 dilution	13 (19.7)
Sodium hypochlorite at 0.1-0.5% in 1:100 dilution	11 (16.7)
	10 (15.2)

PFT: pulmonary function tests

During the pandemic's first peak, only 27.2% of the PFT labs in participants' healthcare facilities continued testing, with most operational labs located in tertiary-care centers (55.4%), followed by secondary-care facilities and a limited number of primary-care centers (4.6%). Test volumes decreased markedly, with most labs performing fewer than eight daily tests. Our findings demonstrate a marked reduction in the number of PFT tests performed daily, with most laboratories conducting fewer than eight tests daily. This decline aligns with global recommendations to limit non-urgent testing during the pandemic to reduce patient exposure and conserve healthcare resources.[5,13-16] Despite its potential for aerosol generation, spirometry remained the most frequently performed procedure (100.0%), with bronchodilator reversibility and diffusion testing conducted in 62% and 17% of cases during the post-peak phase. These findings underscore the critical role of spirometry in diagnosing and monitoring chronic respiratory conditions like asthma and chronic obstructive pulmonary disease (COPD), even during the restrictive conditions imposed by the COVID-19 pandemic. The continued prioritization of spirometry highlights its ability to provide critical diagnostic information quickly, with fewer resources and minimal patient contact compared to more complex procedures.

In contrast, more complex and time-intensive procedures, such as plethysmography (4.5%) and bronchoprovocation testing (4.0%), were rarely conducted during the first peak period. These advanced tests are not only resource-intensive but also carry a higher risk of aerosol generation, particularly in the case of bronchoprovocation, where patients are required to inhale substances that may provoke coughing. Of those 66 centers continuing testing, 12% continued six-minute walking testing. Cardiopulmonary exercise testing (3.0%), which requires prolonged patient interaction and may generate aerosols, was performed infrequently, further emphasizing the focus on safety during this period. The limited use of these procedures likely reflects adherence to international guidelines, emphasizing

Table 3. Personal protective equipment was used in the first peak of the pandemic period (n = 66) and planned to be used in the post-peak phase (n = 242)

	First peak of the pandemic period n (%)	Post-peak phase n (%)
Type of PPE used during PFT		
FFP2/FFP3 + face-shield + gown + gloves	30 (45.4)	110 (45.4)
FFP2/FFP3 + face-shield + gloves	1 (1.5)	10 (4.1)
FFP2/FFP3 + gown + gloves	8 (12.2)	19 (7.9)
FFP2/FFP3 + gloves	4 (6.2)	5 (2.1)
Surgical mask + face-shield + gown + gloves	4 (6.2)	12 (5.0)
Surgical mask + face-shield + gloves	11 (16.2)	36 (14.8)
Surgical mask + gown + gloves	3 (4.6)	19 (7.9)
Surgical mask and gloves	5 (7.7)	4 (1.7)
Hesitant	-	27 (11.1)
Total	66	242

PFT: pulmonary function tests, PPE: personal protective equipment

minimizing non-essential diagnostic procedures to reduce exposure risks for patients and healthcare providers.[5,13,16]

By December 2023, the COVID-19 pandemic had resulted in over 17.1 million confirmed cases and more than 100.000 deaths in Türkiye.[17] Globally, the pandemic prompted strict public health measures, including suspending non-urgent medical services, such as routine diagnostic testing and outpatient consultations.[18] These measures, supported by global and local respiratory societies, led to the closure or significant reduction of PFT laboratory operations.[13,19-21] PFTs, including spirometry and diffusion capacity measurements, were considered high-risk procedures due to their aerosol-generating potential and associated risks of SARS-CoV-2 transmission.[5,10,13,15,19,21]

Modeling studies anticipated the need for sustained restrictions on PFTs for the long term, up to 18-24 months, to prevent resurgences in infection rates.[16,22] To adapt, PFT labs implemented stringent protocols, including mandatory PPE use, pre-visit screening, enhanced disinfection measures, and innovative technologies like personal spirometers.[16,22,23] Despite these adaptations, significantly reduced testing capacities posed challenges for managing chronic respiratory diseases, which rely on objective lung function assessments for diagnosis, monitoring, therapeutic evaluation, and prognosis.[24] The inability to perform routine PFTs risked delays in diagnosis and suboptimal management of conditions such as asthma, COPD, and interstitial lung diseases, potentially leading to long-term health consequences. Maintaining access to PFT services remained critical as healthcare systems navigated these disruptions. PFT provides essential insights into disease severity and progression, making its restoration vital for optimal patient outcomes and preserving high-quality care in chronic respiratory disease management.

Using the data collected from this survey, it is evident that most PFT laboratories in Türkiye are relatively small, with only 40.3% having a surface area greater than 10 m^2, while approximately 15% are less than 5 m^2. This limited space presents a significant challenge in adhering to physical distancing recommendations, a critical component of infection control during the COVID-19 pandemic. The World Health Organization advised maintaining a minimum physical distance of 3 feet [~1 meter (m)] between individuals, while the Centers for Disease Control and Prevention (CDC) in the USA recommended a more conservative distance of 6 feet (~2 meters), reflecting differences in national guidelines.[5,25] Recent studies have further suggested that activities such as coughing or shouting, common during respiratory testing, can propel aerosols beyond 2 meters, emphasizing that distancing rules should account for factors such as ventilation, occupancy, and exposure time.[26-28] In this context, the small size of many PFT labs, particularly those less than 5 m^2, is inadequate to maintain even the minimum recommended distance between patients and healthcare personnel. The proximity required for test supervision, combined with the physical constraints of these smaller labs, significantly heightens the risk of airborne transmission in the absence of additional protective measures. The effect of a larger PFT lab size and more frequent air changes to reduce airborne particulate concentrations by dilution and faster clearance during and after PFT was shown by Li et al.[2] The Pulmonary Service Design Guide suggests that standard rooms designated for PFT ideally have dimensions of at least 12.0 feet (~3.65 m) x 10.0 feet (~3.05 m), corresponding to a surface area of 11-12 m^2.[29] For an extended PFT lab (e.g., for stress testing), the recommended minimum dimensions are 12.6 feet (~3.81 m) and 19.6 feet (~5.94 m), corresponding to a surface area of 24-25 m^2.[29] These dimensions ensure sufficient space to accommodate PFT equipment, a workstation for the PFT technician, a chair, sink, equipment storage, trash, sharps container and other necessary items.[29]

Inadequate room size also exacerbates challenges related to ventilation, as smaller spaces often have poorer airflow dynamics and are more prone to aerosol accumulation. Direct air exchange, such as opening windows or doors, while helpful, is insufficient for ensuring adequate ventilation in such confined areas. Computational fluid dynamics models have demonstrated that in small rooms, factors such as airflow turbulence, air conditioner inlet velocity, and droplet dispersion patterns can lead to hotspots of aerosol concentration, further increasing infection risks.[27,28] In a recent analysis, we have shown that infectious particle dispersion in a hospital examination room is predicted by various factors: airflow turbulence, air conditioner inlet velocity, droplet size, evaporation, surface adherence, and room design, highlighting the need for computational fluid dynamics model-based layout planning and ventilation optimization to reduce infection risks.[27] Consequently, PFT labs with a surface area less than 5 m^2 may fail to provide a safe environment for both patients and staff, highlighting the need for stricter design and ventilation standards for these facilities.

Given these findings, ensuring adequate space and proper airflow is essential for maintaining infection control in PFT labs. Larger rooms combined with optimized ventilation systems such as HEPA filtration or UV germicidal irradiation, are more likely to meet the distancing and air quality requirements necessary to minimize infection risks during respiratory testing.[5] However, our study revealed that 22.6% of PFT labs lacked windows, which are critical for enabling direct air exchange and supporting natural ventilation. The absence of such basic ventilation measures highlights the need for more stringent design and operational guidelines to address ventilation inadequacies, especially in smaller, enclosed spaces.

Proper ventilation plays a pivotal role in mitigating aerosol transmission, particularly in settings where aerosol-generating procedures, such as spirometry, are performed. The CDC provides examples of air exchange rates, appropriate droplet pause periods, and the time required for airborne contaminant removal to ensure a safe testing environment. Ventilation rates are measured in terms of air changes per hour (ACH), which indicates the airflow rate relative to room size. A ventilation rate of six air changes per hour (6 ACH) implies that the room's air volume is replaced six times per hour by the ventilation system. However, this does not mean the entire air volume is replaced each time; instead, the new air mixes with the existing air, causing dilution over time. At a rate of 6 ACH, approximately 95% of airborne contaminants are removed within 30 minutes, demonstrating the critical importance of maintaining adequate

ventilation rates to reduce infection risks in PFT labs.[5,13,30] We believe oncoming international standards for a PFT lab should explicitly address these spatial and ventilation requirements, emphasizing the integration of advanced air filtration technologies, adherence to recommended air exchange rates, and the provision of larger testing spaces. This is particularly crucial for facilities in resource-limited settings, where space and infrastructure constraints often hinder compliance with optimal infection control practices. By addressing these factors, PFT labs can enhance the safety of both patients and staff while maintaining the essential diagnostic capabilities necessary for respiratory care.

During the COVID-19 pandemic, for protecting pulmonary function laboratory staff essential precautions included comprehensive training on PPE usage and strict adherence to infection control protocols.[5,13,19,21] Full PPE—comprising a long-sleeved disposable fluid-repellent gown, N95/FFP2/FFP3 respirator mask, goggles/full-face shield, and disposable gloves—was mandatory for staff conducting tests due to the high aerosol generation during PFTs.[5,13] It was recommended to establish dedicated clean and contaminated areas for donning and doffing PPE, with proper hand hygiene maintained throughout. Separate PPE was recommended for each patient, and guidelines for reusing masks emphasized safe storage and limited reuse under specific conditions.[13,31] Our survey results showed that infection control practices during the COVID-19 pandemic showed significant inconsistencies. Only 45.4% of staff consistently used appropriate PPE, which included items as FFP2/FFP3 masks, gowns, gloves, and face shields, as recommended by international and national guidelines.[5,13] These discrepancies highlight significant barriers to implementing standard infection control measures in high-risk, aerosol-generating environments such as PFT laboratories. The observed variations across healthcare levels, with higher adherence rates in primary and tertiary care settings compared to secondary care ($P = 0.151$), further emphasize systemic challenges in resource distribution and training.

Moreover, cleaning and disinfection practices were varied, with nearly half of the respondents (48%) reporting no information about cleaning protocols (Table 2). UV disinfection through germicidal irradiation, a practice supported by evidence for rapidly reducing viral load in clinical settings, was utilized in only 25.8% of centers. Tertiary healthcare settings were more likely to utilize UV lamps compared to secondary care facilities (76.5% vs. 23.5%, $P < 0.0001$, data not shown). This disparity may reflect resource availability, infrastructure differences, or prioritization of advanced technologies in higher-tier facilities.

Interestingly, the survey revealed flexibility in staff scheduling (81.8%) and a reduction in staff availability in 66.7% of PFT units. These adaptations, while addressing workforce limitations during the pandemic, likely added to the challenges of ensuring consistent infection control. Notably, during the first pandemic peak, only five laboratories (7.6%) performed PFTs on COVID-19-positive patients, with indications including the evaluation of dyspnea, pulmonary fibrosis, and post-COVID-19 disability. Among these, one staff member contracted COVID-19, underscoring the critical need for rigorous protective measures.

Comparing PPE usage between the pandemic peak and post-peak phases, a shift was observed. During the first peak, 45.4% of staff used the full recommended PPE set (FFP2/FFP3 mask, face shield, gown, and gloves), with hesitant adherence reported in other configurations (Table 2). In the post-peak phase, the same proportion (45.4%) adhered to full PPE use, with an increase in the use of other configurations and some hesitation in adopting recommended practices (Table 3). This consistency raises concerns about sustainability and uniformity in infection control measures over time.

The findings reinforce the importance of comprehensive training, adequate supply chains, and clear, evidence-based protocols to mitigate risks to healthcare workers in PFT laboratories. Establishing dedicated donning and doffing areas, adhering to rigorous hand hygiene practices, and maintaining consistent disinfection protocols are vital components. Enhanced efforts to bridge gaps in infection control practices across healthcare levels are imperative to safeguard both healthcare workers and patients in these high-risk settings.

In our study, we observed that screening and triage processes were implemented in 83.3% of the PFT labs during the first phase of the pandemic, a practice strongly recommended by several guidelines, to reduce the risk of COVID-19 transmission.[5,7,13,14,21,32] However, our findings reveal inconsistencies in the application of specific measures, such as body temperature checks or tele-screening, which were variably recommended by guidelines. Notably, most guidelines, emphasized the importance of pre-test COVID-19 screening, such as a documented negative swab test 48-72 hours before testing, particularly for suspected cases.[5,7,13,21,33] This variation in implementation reflects the challenges faced by PFT labs in adhering to evolving guidelines during a rapidly changing public health crisis.

In conclusion, our study underscores the profound impact of the COVID-19 pandemic on PFT services, with substantial reductions in testing volume, procedural prioritization, and widespread adoption of screening protocols. These adaptations align with international recommendations to balance patient safety with the need to maintain essential diagnostic capabilities. Future efforts should focus on standardizing triage and safety protocols across PFT labs to enhance resilience and preparedness for similar public health emergencies.

The findings align with recommendations from the Turkish Thoracic Society and international guidelines, emphasizing the need for strict triage, limited testing, and robust infection control measures during the pandemic.[5,7,13,20,21] For example, routine PFTs were discouraged, and essential procedures such as spirometry and diffusion capacity tests were prioritized. Similarly, full PPE and thorough disinfection protocols were highlighted as critical to minimizing transmission risks.[5,7,13] Notably, pulmonologists demonstrated rapid and moderate-to-good success in implementing adaptations for COVID-19. However, significant gaps in infrastructure, infection control protocols, and staff training persist, indicating a need for continued investment and standardization. However, this

study reveals discrepancies in implementing these measures, particularly in secondary and primary care centers, where resource constraints may be more pronounced.

Despite its strengths, this study has several limitations. The primary and secondary care centers were underrepresented, which may limit the generalizability of findings. It is possible that doctors with a strong interest in PFTs were more likely to volunteer for the study, while those who believe there is limited adherence to standards may have chosen not to participate, potentially introducing bias into the results. Additionally, self-reported data are inherently subject to bias, and the cross-sectional design prevents an evaluation of changes over time. The waiting period between PFT procedures were not assessed, even though it is important to allow at least 20-minute interval between tests to enable airborne particle clearance was shown.[2] Furthermore, specific patient outcomes related to these practices were not evaluated, which could provide additional insights into the effectiveness of implemented measures. Age data of the respondents were not collected, which is a limitation of our study. Age-related differences could potentially influence compliance with safety recommendations. Moreover, this study did not assess infection control standards in PFT laboratories before the pandemic, limiting the ability to compare pre-pandemic and pandemic-era protective measures.

The study underscores the urgent need for standardized guidelines and training programs to ensure consistent infection control practices across all healthcare settings. Investments in infrastructure, such as better ventilation systems and larger lab spaces, are essential for safer PFT practices. Future research should explore longitudinal changes in PFT practices and evaluate patient outcomes to guide policy and practice improvements.

CONCLUSION

In conclusion, this study provides valuable insights into the status and challenges of PFT labs in Türkiye before and during the COVID-19 pandemic. While pulmonologists and healthcare staff have made commendable efforts to adapt to the crisis, continued efforts are needed to address existing gaps and build resilience against future public health emergencies.

Ethics

Ethics Committee Approval: This cross-sectional survey was conducted following approval from the Clinical Research Ethics Board of Başkent University Faculty of Medicine (approval number: KA20/201, date: 01.06.2020).

Informed Consent: Data collection adhered to ethical principles and the Declaration of Helsinki, with voluntary participation and informed consent obtained before survey initiation.

Footnotes

Authorship Contributions

Surgical and Medical Practices: A.G.D., Ş.B., Ö.A.Y., B.G., C.S., G.U., Concept: A.G.D., Ş.B., Ö.A.Y., B.G., C.S., S.B.S., G.U., Design: A.G.D., Ş.B., Ö.A.Y., B.G., C.S., S.B.S., G.U., Data Collection or Processing: A.G.D., Ş.B., Ö.A.Y., B.G., C.S., S.B.S., G.U., Analysis or Interpretation: A.G.D., Ş.B., Ö.A.Y., B.G., G.U., Literature Search: A.G.D., Ş.B., Ö.A.Y., B.G., C.S., S.B.S., G.U., Writing: A.G.D., Ş.B., G.U.

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Review

Effects of Nasal and Oral Breathing on Respiratory Muscle and Brain Function: A Review

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Abstract

Nasal breathing (NB) and oral breathing (OB) are two modes of respiration, and the extent to which they affect respiratory muscles and brain function. The primary objective of this study was to explore the impact of NB versus OB on respiratory muscle and brain function. A literature review was conducted by searching the National Library of Medicine (PubMed) and Scopus databases from January 2000 and May 2024. One hundred twenty-six articles were retrieved from the databases searched, and at the end of the selection process, 11 articles were included in the present review. Most studies (91%) were experimental and had adult healthy volunteers; 64% of the included studies focused on the effects of NB and OB on brain function, while the remaining 36% focused on respiratory muscles. A total of 313 participants comprised the population, most of whom were women (63%). Although most studies were conducted on adults, a percentage of participants (15%) were children. NB and OB elicit different brain areas and heterogeneously influence respiratory muscle function. Knowledge of the underlying mechanisms could be beneficial for, for example, personalizing respiratory and manual techniques when rehabilitating individuals with neurological or respiratory impairments.

KEYWORDS: Brain, breathing mode, electroencephalography, electromyography, respiratory muscles

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INTRODUCTION

Respiration plays a crucial role in metabolism, providing oxygen for efficient physical and mental function. Nasal breathing (NB) is the commonly used mode of respiration and plays a significant role in the development of facial, oral, and respiratory muscles, as well as in the formation and physiological activity of facial bones.[1,2] Increased nasal resistance and conditions such as cold, nasal allergies, persistent rhinitis, and adenoid hypertrophy (producing airway blockage) disrupt the posterior oral seal with the soft palate and tongue, allowing air to flow into the oral cavity and causing the lips to open. It is possible for the NB to be replaced by the oral breathing (OB) in the absence of factors preventing air passage through the nasopharynx. In such cases, individuals frequently exhibit OB patterns that can result in a number of negative consequences, including headache, alterations in head position, fatigue, drowsiness, mouth-opening during sleep, snoring, nasal itching, saliva dripping onto the pillow, nocturnal dyspnea and nasal obstruction.[2-6] If the air breathed through the mouth is not filtered, humidified, and heated, this can result in decreased lung function and electromyography (EMG) activation of the respiratory muscles.[7] Previous evidence suggests that OB may be associated with an increased risk of impaired brain function related to low oxygen saturation in the human brain.[8,9] A study utilizing functional magnetic resonance imaging (fMRI) discovered that, in addition to impairments in working memory, olfactory memory, arithmetic abilities, and learning skills, individuals with OB exhibited a diminished blood oxygenation level-dependent signal in the hippocampus, brainstem, and cerebellum. Studies have found the achievements of academic skills in children using OB to be lower than those breathing via NB.[9-11] The impact of breathing mode on EMG activity

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of the respiratory muscles remains a topic of contention among researchers, with no consensus yet reached. Current evidence suggests that OB produces different brain activity than NB, but there is a lack of electroencephalographic (EEG) research on the relationship between cognitive ability and the breathing mode used.[10]

Aim

The present study aimed to investigate the effects of OB and NB on respiratory muscle and brain function.

Search Process

A literature review[12] was conducted by searching the National Library of Medicine (PubMed) and Scopus databases from January 2000 to May 2024. Two search strings, 'oral breathing' AND 'nasal breathing' AND 'EMG' and 'oral breathing' AND 'nasal breathing' AND 'EEG' were built, and an additional search was conducted on Google.

Two authors independently searched databases and assessed citations for inclusion, while a third author contributed to resolve disagreements over the appropriateness of the articles.

Duplicates were removed from the retrieved citations, and abstracts were evaluated for eligibility. The PRISMA guidelines were used as a guide.[13]

Inclusion and Exclusion Criteria

To be included in the study, research must focus on comparing NB and OB with EMG of respiratory muscles [upper trapezius (UT), sternocleidomastoid, and diaphragm] and reporting EEG activity and brain function.

There were no limits on age or gender, and only studies conducted in the English language were included.

Letters to the editor, conference proceedings, abstracts, and studies that did not describe NB or OB were excluded.

Data Analysis

The included citations were categorized based on their descriptive and experimental methodology and then analyzed. From the included articles, the first author's name, publication year, country where the study was conducted, study design, demographic characteristics of participants and their number, type of assessments, and main findings were retrieved and tabulated.

One hundred twenty-six articles were retrieved from the searched databases, and after removing duplicates (n = 24), 102 citations were screened for eligibility, with 86 being excluded for not meeting the inclusion criteria. At the end of the selection process, 11 articles were included in this review (Figure 1). The majority of studies (91%) were experimental and had adult healthy volunteers (Table 1); 64% of the included studies focused on the effects of NB and OB on brain function (Table 2), while the remaining 36% focused on respiratory muscles (Table 3). A total of 313 participants comprised the population, most of whom were women (63%). Although most studies were conducted on adults, a minority of participants (15%) were children (Table 1).

DISCUSSION

Effects of Nasal and Oral Breathing on Brain Function

NB enhances the activity and connectivity of brain regions associated with the default mode network (DMN) in healthy subjects.[14] This effect is not limited to the DMN, but may also spread to a broader brain area, as DMN connectivity indicates proper attention and self-cognitive skills. NB can affect different olfactory cortical and subcortical regions, which may be essential in transitioning from unconsciousness to wakefulness.[14]

In a study on the effects of music and breathing mode on emotions, listening to various types of music during NB increased the participants' arousal levels and perceived relaxation.[15]

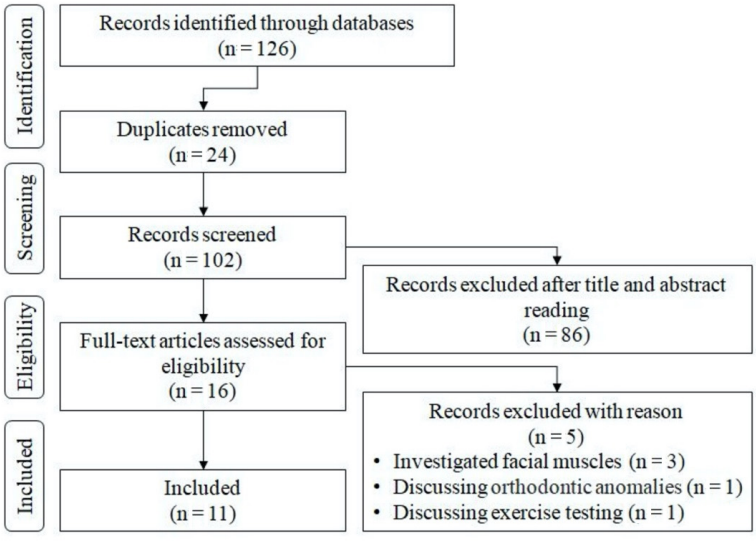

Figure 1. Study flowchart

Table 1. Characteristics of the included studies

First author (year)	Country	Study design	Participants n of the defined	Age years	Gender n of men, (%)
Salimi et al.[14] (2023)	Iran	Experimental	16 healthy volunteers	30 (IQR 25-38)	7 (44)
Mollakazemi et al.[15] (2023)	USA	Experimental	12 healthy individuals	18-35	6 (50)
Zaccaro et al.[16] (2022)	Italy	Experimental	12 healthy volunteers	48±12	3 (25)
Jung and Kang[21] (2021)	Korea	Experimental	22 healthy volunteers	22.27±1.42	10 (45)
Hong et al.[22] (2021)	Korea	Experimental	20 healthy volunteers	23.7±2.28	7 (35)
Lee et al.[10] (2020)	Korea	Experimental	20 healthy volunteers	23.7±2.28	7 (35)
Zelano et al.[23] (2016)	USA	Experimental	8 patients with temporal lobe epilepsy	48 (IQR 29-59)	8 (100)
Trevisan et al.[6] (2015)	Brazil	Cross-sectional	39 healthy volunteers (NB)	22.6±2.9	11 (28)
			38 healthy volunteers	22.7±3.5	13 (34)
Ribeiro et al.[26] (2004)	Brazil	Experimental	46 healthy children	8-12	33 (72)
Tafil-Klawe and Klawe[27] (2003)	Poland	Experimental	35 healthy volunteers	20-30	N/A
			35 healthy volunteers	41-55	N/A
Takahashi et al.[28] (2002)	Japan	Experimental	10 healthy volunteers	28.6±2.3	10 (100)

IQR: interquartile range, NB: nasal breathing, OB: oral breathing, N/A: not available

Table 2. Procedures and main findings of the included studies investigating the effects of NB and OB on brain function

First author (year)	Performed analyses	Main findings
Salimi et al.[14] (2023)	Three random experiments with EEG acquisition were performed to evaluate DMN: 1) NB, 2) OB, 3) OB + nasal air puff. EEG data were recorded using a 32-channel active electrode system. EEG electrodes were attached according to the 10-20 system, with reference and ground channels placed respectively on the left mastoid and right earlobe. Nasal air puffs consisted of a brief puff of odorless air delivered to the nasal cavity via a nasal cannula for 3 min (7-10 L/min; 1.1 bar, frequency 0.2 Hz).	NB had a higher DMN power, particularly in the gamma range, than OB. OB + nasal air puff significantly increased signal power compared to OB. In the frontal area, the power of signals was enhanced during OB + nasal air puffing (not observed during NB). NB and OB + nasal air puffs were associated with increased signal coherence compared with OB. OB + nasal air puff increased the number of synchronized channels compared to OB.
Mollakazemi et al.[15] (2023)	8-channel EEG recording from the scalp to evaluate whether NB or OB affect emotions triggered by music delivered to participants through a pair of circumaural headphones. The music comprised three two-minute songs (one happy, one peaceful, and one sad song).	Participants found songs more relaxing during NB than OB ($P = 0.00013$), and felt more aroused than during OB ($P = 0.036$). During NB, participants found the songs happier ($P = 0.069$), more exciting ($P = 0.063$), and less boring ($P = 0.082$) than during OB. During NB, the respiratory rate ($P < 0.001$) and heart rate were higher than during OB.
Zaccaro et al.[16] (2022)	SNB and SOB recordings were compared with EEG recordings to investigate olfactory epithelium stimulation's role in disentangling its effects from those related to respiratory vagal stimulation. For SOB, participants were asked to breathe only through their nostrils for 15 min at a respiratory rate of 2.5 breaths per min; A respiratory cycle consisted of four consecutive phases, each lasting 6 s (inspiration-pause-expiration-pause). For SNB, participants were asked to breathe only through their mouth for 15 min at a respiratory rate of 2.5 breaths per min. Nostrils were closed using a clinically approved nasal clip.	A higher power spectral density in the theta and delta bands was observed after SNB compared to post-SOB in the prefrontal and frontal areas. Higher theta band connectivity during post-SNB compared to post-SOB. The connectivity increase was mostly lateralized, involving the left hemisphere (from prefrontal to occipital regions). Increase of theta-high-beta coupling after SNB compared with baseline and post-SOB. Significant increases were found in midline prefrontal/frontal areas and midline posterior regions with the theta phase modulating the high-beta amplitude. Post-SNB was accompanied by an increase in experienced positive emotions compared with post-SOB ($P < 0.04$). During post-SNB, participants experienced a heightened perception of being in an altered state of consciousness. The post-SNB phase was associated with lower physical and psychological tension than the post-SOB phase, although the differences were not significant ($P < 0.32$ and $P < 0.06$).

Table 2. Continued

First author (year)	Performed analyses	Main findings
Jung and Kang[21] (2021)	Determine the differences in active brain regions and functional connectivity between the NB and OB groups during a 2-back working memory task using fMRI. On the same day, participants underwent one brain structure scan and two fMRI scans for the working memory task during NB and OB.	Fifteen and 10 regions were activated during NB, while 10 were activated during OB. Among the 15 regions during NB, five (inferior parietal gyrus, insula, cerebellum, precentral gyrus and middle frontal gyrus) appeared in both hemispheres. The functional connection decreased significantly during a working memory task in the OB group compared with the NB group. Functional connections of the left cerebellum and left and right inferior parietal gyrus were observed only during NB but not during OB. Brain areas closely related to working memory function were less active during OB.
Hong et al.[22] (2021)	EEG analysis of changes in brain oscillatory activity caused by breathing. Measurements were performed using a 32-channel EEG in a soundproof room. To examine the EEG signal differences in working memory performance during NB and OB tasks, the EEG signals were measured for 5 min each in the rest, 1-back, and 2-back task states. During the rest state with closed eyes, the tasks included NB, OB, and OB with O_2 supply.	The working memory accuracy did not differ significantly between NB and OB ($P = 0.711$). An additional O_2 supply during OB is recognized as NB, at least by the brain waves.
Lee et al.[10] (2020)	EEG recording was performed to analyze the physiological changes associated with NB and OB. A multi-parameter patient monitor was used to measure the physiological data, SpO_2, $ETCO_2$, and RR during resting and n-back working memory tasks.	Compared with NB, discomfort scores were significantly higher during OB in all three states (resting $P < 0.001$, 0-back $P < 0.001$, 2-back $P < 0.001$). $ETCO_2$ was significantly increased during OB ($P = 0.0064$). The delta wave power increased during OB in the 2-back task. The beta and gamma wave power decreased significantly in the 2-back task during OB (β $P = 0.0031$, γ $P = 0.0057$).
Zelano et al.[23] (2016)	iEEG from depth electrodes inserted into the PC, amygdala, and hippocampus of seven patients with surgical epilepsy during natural breathing (five with PC coverage; all seven with amygdala and hippocampal coverage).	The inspiratory phase of NB was associated with increased power in the delta frequency range in five patients in PC and seven patients in the amygdala and hippocampus. The nasal route of respiration provides an entry point to limbic brain areas for modulating cognitive function. Air plumes periodically entering the nose at a quiet breathing rate may elicit slow and rhythmic neuronal oscillations that propagate throughout limbic brain networks.

EEG: electroencephalography, DMN: default mode network, NB: nasal breathing, OB: oral breathing, SNB: slow nasal breathing, SOB: slow oral breathing, fMRI: functional magnetic resonance imaging, SpO_2: oxygen saturation, $ETCO_2$: end-tidal CO_2, RR: respiratory rate, β: beta, γ: gamma, iEEG: intracranial electroencephalography, PC: piriform cortex

Table 3. Procedures and main findings of the included studies investigating the effects of NB and OB on respiratory muscles

First author (year)	Performed analyses	Main findings
Trevisan et al.[6] (2015)	sEMG signals were acquired using a 14-bit surface electromyograph to evaluate the electrical activity of the SCM, UT, sternocleidomastoid, upper trapezius, and amplitude of diaphragm movement during NB and OB. Muscle activity was recorded at rest for 10 s and in four inspiratory tests: Sniff, TLC, PNIF, and MIP.	The EMG activities of the SCM and UT did not differ between the OB and NB groups at rest and at TLC, except for the left UT, which exhibited significantly higher activity at TLC in the OB group. The mean MIP value was significantly lower in the OB group than in the NB group. Among the Sniff, PNIF, and MIP, SCM activity was lower in the OB group.
Ribeiro et al.[26] (2004)	EMG recording analysis to evaluate SCM and UT muscle activity in children during NB and OB, during relaxation and maximal voluntary contractions.	At rest, children had higher electrical activity during OB than during NB ($P < 0.05$). In the maximal voluntary contraction, there was lower activity during OB compared with NB ($P < 0.05$).

Table 3. Continued

First author (year)	Performed analyses	Main findings
Tafil-Klawe and Klawe[27] (2003)	EMG recording of the GG muscle activity during NB and OB to determine the influence of NB on GG in progressive hypoxia.	Compared with NB, there are smaller increases in GG-EMG-activity in response to hypoxia during OB. Participants aged >40 years showed reduced GG muscle response to hypoxia, which was most pronounced during OB.
Takahashi et al.[28] (2002)	EMG recording of the GG and GH muscles to evaluate the influence of NB and OB can influence their activity. Activities were recorded simultaneously over 20 respiratory cycles during NB and repeated during OB.	A substantial difference was observed during NB in the upright position, with greater activity in the GG muscle. The GH muscle showed greater EMG activity during maximal jaw opening.

NB: nasal breathing, OB: oral breathing, sEMG: surface electromyography, SCM: strenocleidomastoideus, UT: upper trapezius, TLC: total lung capacity, PNIF: peak nasal inspiratory flow, MIP: maximal inspiratory pressure, GG: genioglossus muscle, GH: geniohyoid

A study was conducted to compare the psychophysiological and phenomenological impacts of slow nasal breathing (SNB) and slow oral breathing (SOB) among meditation practitioners. The cardiorespiratory parameters were not significantly different between the SNB and SOB groups.[16] After SNB and SOB, an elevation in slow rhythms (delta and theta rhythms) in EEG activity compared with baseline was observed. The increase after SNB was related to the prefrontal and central posterior areas associated with the intrinsic network[17] and/or the DMN,[18] whereas the enhancement after SOB was limited to posterior areas. Compared with SOB, SNB led to a significant amplification of slow rhythms in the medial prefrontal region. The results suggest that there is an increase in theta-high-beta coupling following SNB, potentially contributing to the regulation of brain functions supported by frontoparietal networks,[17] thus facilitating large-scale integration processes associated with self-awareness[19] and consciousness.[20]

This study aimed to investigate how cognitive function is affected during OB using fMRI. The authors performed a 2-back working memory task on a group of healthy participants during NB and OB and measured changes in neural activity.[21] Specifically, the study found a significant association between working memory and functional connections among the left cerebellum and the left and right inferior parietal gyri, which were more activated in nasal breathers.

Another study investigated the effects of oxygen deprivation during OB on brain function in different working memory tasks with varying oxygen demand levels.[22] The analysis of the EEG signals revealed that the difference in oxygenation was one of the main factors differentiating the influence of OB and NB on brain function.

The oxygen supply was more effective in reducing the characteristic changes between the EEG signals during NB and OB during the more complex tasks that required more oxygen.[22]

A previous study investigated alterations in brain activity during OB while simultaneously performing a cognitive task, utilizing EEG to measure brain waves at rest and during the n-back tasks (0-back and 2-back), alongside physiological variables, including SpO_2, $ETCO_2$, and respiratory rate.[10] Theta and alpha powers exhibited decreased levels during OB compared to NB while at rest, and alpha power demonstrated reduced levels during the 0-back and 2-back tasks. Beta and gamma waves exhibit diminished power, specifically during the 2-back task. Additionally, SpO_2 and respiratory rate significantly decreased during OB compared with NB, whereas $ETCO_2$ levels were substantially elevated during OB. Although behavioral outcomes, including accuracy and reaction time, did not differ significantly between the two groups, the observed pattern of cerebral activity in the OB group was distinct from that of the NB group. This pattern of activity was linked to brain regions involved in cognitive processes. The observed alterations seem connected to the reduced oxygen saturation during OB, suggesting that OB could be a factor leading to different brain activity patterns when cognitive skills are involved.

To explore the hypothesis suggesting a connection between cortical oscillatory activity and the human respiratory cycle, albeit at a considerably slower rhythm of approximately 0.16-0.33 Hz, researchers gathered intracranial EEG data from a limited sample of patients with medically refractory epilepsy.[23] They found that high-frequency oscillations were entrained not only in the piriform cortex but also in the amygdala and hippocampus, and dysregulation of limbic oscillatory synchrony occurred in all three brain regions, suggesting that variations in low-frequency (delta) power might act like a carrying rhythm within the lower rate of NB, with higher frequency oscillations embedded or entangled within the limbic system.[24] It has been demonstrated that OB has a detrimental effect on cognitive performance, whereas NB has been shown to have a beneficial effect, including improvement in reaction time to fearful stimuli and accuracy in visual object recognition.

Effects of Nasal and Oral Breathing on Respiratory Muscle Activity

The EMG activities of the UT and sternocleidomastoideus (SCM) muscles and DA were evaluated in adults during NB and OB.[6] The EMG activity of the SCM muscle was significantly lower in the OB group during sniffing, peak nasal inspiratory flow, and maximum inspiratory pressure, whereas no changes were found in the resting state and total lung capacity (TLC). For the UT muscle during rest and TLC, EMG activity did not differ between the OB and NB groups, but for the left part of the UT muscle, EMG activity was significantly higher in the OB group. The SCM muscle had greater activation in both groups during fast and short inspiratory workloads, with lower activation in the OB group. DA was markedly lower in the OB group at

TLC, but no change was observed during sniffing.[6] The forward head posture commonly seen in OB causes the chest to rise due to overuse of the SCM, which reduces the effectiveness of the diaphragm. In addition, OB can lead to hypertrophy of the accessory inspiratory muscles, which impede diaphragmatic movement because of their reduced mobility and lack of coordination with the abdominal muscles.[25]

A further study will examine the SCM and UT EMG activities during OB and NB in children. The results indicated that children who breathe through their mouths exhibited increased EMG activity during rest and decreased EMG activity during maximal voluntary contraction compared to children who breathe through their noses.[26] In children with OB, increased SCM and UT activity indicates a change in head posture due to nasal obstruction, which requires more effort for inspiration and consequently heightens the EMG activity of the accessory inspiratory muscles.

One study examined the effects of NB and OB on genioglossus-EMG (GG-EMG) activity in response to hypoxia and found that OB resulted in significantly less increased GG-EMG activity compared with NB.[27] Additionally, older subjects exhibited decreased GG response to hypoxia, which was most prominent during OB. In both examined groups, there was no difference in minute ventilation (MV) and tidal volume/inspiratory time (VT/TI). All subjects displayed a linear increase in MV, VT/TI, and GG-EMG activity in response to progressively induced isocapnic hypoxia. The authors have investigated the EMG activity of the GG and geniohyoid (GH) muscles and whether differences in breathing mode, as well as changes in posture, affect GG and GH activity.[28] During maximal jaw opening, GH-EMG activity was higher than GG activity; moreover, GG activity varied significantly in terms of breathing mode and posture (the OB group had higher EMG activity than the NB group). In human studies, the GH has been identified as an accessory respiratory muscle. However, the GH muscle EMG activity remained unaffected by changes in breathing mode and posture, whereas the GG muscle was affected, as previously noted. Although the GH muscle may have a lesser role as a respiratory muscle compared with the GG muscle, it still plays a significant role in respiratory function by virtue of its direct attachment to the hyoid bone, which is crucial for maintaining upper airway patency. Despite the absence of detectable alterations in GH muscle activity in response to changes in respiratory mode and posture, the authors observed that under more challenging conditions, such as severe hypoxia, the capacity of the GH muscle to maintain force output during high activation levels may be negatively impacted.[28] In summary, the EMG activity of the GG muscle was more efficient than that of the GH muscle in maintaining proper upper airway function.

In a related study, the impact of the respiratory pathway on the GG and NDM muscles during cycling exercise in an upright position was investigated.[29] The findings revealed that NDM EMG activity was markedly elevated during NB, whereas GG-EMG activity was not influenced by NB or OB. Moreover, the EMG activity of the NDM muscle exhibited significantly greater sensitivity to nasal ventilation than to oral or total ventilation during both upright and supine exercise.

The primary limitation of this review is that the material retrieved was heterogeneous because it included studies conducted both in healthy individuals and patients and with high variance in age because of the presence of children and adults. Therefore, the results reported here should be considered with caution because they cannot be extended to a wider context. Furthermore, given that most participants were healthy individuals, extending the findings of the present review to a clinical context is difficult.

CONCLUSION

The present review confirms that the nasal and OB elicit different brain areas and heterogeneously influence respiratory muscle function. Knowledge of the underlying mechanisms could be beneficial, for example, in personalizing respiratory and manual techniques when rehabilitating individuals with neurological or respiratory impairments. Additionally, changes in posture, respiratory muscle EMG activity, and respiratory function resulting from different breathing modes are clinically significant, as they can affect rehabilitation components in individuals with respiratory impairments. To enhance the generalizability of the findings, future research should conduct randomized controlled trials involving a broader range of pathologies and patients from various age groups. This approach would increase the applicability of the results in clinical contexts.

Footnotes

Authorship Contributions

Concept: Ö.B., E.P., Design: Ö.B., M.P., E.P., Data Collection or Processing Ö.B., M.P., Analysis or Interpretation: Ö.B., M.P., E.P., Literature Search: Ö.B., M.P., Writing: Ö.B., M.P., E.P.

Conflict of Interest: No conflict of interest was declared by the authors.

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Letter to the Editor

Comment on: Normative Values and Calculation Formulas of Respiratory Muscle Strength of Adults in Turkish Society: A Population-based Study

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KEYWORDS Maximal respiratory pressures, respiratory muscle, ethnicity

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DEAR EDITOR,

The research published by Pehlivan et al.[1] in September 2024 issue of the Thoracic Research and Practice is interesting and commendable. Pehlivan et al.[1] set normative data (ND) for maximum inspiratory pressure (MIP) and maximal expiratory pressure (MEP) in the Turkish population and created specific equations to estimate these data. In addition to the numerous study limitations stated by Pehlivan et al.,[1] we present an insightful one. In addition to age, sex, and anthropometric characteristics,[2] ethnicity is an important determinant of respiratory muscle strength and influence the setting of MIP and MEP.[3] Türkiye is an amalgam of multiethnic groups that recruits Turks, Kurds, and other minorities, such as Arabs, Bosniaks, Albanians, Chechens, Circassians, Romani, Georgians, and Laz people.[4] In their study methodology, Pehlivan et al.[1] didn't take into account the ethnic categories of the study population. As a result, this limitation might significantly impact the introduction of the constructed ND of MIP and MEP into research and clinical setups. Putting aside the study limitations, the formulated ND of MIP and MEP[1] can help practicing physicians and researchers approach clinical practice, conduct scientific research, and administer suitable healthcare for the Turkish population.

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Letter to the Editor

Response to: Normative Values and Calculation Formulas of Respiratory Muscle Strength of Adults in Turkish Society: A Population-based Study

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KEYWORDS

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DEAR EDITOR,

We would like to thank the authors for their interest in our study[1] and for their thoughtful comments regarding the influence of ethnicity on the normative data (ND) for maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP). We appreciate the opportunity to address their insights and clarify our study's scope and limitations.

As noted, our study aimed to establish normative values for MIP and MEP specific to the Turkish population, taking into consideration key factors like age, gender, and anthropometric characteristics. We acknowledge that ethnicity can indeed play a role in respiratory muscle strength.[2] However, due to limited data and the challenges in defining clear ethnic categories within Türkiye, we chose not to stratify our sample based on ethnicity.

Türkiye's population is indeed diverse, with multiple ethnic groups including Turks, Kurds, Arabs, and other minorities, as mentioned by the authors. Due to the nature of Turkish society, individuals may identify with multiple ethnic backgrounds simultaneously, such as Arab and Circassian. Comparable studies have been conducted in countries with complex demographic compositions, such as Türkiye.[3-10] For instance, studies conducted in Brazil[11] and Germany,[10] which illustrate this approach. In Brazil—a country with a diverse population including White, mixed-race, Black, Asian, and Indigenous groups—ethnic categorization was deliberately avoided, mirroring the methodology in our study. This approach reflects a nuanced understanding of ethnic identity that recognizes the limitations of rigid classifications within diverse populations. Nonetheless, establishing ethnic-specific normative values for respiratory parameters would require a larger, more segmented sample size and more detailed data on ethnic backgrounds, which were beyond the scope and resources of our current study.

We agree that future research could further refine normative values by incorporating ethnicity, if feasible. This could provide even more tailored references for clinical and research applications. However, we believe that our study offers valuable and applicable ND that can aid healthcare practitioners and researchers in assessing respiratory muscle strength among the Turkish population.

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Thank you for your valuable feedback. We hope that our response clarifies the considerations and limitations inherent in our methodology.

Footnotes

Authorship Contributions

Concept: E.P., H.Ç., Design: E.P., H.Ç., Data Collection or Processing: E.P., H.Ç., Literature Search: E.P., Writing: E.P., H.Ç.

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