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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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Abstracting and indexing

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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.

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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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Original Article

Are Sleep Quality, Physical Activity Levels, and Fear of Movement of Obstructive Sleep Apnea Syndrome Patients Different From Healthy People During the Coronavirus Disease 2019 Pandemic?

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Abstract

OBJECTIVE: The sleep quality and physical activity levels of patients with obstructive sleep apnea syndrome during the lockdown period have not yet been investigated. The aim of this study was to evaluate the sleep quality, physical activity level, and fear of movement in patients with obstructive sleep apnea syndrome and healthy individuals during the coronavirus disease 2019 pandemic.

MATERIAL AND METHODS: Patients with obstructive sleep apnea syndrome (n = 33) and healthy individuals (n = 30) were included in the study. Physical activity levels, sleep quality, and fear of movement were evaluated.

RESULTS: The total physical activity amount of patients with obstructive sleep apnea syndrome and healthy individuals was lower than the acceptable levels. The obstructive sleep apnea syndrome group had significantly lower leisure-time physical activity ($P = .006$) and higher sitting time ($P = .008$) than the healthy individuals. Patients with obstructive sleep apnea syndrome had significantly more sleep disturbances, daytime dysfunction, and daytime sleepiness than healthy people ($P < .001$). Fear of movement was negatively correlated with the amount of vigorous ($r = –0.395$, $P = .023$) and leisure activities ($r = –0.557$, $P = .001$) in the obstructive sleep apnea syndrome group.

CONCLUSION: During the coronavirus disease 2019 pandemic, patients with obstructive sleep apnea syndrome and healthy individuals had lower physical activity levels. Physical activity counseling is an important strategy for increasing the physical activity of patients with obstructive sleep apnea syndrome and healthy individuals during and after the coronavirus disease 2019 pandemic.

KEYWORDS: Obstructive sleep apnea, sleep quality, physical activity, fear of movement
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INTRODUCTION

Mandatory restrictions, such as the limitations dictated by epidemiologic strategies such as curfews, home quarantine, and social distancing due to the coronavirus disease 2019 (COVID-19) outbreak, have resulted in altered lifestyles of people in Turkey and many other countries. The time spent outside decreased, whereas the duration and pattern of physical activity (PA) habits and sleep quality were affected.[1-3] Additionally, social restrictions are generally accepted as a risk factor for sedentary lifestyle, thus negatively affecting sleep quality.[4] Physical activity potentially causes unwanted side effects, including symptoms related to extra effort, pain, and cardiac dysfunction, in patients with obstructive sleep apnea syndrome (OSAS) and obesity.[5] Otherwise, the increased total amount of PA in patients with OSAS is closely related to decreased excessive daytime sleepiness and the effects of fatigue on physical and psychosocial functions.[6]

As long as home lockdown due to the COVID-19 outbreak occurs, OSAS patients can be assumed to continue to suffer from restricted PA, like everyone else, and disruptions in staying asleep. Although there have been some studies on the changes in healthy lifestyle and PA behavior during the COVID-19 quarantine in different populations, such as older individuals and patients with cardiovascular disease[7], there are limited data on OSAS patients during the pandemic. Low PA has been shown to be associated with higher OSAS.[8] Fatigue and a decreased desire to act due to daytime sleepiness cause obesity and many other chronic diseases in patients with OSAS.[5] Obstructive sleep apnea syndrome is associated with hypertension, arrhythmia, hyperlipidemia, depression, and many chronic psychological diseases.[9] The reason for the fear of movement mentioned in OSAS may not be orthopedic problems but also the responses that occur with movement.[5] Causes of inactivity include daytime sleepiness and fatigue as well as early cardiac responses to activity.[5] No previous studies have evaluated the PA level, sleep quality, and fear of movement in patients during the COVID-19 pandemic.

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Therefore, our aim was to evaluate the sleep quality, PA, and fear of movement levels in patients with OSAS and compare the findings of healthy individuals during the home detention required by the COVID-19 pandemic.

MATERIAL AND METHODS

Participants

The study was conducted between May 2020 and September 2020 at the Department of Chest Diseases and Sleep Disorders of the Ahi Evren Thoracic and Cardiovascular Surgery Training and Research Hospital. The individuals consisted of patients aged 18-70 years diagnosed with OSAS and age- and sex-matched healthy individuals.

Individuals between the ages of 18 and 70 years, with a body mass index (BMI) of <40 kg/m^2, who volunteered to participate in the study, whose native language was Turkish, and who did not have mental problems that would prevent their cooperation were included in the study. Patients with severe orthopedic, neurological, or cardiovascular disorders or cognitive problems were excluded from the OSAS group. Similarly, individuals with any orthopedic, cardiovascular, neurological, psychiatric, or pulmonary diseases were excluded from the healthy group.

Verbal consent for the study protocol on the phone was obtained from individuals who participated in the study. After the participants sent a written consent to us via e-mail, they answered the questionnaires by phone. The study was approved by the Hacettepe University Non-Interventional Clinical Research Ethics Committee (protocol number: 2020 GO 11/31), and all patients signed an informed consent form. The trial was registered at ClinicalTrials.gov (NCT04451993).

Data Collection Tools

Physical characteristics, occupation status, educational level, chronic diseases, sleep symptoms, total working time, and working status of individuals during the pandemic were recorded. Disease severity was evaluated according to polysomnography apnea–hypopnea index recordings and classified as mild OSAS (5-15 events/hour), moderate OSAS (15-30 events/hour), or severe OSAS (over 30 events/hour).[10] The presence of a fear of COVID-19 was questioned as yes or no. Sleep quality, daytime sleepiness, PA, fear of movement, and health literacy (HL) were evaluated using questionnaires.

MAIN POINTS

- During the coronavirus disease 2019 (COVID-19) pandemic, compared to healthy subjects, obstructive sleep apnea syndrome (OSAS) patients first reduced their leisure-time and moderate-intensity activities.
- The total physical activity (PA) level was lower than the recommended levels in patients with OSAS and healthy individuals during the COVID-19 pandemic.
- The sleep quality of healthy individuals was higher than that of OSAS patients during the COVID-19 pandemic.
- High body mass index, daytime sleepiness level, and the presence of relevant symptoms with deterioration of sleep quality were associated with low PA levels in the OSAS group.
- Low health literacy levels and fear of movement should be considered during physical activity counseling in patients with OSAS.

Sleep Quality. The Pittsburgh Sleep Quality Index (PSQI) was used to assess sleep quality. The total PSQI score ranges from 0 to 21. A PSQI total score >5 indicates poor sleep quality.[11]

Daytime Sleepiness

Daytime sleepiness was evaluated using the Epworth Sleepiness Scale (ESS) consisting of 8 questions. An ESS score >10 has high sensitivity and specificity for daytime sleepiness.[12]

Physical Activity

The Turkish version of the long form of the International Physical Activity Questionnaire (IPAQ) was used to evaluate PA levels. The IPAQ-long form consists of 27 questions related to PA in the last 7 days.[13] The first score is special scoring for work, transportation, home-garden work, and leisure activities and the second is an intensity of activity-specific score (walking, moderate activity, and vigorous activity). The total score was the sum of the walking, moderate activity, and vigorous activity scores. The "metabolic equivalent (MET)-minutes/week" value was obtained by multiplying the days and minutes by the MET, and the values used for the calculation were 3.3 MET for light PA, 4.0 MET for moderate PA, 5.5 MET for moderate-to-vigorous PA, 6.0 MET for vigorous PA, and 8.0 MET for very vigorous PA. Sitting time was recorded as the total duration of sitting in a day. Physical activity levels are classified as inactive, minimally active, and active according to the total PA score.[13]

Fear of Movement

The Tampa Scale of Kinesiophobia (TSK) is a 17-question checklist for evaluating the fear of movement. The total TSK score ranges from 17 to 68. A score of 37 or above confirms the presence of fear of movement.[14]

Health Literacy

The Turkish Health Literacy Scale-32 (TSOY-32) was used to evaluate HL. This scale included 8 components. Each component has 2 dimensions. A total TSOY-32 score of 0 indicates the lowest level of literacy and 50 indicates the highest HL. Additionally, the total score was classified into 4 subcategories. These are as follows: 0-25 points: insufficient HL, 25-33: problematic limited literacy, 33-42: adequate HL, 42-50: excellent HL.[15]

Statistical Analysis

For sample size calculation, the sleep quality scores of patients with OSAS and healthy individuals reported in the study by Calik-Kutukcu et al[16] were used as the primary outcome. The sample size was calculated as at least 15 individuals for each group with %90 power of the study, using the G*Power statistical program (G*Power ver. 3.1, Henri ch-Heine-University, Dusseldorf, Germany).[17] Statistical evaluation was performed using the Statistical Package for the Social Sciences 23.0 for Windows (version 18.0, IBM Inc., Armonk, NY, USA). Descriptive variables are expressed as mean ± SD, median (minimum–maximum), frequency, and

percentage. The Kolmogorov–Smirnov test was used to determine whether they were normally distributed. The Mann–Whitney *U*-test was used for the non-normally distributed parameters and the Student's *t*-test was used for the normally distributed parameters to compare the parameters between the OSAS patients and healthy individuals. The chi-square test was used to analyze the qualitative variables. The 2-way analysis of variance test or the Kruskal–Wallis test was used to compare the levels of sleep quality, PA, fear of movement, and daytime sleepiness between patients with various OSAS severities during the pandemic. The level of significance was set at $P < .05$.[18]

RESULTS

This study included 33 patients with OSAS and 30 healthy individuals. Age, sex, and height values were similar between the groups ($P > .05$), but there was a significant difference in body weight and BMI ($P < .05$) (Table 1). The marital status, educational level, profession, HL status, and chronic diseases of the participants are presented in Table 1. The TSOY-32 total score of the OSAS patients was significantly lower than that of healthy individuals ($P = .045$, Table 1). The OSAS severity was mild in 30.3% of patients (n = 10), moderate in 33.3% (n = 11), and severe in 36.4% (n = 12). At the time of our study, Continuous Positive Airway Pressure (CPAP) therapy was recommended for 42% of the patients (n = 14), but they had not yet begun active therapy.

The working status and symptom perception of individuals during the pandemic are shown in Table 2. There was no significant difference in the total daytime and nighttime work status during the COVID-19 pandemic between the groups ($P > .05$, Table 2). Worry about COVID-19 infection was similar between the 2 groups ($P > .05$, Table 2). The mean TSK score of the OSAS patients was 38.21 ± 9.21. Fear of movement was present in 60.6% (n = 20) of the patients with OSAS.

The total IPAQ PA scores of OSAS patients and healthy individuals were similar ($P > .05$, Table 3). The ratios of inactive/minimal active/active individuals in each group were statistically comparable ($P > .05$, Table 3). The leisure-time PA score ($P = .006$, Table 3) was significantly lower and the sitting time ($P = .008$, Figure 1) was higher in patients with OSAS than in healthy individuals during the pandemic. Sleep quality was normal in healthy individuals, according to the total PSQI score. The PSQI sleep disturbance, daytime dysfunction, total scores ($P < .001$, Table 3, Figure 2), and ESS scores ($P = .039$, Table 3) of the OSAS patients were significantly higher than those of healthy individuals.

The IPAQ moderate PA and total PA scores were significantly different according to disease severity among the patients with OSAS ($P = .023$, $P = .004$, respectively, Figure 3). The IPAQ moderate PA and total PA scores of severe OSAS patients were significantly lower than those of moderate OSAS patients ($P = .004$ and $P < .001$, respectively). There was no significant difference between the mild, moderate, and severe OSAS patients in terms of PSQI, TSK, and ESS total scores during the pandemic ($P > .05$). Additionally, the TSK score was significantly related to the IPAQ vigorous PA score ($r = –0.395$, $P = .023$) and leisure-time PA score ($r = –0.557$, $P = .001$) in patients with OSAS. The total PA score was also related to the PSQI total score ($r = –0.365$, $P = .037$), whereas the PA sitting time was not correlated with HL ($r = 0.597$, $P = –0.095$), TSK ($r = 0.260$, $P = .202$), or PSQI total ($r = 0.831$, $P = .039$) scores in the OSAS group.

DISCUSSION

The main finding of this study was that the total PA level was low in both patients with OSAS and healthy individuals during the pandemic. The sleep quality of patients with OSAS was worse than that of healthy individuals during the COVID-19 pandemic. Lower PA levels were associated with poor sleep quality, and a higher level of fear of movement was related to lower vigorous and leisure-time PA levels in the OSAS. When evaluated according to the severity of the disease, the moderate and total PA levels of patients with severe OSAS were significantly lower than those of patients with moderate OSAS.

The recommended PA level is a minimum of 3000 MET-minutes/week for adults, corresponding to a combination of 7 or fewer days of walking and moderate or vigorous activity.[13] A prospective cohort study showed that the leisure activity score of patients with OSAS was considerably lower than that of healthy individuals.[19] Such low PA levels in patients with OSAS are also thought to be associated with daytime sleepiness, obesity, the presence of concomitant diseases, a higher anxiety level, fatigue, pain, and fear of movement.[5,6] Additionally, home restrictions and social distance warnings during the COVID-19 pandemic decreased the level of PA in patients with OSAS as well as in healthy individuals, and the total weekly PA amount of patients with OSAS and healthy individuals was lower than the recommended threshold levels in our study. A study of Spanish adults showed that home restrictions during the COVID-19 pandemic negatively affected the amount of PA and sleep quality.[1] Reduced working hours because of one of the infection's spread prevention strategies during COVID-19 may also be associated with lower PA levels in both OSAS patients and healthy individuals.[1]

Although the rate of fear of movement was higher in patients with OSAS than in healthy individuals, the presence of fear of movement in patients with OSAS negatively affected participation in leisure and vigorous activities. In our study, OSAS patients' sitting times were also significantly greater than those of healthy individuals; however, PA sitting time in the OSAS group was not correlated with HL, fear of movement, or sleep quality. A previous study found that excessive sitting or screen time was not associated with OSAS.[20] Studies have reported that the average duration of immobility per day was 5-6 hours according to self-reports or 7 hours and 39 minutes based on an accelerometer for the general population.[21] The sitting time for OSAS patients, as reported by an accelerometer, was 9 hours and 55 minutes per day.[5] In the current study, the sitting time per day, excluding the periods spent asleep, was 7 hours for OSAS patients and 6 hours for healthy individuals. A study reported that the pandemic significantly reduced the activity durations of active workers, whereas inactive workers did not change their activity duration.[1] Another study found that patients did not engage

Table 1. Characteristics of Patients with OSAS and Healthy Individuals

Variables	OSAS (n = 33)	Healthy (n = 30)	*P*
Physical			
Age (years)	48.78 ± 9.24	44.23 ± 9.16	.056
Height (cm)	168.45 ± 10.14	167.24 ± 11.33	.708
Weight (kg)	91.23 ± 11.28	75.20 ± 12.12	**<.001***
BMI (kg/m^2)	32.22 ± 3.98	26.72 ± 2.72	**<.001***
Gender (male/female)	19/14	13/17	.259
AHI (events/h)	28.02 ± 17.79	—	—
Marital status			
Married	25 (75.8%)	22 (73.3%)	.825
Single	8 (24.2%)	8 (26.7%)	
Educational level			
Literate	1 (3.0%)	1 (3.3%)	.097
Primary school	6 (18.2%)	1 (3.3%)	
Middle school	1 (3.0%)	3 (10.0%)	
High school	11 (33.3%)	4 (13.3%)	
Graduate	9 (27.3%)	15 (50.0%)	
Postgraduate	5 (15.2%)	6 (20.0%)	
Profession			
Unemployed	1 (3.0%)	2 (6.7%)	.143
Housewife	9 (27.3%)	3 (10.0%)	
Officer	4 (12.1%)	6 (20.0%)	
Health employee	4 (12.1%)	8 (26.7%)	
Academician	1 (3.0%)	1 (3.3%)	
Teacher	2 (6.1%)	1 (3.3%)	
Engineer/architect	7 (21.2%)	1 (3.3%)	
Self-employed	1 (3.0%)	0 (0.0%)	
Retired	3 (9.1%)	3 (10.0%)	
Other	1 (3.0%)	5 (16.7%)	
Health literacy level			
TSOY-32 total score (0-50)	30.00 ± 16.80	38.92 ± 9.10	**.045***
HL level classification			
Inadequate	14 (42.4%)	2 (6.7%)	**.007***
Problematic	2 (6.1%)	7 (23.3%)	
Adequate	5 (15.2%)	7 (23.3%)	
Excellent	12 (36.4%)	14 (46.7%)	
Chronic diseases			
Hypertension	9 (27.3%)	0 (0.0%)	—
Diabetes mellitus	6 (18.2%)	0 (0.0%)	
Dysrhythmia	2 (6.1%)	0 (0.0%)	
Psychiatric disorders (depression and panic attacks)	4 (12.1%)	0 (0.0%)	
Asthma	2 (6.1%)		
Goiter	4 (12.1%)		

*$P < .05$.
AHI, apnea–hypopnea index; BMI, body mass index; HL, health literacy; OSAS, obstructive sleep apnea syndrome; TSOY-32, The Turkish Health Literacy Scale-32.

Table 2. Working Status and Symptom Perceptions of Patients with OSAS and Healthy Individuals During Pandemic Process

Variables	OSAS (n = 33)	Healthy (n = 30)	*P*
Working status			
He/she is not working	14 (42.4%)	9 (30.0%)	.345
He/she was working, is not working now	1 (3.0%)	0 (0.0%)	
He/she is working in shifts	3 (9.1%)	8 (26.7%)	
He/she is working at home or at work from time to time	3 (9.1%)	5 (16.7%)	
He/she is managing her/his business from the workplace	11 (33.3%)	7 (23.3%)	
He/she is working from home	1 (3.0%)	1 (3.3%)	
Total working time			
Daytime (hours/week)	22.36 ± 26.96	26.57 ± 21.86	.410
Nighttime (hours/week)	5.90 ± 14.36	8.47 ± 17.95	.416
Worry related with COVID-19			
Yes	20 (60.6%)	24 (80%)	.094
No	13 (39.4%)	6 (20%)	
Symptom perceptions			
Difficulty in falling asleep	7 (21.2%)	7 (23.3%)	.840
Waking up at night (n)			**.004***
0-1	10 (30.3%)	21 (70.0%)	
2-4	20 (60.6%)	9 (30.0%)	
5-8	3 (9.1%)	0 (0.0%)	
Debility	17 (51.5%)	5 (16.7%)	**.004***
Forgetfulness	18 (54.5%)	6 (20.0%)	**.005***
Difficulty in making decisions	9 (27.3%)	1 (3.3%)	**.014***
Night sweats	17 (51.5%)	0 (0.0%)	**<.001***
Lack of concentration	10 (30.3%)	1 (3.3%)	**.005***
Morning headache	10 (30.3%)	2 (6.7%)	**.017***
Dry mouth	17 (51.5%)	2 (6.7%)	**<.001***
Hearing loss	4 (12.1%)	0 (0.0%)	.115
Drowning sensation in sleep	13 (39.4%)	1 (3.3%)	**.001***
Nighttime cough	7 (21.2%)	0 (0.0%)	**.011***
Poor memory	8 (24.2%)	0 (0.0%)	**.004***

*$P < .05$.
COVID-19, coronavirus disease 2019; OSAS, obstructive sleep apnea syndrome.

in recreational activities such as dancing, sports, or gardening and did not move unless they had to.[5] The combination of anxiety and depression caused by the pandemic and social isolation, daytime sleepiness, disease symptoms, and fatigue[22] of OSAS patients are reported reasons for such a worsening PA level.[23] A recent US cohort study reported that higher PA levels and lower sedentary duration were associated with a lower incidence of OSAS. The potential mediating role of metabolic factors in the association between sedentary behavior and OSAS incidence may depend on the type of sedentary behavior.[24] These results suggest that promoting an active lifestyle can reduce the incidence of OSAS. A previous study suggested that a healthy lifestyle is inversely associated with OSAS risk. Strategies leading to an active lifestyle may be more appropriate for preventing OSAS.[25]

Age, sex, hypertension, BMI, and waist circumference were associated with OSAS.[20] According to the second hypothesis, high BMI, daytime sleepiness level, and the presence of relevant symptoms with the deterioration of sleep quality were associated with low PA levels in the OSAS group. A systematic review has shown that most observational studies consistently report a relationship between PA and HL, and individuals with a more active lifestyle tend to have higher HL than those with a more sedentary lifestyle.[26] Our patients with OSAS in this study also had at least 1 cardiovascular disease. Increased expression of angiotensin-converting enzyme 2 and renin–angiotensin system dysregulation were observed in untreated OSAS patients due to chronic intermittent hypoxia. Otherwise, they may have cardiovascular comorbidities that are risk factors for mortality in COVID-19.[27] Although the HL level was lower in the OSAS group than in the healthy group,

Table 3. The Physical Activity, Sleep Quality, Daytime Sleepiness Levels of Patients with OSAS and Healthy Individuals

Variables	OSAS (n = 33)	Healthy (n = 30)	*P*
IPAQ PA scores			
Total PA (MET-minutes/week)	2772 (0-12264)	2804.3 (0-23471.5)	.397
Vigorous PA (MET-minutes/week)	0 (0-6720)	247.5 (0-9845.5)	.069
Moderate PA (MET-minutes/week)	960 (0-8520)	1290 (0-14580)	.271
Walking PA (MET-minutes/week)	540 (0-5544)	792 (0-6237)	.367
Occupational PA (MET-minutes/week)	0 (0-10878)	198 (0-15192)	.152
Transportation PA (MET-minutes/week)	232.5 (0-4518)	280.5 (0-2079)	.646
House yard work PA (MET-minutes/week)	435 (0-11520)	765 (0-8820)	.306
Leisure-time PA (MET-minutes/week)	0 (0-2880)	639.8 (0-6488)	**.006***
Sitting time (minutes)	420 (0-960)	300 (60-780)	**.008***
Physical activity category			
Low	16 (48.5%)	12 (40.0%)	.367
Moderate	12 (36.4%)	9 (30.0%)	
High	5 (15.2%)	9 (30.0%)	
Sleep quality			
Sleep duration (0-3)	1.12 ± 1.11	0.58 ± 0.95	.038
Sleep disturbance (0-3)	2.00 ± 0.75	0.62 ± 0.73	**<.001***
Sleep onset latency (0-3)	1.27 ± 1.23	0.89 ± 0.90	.277
Daytime dysfunction (0-3)	1.36 ± 1.08	0.35 ± 0.67	**<.001***
Sleep efficiency (0-3)	1.03 ± 1.31	0.41 ± 0.95	.036
Sleep quality (0-3)	1.82 ± 0.98	0.79 ± 0.82	.097
Hypnotic drugs (0-3)	0.55 ± 1.18	0.14 ± 0.58	.167
Total score (0-21)	9.12 ± 4.82	3.79 ± 3.79	**<.001***
Daytime sleepiness			
ESS score (0-24)	8.06 ± 5.92	5.20 ± 4.43	**.039***
Daytime sleepiness classification			
Lower normal daytime sleepiness	11 (33.3%)	6 (60.0%)	.092
Higher normal daytime sleepiness	12 (36.4%)	8 (26.7%)	
Mild excessive daytime sleepiness	1 (3.0%)	2 (6.7%)	
Moderate excessive daytime sleepiness	4 (12.1%)	0 (0.0%)	
Severe excessive daytime sleepiness	5 (15.2%)	2 (6.7%)	

*$P < .05$.
ESS, Epworth Sleepiness Scale; IPAQ, International Physical Activity Questionnaire; MET, metabolic equivalent; PA, physical activity.

patients have restricted PA duration because of increased awareness about the relationship between the time spent outside and prolonged contact in crowded environments and the risk of COVID-19 infection and increased number of comorbidities. Moreover, OSAS patients have protected themselves by reducing their PA outside as the disease severity increases because of the increase in the frequency of comorbidities associated with OSAS, which makes the patient's condition related to a COVID-19 infection more dangerous. During the COVID-19 pandemic, compared with healthy individuals, patients with OSAS first had reduced leisure-time and moderate-intensity activities. This may be due to home restrictions, increased daytime sleepiness, low HL, or the presence of cardiovascular symptoms. The common point between healthy and OSAS patients in our study was the continuation of their working status during the COVID-19 pandemic.

Research has shown that the social isolation due to the COVID-19 pandemic increases physical inactivity and sedentary lifestyles globally.[28,29] The pernicious consequences of the physical inactivity pandemic were also mentioned before the COVID-19 pandemic.[30] Physical inactivity is the primary factor that increases the risk of cardiovascular disease, especially obesity and hypertension, in both patients and healthy individuals.[31,32] For patients with OSAS, both physical inactivity and the burden of cardiovascular disease increase the rate of mortality and morbidity, and these paradoxes may be exacerbated by the COVID-19 pandemic.[28,33]

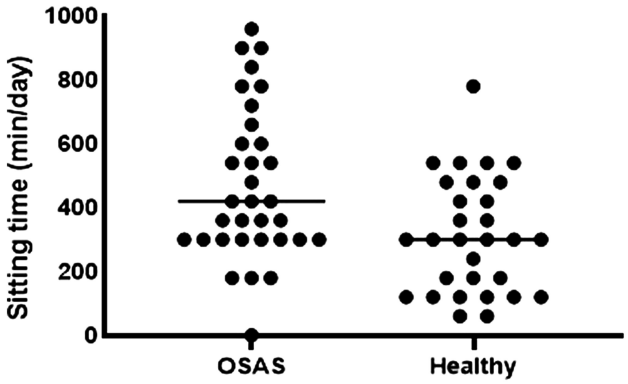


Figure 1. The comparison of the sitting times during the pandemic between OSAS patients and healthy individuals. OSAS, obstructive sleep apnea syndrome.

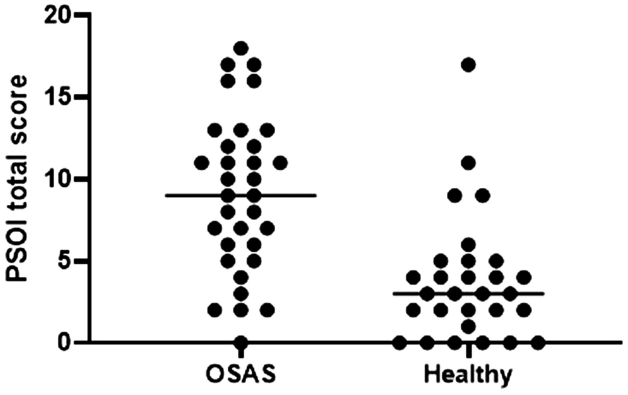


Figure 2. The comparison of sleep quality during the pandemic between OSAS patients and healthy individuals. OSAS, obstructive sleep apnea syndrome; PSQI, Pittsburgh Sleep Quality Index.

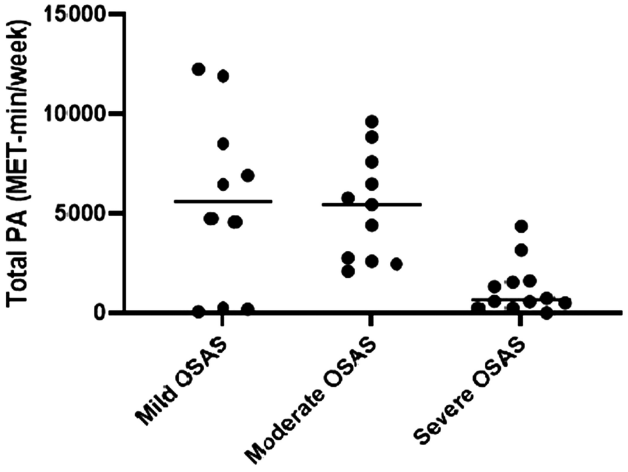


Figure 3. The differences in the IPAQ total PA scores of the OSAS patients according to disease severity. IPAQ, International Physical Activity Questionnaire; MET, metabolic equivalent; OSAS, obstructive sleep apnea syndrome; PA, physical activity.

Various studies have evaluated the impact of the COVID-19 pandemic on sleep quality in adults.[1,34] Findings related to sleep quality during pandemics have yielded conflicting results. Although there was a significant decrease in sleep quality in a study that used the PSQI,[1] another study found that home restriction did not affect sleep quality.[34] Patients with OSAS and healthy people in our study had similar concerns about COVID-19 infection, but the sleep quality of OSAS patients was lower during the pandemic period, as expected. Otherwise, healthy people's sleep quality was normal and not adversely affected.

The first limitation of this study was that we did not have information on the PA levels and sleep quality of the participants before the COVID-19 pandemic. Therefore, we were unable to compare it with the pre-pandemic situation. Another limitation was that, despite the observation of anxiety and depression caused by social restrictions in patients with OSAS, we did not evaluate anxiety and depression levels. Moreover, the restrictions of the pandemic made it impossible to evaluate PA using objective criteria. Another overlooked factor was the absence of data on screen (blue light) exposure in patients with OSAS. The increase in the time spent in front of the television, phone, and tablet until late reduces the time spent sleeping and may cause problems in falling asleep. The strength of this study is that it compared sleep quality and PA levels of patients with OSAS and healthy individuals during the pandemic. This research is important and valuable as a guide for taking action for PA interventions in patients with OSAS.

CONCLUSION

The results of this study indicate that patients with OSAS and healthy individuals had lower PA levels, worse sleep quality, and lower HL than their healthy counterparts during the pandemic. Additionally, patients with more severe OSAS had a greater reduction in the amount of PA. Physical activity counseling is an important strategy for increasing PA levels in patients with OSAS, particularly during the pandemic period. Informative initiatives should be implemented to reduce sitting time and increase PA. Future studies considering screen (blue light) exposure, with detailed evaluation of sleep times with objective measurements, and determining the relationship with PA are necessary for patients with OSAS.

Data Access Statement: All relevant data are within the paper.

Ethics Committee Approval: This study was approved by the Hacettepe University Non-Inverventional Clinical Research Ethics Committee with protocol number 2019/11. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards (trial registration number and date of registration: NCT04451993/30.06.2020).

Informed Consent: Verbal consent for the study protocol on the phone was obtained from individuals who participated in the study. After the participants sent a written consent to the authors via e-mail, they answered the questionnaires by phone.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – N.E., E.Ç.K.; Design – N.E., E.Ç.K.; Supervision – E.Ç.K., N.V.Y.; Resources – N.E.; Materials – N.E.; Data Collection and/or Processing – N.E., A.Ç.; Analysis and/or Interpretation – E.Ç.K.; Literature Search – N.E.; Writing – N.E.; Critical Review – E.Ç.K., N.V.Y., N.E.

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Original Article

Clinical Significance of Pleural Lactate Measurement in Critically Ill Patients with Parapneumonic Pleural Effusion

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Abstract

OBJECTIVE: Pleural fluid pH measurement is recommended for tube thoracostomy decisions in complicated parapneumonic pleural effusions. However, pleural fluid pH may be affected by blood pH in critically ill patients with common systemic acid-base disorders. We aimed to investigate the use of pleural fluid lactate to distinguish culture-positive parapneumonic effusions from other pleural effusions.

MATERIAL AND METHODS: This prospective observational study included 121 eligible patients (51 female and 70 male). All patients with pleural effusion who underwent thoracentesis were assessed. Pleural fluid lactate was measured by a blood gas analyzer.

RESULTS: Of the 121 patients, 30 (24.8%) were transudate and 91 (75.2%) were exudate. Of the 91 patients with exudative pleural effusion, 61 were diagnosed as culture-negative parapneumonic, 13 as culture-positive parapneumonic, 9 as malignant, and 8 as other exudative effusion. There was a strong positive linear association between serum pH and pleural fluid pH ($R = 0.77$, $P < .001$). The post hoc tests for pleural fluid lactate revealed there was a significant difference between culture-positive parapneumonic versus culture-negative parapneumonic groups ($P = .004$), culture-positive parapneumonic versus transudative effusion groups ($P < .001$), culture-negative parapneumonic versus transudative effusion groups ($P = .008$) and lastly; malignant effusion versus transudative effusion groups ($P = .001$). Receiver operating characteristics curve analysis for culture-positive parapneumonic indicated a cutoff of 4.55 mmol/L for pleural fluid lactate to have a sensitivity of 76.9% and a specificity of 84.3% (positive predictive value: 37%, negative predictive value: 96.8%).

CONCLUSION: A cutoff of 4.55 mmol/L of pleural fluid lactate can be used as a useful tool to distinguish culture-positive parapneumonic effusions from other effusions in critically ill patients.

KEYWORDS: Pleural effusion, complicated parapneumonic pleural effusion, pleural fluid lactate, critical illness
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INTRODUCTION

Parapneumonic effusion is the exudative pleural fluid accumulation related to ipsilateral lung infection, primarily pneumonia.[1] Parapneumonic pleural effusions are a common finding that affects mortality in intensive care unit (ICU) patients.[2,3] Chest tube drainage is required for optimal management when parapneumonic effusions are complicated.[4,5] However, it may be difficult to distinguish patients with complicated parapneumonic effusion from patients with simple parapneumonic effusion on the basis of clinical presentation.[5] Therefore, pleural fluid analysis and pleural fluid pH measurement are recommended by guidelines to aid in the management of parapneumonic effusions.[4,5] In complicated parapneumonic effusions and empyema, the increased metabolic activity of leukocytes and bacteria in the pleural fluid increases acid generation.[6] Acid generation is a result of glucose metabolism and its end products, lactic acid and carbon dioxide.[6] A parapneumonic effusion with a pleural fluid pH <7.2 predicts a complicated clinical course that necessitates tube thoracostomy.[4,5,7]

In an experimental study conducted on normal rabbits without pleural effusions, the pleural fluid pH was around 7.66.[8] In patients with pleural effusions, the pH of pleural fluid usually approaches that of the blood.[9] Recommendations using pleural fluid pH <7.2 are based on the assumption that patients have no systemic acid-base disorders.[4,5] However, almost half of the intensive care patients have systemic acid-base disorders.[10] As the blood pH affects pleural fluid pH,[9] the guidance of pleural fluid pH in critically ill patients with potential acid-base disorders may be confusing.

In this study, we aimed to (i) examine the diagnostic utility of pleural fluid pH in critically ill populations, (ii) investigate the correlation of pleural fluid pH with systemic pH, (iii) describe the level of pleural fluid lactate in pleural effusions due to different causes, and (iv) determine a cutoff level of pleural fluid lactate to distinguish culture-positive parapneumonic effusions from other pleural effusions.

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MATERIAL AND METHODS

Study Population

After approval from the local ethics committee (with date July 13, 2020, and number 2020/16-07), this prospective observational study was conducted in the adult intensive care units of our center. All participants provided written informed consent. Between July 2020 and February 2022, all patients with pleural effusion (18 years and older) who underwent thoracentesis were assessed. Only the patients who underwent both blood gas analysis and pleural fluid gas analysis after thoracentesis were included. Patients with a history of acute trauma, patients with a loculated pleural effusion detected by ultrasound or chest CT, and patients with frank pus were excluded. Patients who received local lidocaine before thoracentesis were excluded from the study, as it may artificially alter the pleural fluid pH.

Pleural Fluid Sample Collection

The pleural effusion was collected by a physician using ultrasound-guided thoracentesis. Thoracentesis was performed for diagnostic and/or therapeutic reasons. In our center, 4 pleural fluid samples are routinely collected according to international recommendations[4]: (1) a sample for biochemistry, (2) a sample for pH and lactate analysis, (3) a sample for microbiology cultures, and (4) a sample for cytology. The pleural fluid is collected into an uncoated syringe, immediately transferred to a heparinized blood gas syringe for pH analysis, and processed within a maximum of 5 minutes. The pH and lactate were measured using a gas analyzer ABL800 FLEX (Radiometer Medical ApS, Denmark).

Variables

The following data were recorded for this study: (1) the demographic data (age, sex, body mass index, smoking history, and comorbidities), Acute Physiology and Chronic Health Evaluation (APACHE) II Score, Sequential Organ Failure Assessment (SOFA) Score, and Charlson Comorbidity Index (CCI); (2) major events during ICU stay (presence of sepsis/septic shock, presence of acute kidney injury [AKI], need for renal replacement therapy [RRT], and need for invasive mechanical ventilation [IMV]); (3) the durations from hospitalization to thoracentesis and from ICU admission to thoracentesis; (4) lengths of ICU, and hospital stays, and mortality; (5) effusion-related characteristics (estimated pleural fluid volume measured by ultrasound, diuretic use before thoracentesis, side of thoracentesis, complications, and the number of tube tracheostomies); (6) biochemical test results on the day of thoracentesis (glucose, total protein, albumin, and lactate dehydrogenase) and laboratory results of pleural fluid (glucose, total protein, albumin, and lactate dehydrogenase); (7) the results of pleural fluid gas analysis (pH and lactate) and blood gas analysis (pH and lactate); and (8) results of microbiology and cytology were recorded.

MAIN POINTS

- Pleural fluid pH is strongly affected by systemic serum pH.
- A pleural fluid pH <7.20 may not be a good predictor for complicated parapneumonic effusions in the critically ill population.
- A cutoff of 4.55 mmol/L for pleural fluid lactate can be used to distinguish culture-positive parapneumonic effusions from other effusions.

Definitions

Transudative and exudative pleural effusions were defined according to Light's criteria.[11] Pleural effusions were classified as culture-negative parapneumonic, culture-positive parapneumonic, malignant, and transudative. The exudative effusions not meeting the criteria for these groups are classified under other exudative effusions. Parapneumonic effusions were defined as exudative effusions with no other cause in patients with clinical/radiological evidence of pneumonia. Parapneumonic effusions were classified as culture-negative and culture-positive parapneumonic effusions. Malignant pleural effusion was defined as effusion with positive cytological results on pleural fluid analysis or radiological evidence of malignant pleural disease in the context of a known malignancy without any other identified cause.

Statistical Analysis

Categorical variables were expressed as numbers and percentages (n, %), and continuous variables were expressed as median with interquartile range (IQR). Normal distribution was assessed based on histograms and Shapiro–Wilk test. Continuous variables between 5 pleural effusion groups were compared using Kruskal–Wallis test. If there was a significant difference, we performed post hoc Dunn's test with Bonferroni adjustment. The linear association between blood pH and pleural fluid pH was evaluated with Spearman's rank correlation test. We performed receiver operating characteristics (ROC) curve analysis to measure the diagnostic performance of pleural fluid lactate and pleural fluid/serum lactate for culture-positive parapneumonic effusion. The optimal cutoff value was determined according to the Youden index, and sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated. Data analysis and visualizations were done using R version 4.2.0 (https://www.r-project.org/). Double-sided *P*-values of less than .05 were considered significant.

RESULTS

General Characteristics

A total of 121 eligible patients were included in the study. The median age of the study population was 73.0 (63.0-81.0) years, and 57.9% (n = 70) were male. Table 1 provides the general characteristics of the study population. Common comorbidities were hypertension (59.5%), diabetes mellitus (39.7%), and congestive heart failure (29.8%). Chest tube drainage was performed in 76.9% (n = 93) of the patients. The ICU mortality rate was 62.8% (n = 76).

Results of Serum and Pleural Fluid Analysis

Of the 121 patients, 30 (24.8%) were transudate and 91 (75.2%) were exudate (Table 2). Of the 91 patients with exudative pleural effusion, 61 were diagnosed as culture-negative parapneumonic, 13 as culture-positive parapneumonic, and 9 as malignant. Eight patients with exudative pleural effusion could not reach a definitive diagnosis and were classified under the other exudative effusion group. Three

Table 1. Baseline Characteristics of Patients

Characteristics	Value
Age, years	73.0 (63.0-81.0)
Gender	
Female	51 (42.1)
Male	70 (57.9)
Smoking history	29 (24.0)
Body mass index, kg/m²	24.2 (20.9-28.3)
Comorbidities	
Hypertension	72 (59.5)
Diabetes mellitus	48 (39.7)
Congestive heart failure	36 (29.8)
Chronic kidney disease	23 (19.0)
Coronary artery disease	19 (15.7)
Dementia	17 (14.0)
COPD	16 (13.2)
Liver cirrhosis	8 (6.6)
APACHE II score	24.0 (16.0-29.0)
SOFA[a] score	7.0 (5.0-9.5)
CCI	6.0 (4.0-8.0)
Events/therapies during ICU stay	
IMV	100 (82.6)
Sepsis/septic shock	80 (66.1)
Acute kidney injury	63 (52.1)
Renal replacement therapy	29 (24.0)
Diuretic use before hospitalization	43 (35.5)
Diuretic use before thoracentesis[b]	89 (73.6)
Estimated pleural fluid volume measured by Ultrasound, mL	
Right sided	600 (200-800)
Left sided	300 (145-750)
Side of thoracentesis	
Right sided	77 (63.6)
Left sided	44 (36.4)
Tube thoracostomy	
Yes	93 (76.9)
No	28 (23.1)
Complications	
No	116 (95.9)
Hemothorax	3 (2.5)
Pneumothorax or emphysema	2 (1.7)
Diagnosis of pleural effusion according to Light's criteria	
Transudate	30 (24.8)
Exudate	91 (75.2)
Positive pleural fluid microbiology	13 (10.7)
Acinetobacter baumannii	5 (4.1)
Klebsiella pneumoniae	3 (2.5)
Staphylococcus aureus	2 (1.7)
Pseudomonas aeruginosa	2 (1.7)
Burkholderia cepacia	1 (0.8)
Duration from hospitalization to thoracentesis, days	9.0 (2.0-22.5)
Duration from ICU admission to thoracentesis, days	2.0 (0.0-8.5)
Length of ICU stay, days	11.0 (6.0-22.5)
Length of hospital stay, days	26.0 (13.0-42.5)
ICU mortality	76 (62.8)
Hospital mortality	79 (65.3)

All values are expressed as numbers (percentages) or median (interquartile range).
APACHE II, Acute Physiology and Chronic Health Evaluation II; CCI, Charlson Comorbidity Index; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; IMV, invasive mechanical ventilation; SOFA Score, The Sequential Organ Failure Assessment Score.
[a]Calculated on the day of ICU admission.
[b]Includes patients using oral diuretics before hospital admission and patients receiving intravenous diuretics before thoracentesis at hospital follow-up.

of 8 patients died without a definitive diagnosis. Five of the 8 patients were clinically expected to be transudative, while the analysis resulted in exudative.

In 16.5% (n = 20) of all cases, blood pH was <7.20. In all cases, 26 (21.5%) patients had pleural fluid pH <7.2. In the culture-negative parapneumonic group, the proportion of patients with a pleural fluid pH <7.20 was 13.1% (n = 8), while the proportion of patients with a blood pH <7.20 was the same as 13.1% (n = 8). In the culture-positive parapneumonic group, the proportion of patients with a pleural fluid pH <7.20 was 53.8% (n = 7), while the proportion of patients with a blood pH <7.20 was 15.4% (n = 2). In the transudative pleural fluid group, 20.0% (n = 6) of patients had a pleural fluid pH <7.20. The proportion of patients with a blood pH <7.20 was 23.3% (n = 7) in this group. The comparison of pleural fluid pH levels across the groups is indicated in Figure 1. There was no statistically significant difference between the groups in terms of pH levels ($P = .079$).

Correlation between Blood pH and Pleural Fluid pH

There was a strong positive linear association between serum pH and pleural fluid pH ($R = 0.77$, $P < .001$; Figure 2).

Pleural Fluid Lactate Levels in Different Pleural Effusions

Comparisons of pleural fluid lactate and pleural fluid/serum lactate across the effusion groups depicted a statistically significant difference (in both, $P < .001$; Figure 3). The post hoc tests for pleural fluid lactate revealed there was a significant difference between culture-positive parapneumonic versus culture-negative parapneumonic groups ($P = .004$), culture-positive parapneumonic versus transudative

Table 2. Serum and Pleural Fluid Analysis Data Based on Pleural Effusion Type and Final Diagnosis

Characteristics	All Cases	Overall Parapneumonic	Culture-Negative Parapneumonic	Culture-Positive Parapneumonic	Malignant	Other Exudative*	Transudative
	(n = 121)	(n = 74)	(n = 61)	(n = 13)	(n = 9)	(n = 8)	(n = 30)
Serum							
LDH, U/L	314 (222-454)	319 (229-463)	315 (225-463)	353 (290-470)	507 (252-753)	304 (218-518)	251 (207-327)
Total protein, g/L	5.25 (4.81-5.83)	5.18 (4.84-5.87)	5.13 (4.83-5.92)	5.33 (4.98-5.86)	5.40 (4.32-6.45)	5.81 (4.70-6.72)	5.29 (4.78-5.66)
Albumin, g/L	2.48 (2.22-2.70)	2.52 (2.27-2.66)	2.53 (2.30-2.67)	2.39 (2.15-2.56)	2.28 (1.92-3.04)	2.67 (2.21-3.65)	2.41 (2.19-2.91)
Glucose, mg/dL	141 (114-194)	149 (112-196)	156 (116-207)	120 (100-151)	138 (123-186)	125 (89-146)	147 (118-202)
pH	7.37 (7.27-7.45)	7.38 (7.29-7.45)	7.38 (7.29-7.45)	7.38 (7.26-7.48)	7.25 (7.02-7.42)	7.39 (7.32-7.43)	7.36 (7.22-7.42)
pH <7.20	20 (16.5)	10 (13.5)	8 (13.1)	2 (15.4)	3 (33.3)	0 (0.0)	7 (23.3)
Lactate, mmol/L	1.80 (1.20-2.40)	1.60 (1.10-2.20)	1.60 (1.10-2.10)	1.90 (1.15-3.85)	3.30 (1.65-6.05)	2.30 (1.93-2.98)	1.55 (1.20-2.20)
Pleural fluid							
LDH, U/L	246 (111-473)	354 (216-662)	321 (202-579)	654 (317-4773)	298 (211-600)	228 (141-321)	92 (55-106)
LDH > 1000 U/L	14 (11.6)	12 (16.2)	6 (9.8)	6 (46.2)	1 (11.1)	1 (12.5)	0 (0.0)
Total protein, g/L	2.39 (1.65-3.24)	2.90 (2.00-3.30)	2.92 (2.00-3.35)	2.69 (2.36-3.25)	3.10 (1.68-4.50)	2.59 (2.23-3.98)	1.62 (1.38-2.02)
Albumin, g/L	1.23 (0.81-1.58)	1.39 (1.00-1.63)	1.39 (1.00-1.69)	1.33 (1.09-1.56)	1.64 (0.93-2.29)	1.47 (1.15-2.05)	0.79 (0.67-0.99)
Glucose, mg/dL	138 (105-182)	136 (102-183)	156 (120-192)	86 (12-118)	136 (92-148)	140 (98-174)	148 (112-188)
Glucose < 40 mg/dL	7 (5.8)	7 (9.5)	2 (3.3)	5 (38.5)	0 (0.0)	0 (0.0)	0 (0.0)
pH	7.33 (7.23-7.41)	7.33 (7.23-7.43)	7.34 (7.25-7.43)	7.16 (6.85-7.41)	7.19 (7.06-7.36)	7.36 (7.28-7.40)	7.35 (7.24-7.40)
pH <7.20	26 (21.5)	15 (20.3)	8 (13.1)	7 (53.8)	5 (55.6)	0 (0.0)	6 (20.0)
Lactate, mmol/L	2.40 (2.00-4.25)	2.95 (2.10-4.60)	2.40 (2.05-4.00)	10.10 (4.00-13.80)	4.10 (3.70-6.05)	3.20 (1.60-4.55)	1.60 (1.20-2.10)
Pleural fluid/ serum lactate, mmol/L	1.33 (1.00-2.35)	1.70 (1.14-3.04)	1.61 (1.10-2.57)	3.10 (1.57-8.15)	1.27 (0.89-1.80)	1.21 (0.70-2.67)	1.07 (0.88-1.25)

All values are expressed as numbers (percentages) or median (interquartile range).
*Three of 8 patients with exudative pleural fluid died without a definitive diagnosis. Although clinically transudative, 5 of 8 patients had exudative pleural effusion according to Light's criteria.
LDH, lactate dehydrogenase.

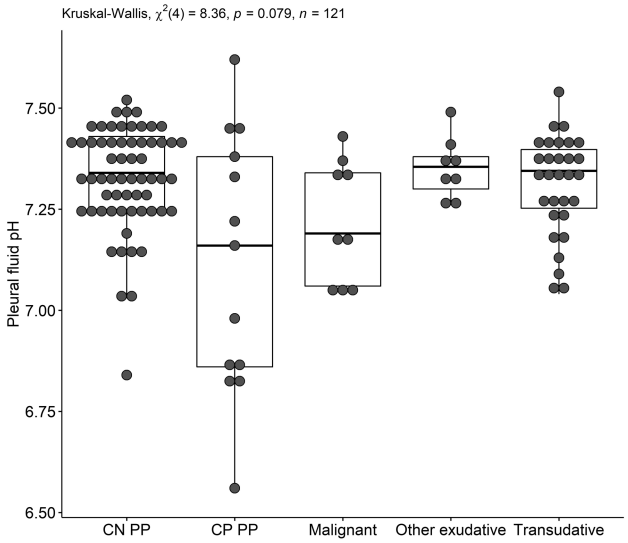


Figure 1. The comparison of pleural fluid pH levels between culture-negative parapneumonic (CN PP), culture-positive parapneumonic (CP PP), malignant, other exudative and transudative effusion groups.

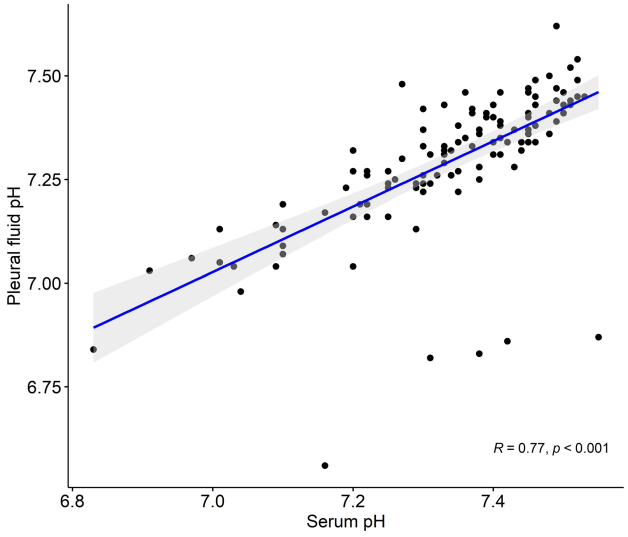


Figure 2. Correlation between blood pH and pleural fluid pH

effusion groups ($P < .001$), culture-negative parapneumonic versus transudative effusion groups ($P = .008$) and lastly; malignant effusion versus transudative effusion groups ($P = .001$). According to the post hoc tests for pleural fluid/serum lactate, comparisons between transudative effusion versus culture-positive parapneumonic groups ($P < .001$) and transudative effusion versus culture-negative parapneumonic groups ($P = .001$) were significant.

Receiver Operating Characteristic Curve Analysis

The ROC curve analysis for culture-positive parapneumonic indicated a cutoff of 4.55 mmol/L for pleural fluid lactate to have a sensitivity of 76.9% and a specificity of 84.3% (PPV: 37%, NPV: 96.8%; Table 3). The ROC analysis depicting the predictive value of the pleural fluid lactate for culture-positive parapneumonic effusions is shown in Figure 4. For the pleural fluid/serum lactate ratio, ROC curve analysis determined a 1.76 cutoff with 76.9% sensitivity and 72.2% specificity (PPV: 25%, NPV: 96.3%).

The Comparison of Pleural pH < 7.20 and Pleural Lactate > 4.55 in Patients with Culture-Positive and Culture-Negative Parapneumonic Pleural Effusions

The predictive rates of pleural pH <7.20 and pleural lactate >4.55 in patients with culture-positive and culture-negative parapneumonic pleural effusions were indicated in Table 4. In patients with blood pH <7.35 (n = 53), 5 patients were diagnosed as culture-positive parapneumonic, and 27 patients were diagnosed as culture-negative parapneumonic pleural effusions. In this population, 80.0% of patients with culture-positive parapneumonic pleural effusions and 29.6% of patients with culture-negative parapneumonic pleural effusions had a pleural pH <7.20 ($P = .053$). In the same population, 80.0% of patients with culture-positive parapneumonic pleural effusions and 14.8% of patients with culture-negative parapneumonic pleural effusions had a pleural lactate >4.55 ($P = .009$).

DISCUSSION

This prospective study evaluated the serum and pleural fluid biochemical results in critically ill patients with pleural effusion and has 3 important results. First, pleural fluid pH is strongly affected by systemic serum pH. Second, a pleural fluid pH <7.20 may not be a good predictor for complicated parapneumonic effusions in the critically ill population. Third, a cutoff of 4.55 mmol/L for pleural fluid lactate can be used to distinguish culture-positive parapneumonic effusions from other effusions.

In pleural effusion, the primary goal is to identify the underlying cause. Differentiating exudate from transudate is the

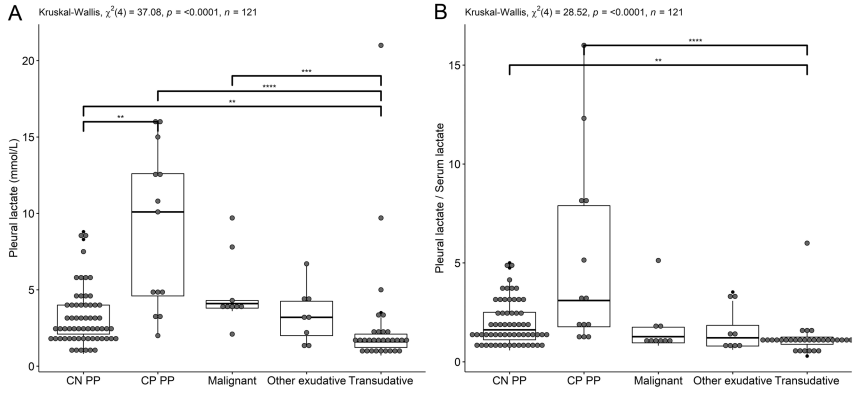


Figure 3. Pleural fluid lactate levels in different pleural effusions.

Table 3. ROC Curve Analyses of Pleural Lactate, Pleural/Serum Lactate, and Pleural pH for Culture-Positive Parapneumonic Effusion

	AUC (95% CI)	Cutoff	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
All patients, n = 121						
Pleural lactate, mmol/L	0.86 (0.74-0.97)	4.55	76.9	84.3	37.0	96.8
Pleural/serum lactate	0.81 (0.69-0.93)	1.76	76.9	72.2	25.0	96.3
Pleural pH	0.68 (0.46-0.89)*	7.01	46.2	99.1	85.7	93.9
Patients with blood pH ≥7.35, n = 68						
Pleural lactate, mmol/L	0.85 (0.68-1.00)	4.55	75.0	88.3	46.2	96.4
Pleural/serum lactate	0.83 (0.66-1.00)	3.09	75.0	85.0	40.0	96.2
Pleural pH	0.62 (0.32-0.93)*	7.24	50.0	100.0	100.0	94.0
Patients with blood pH <7.35, n = 53						
Pleural lactate, mmol/L	0.87 (0.71-1.00)	3.35	100.0	60.4	20.8	100.0
Pleural/serum lactate	0.79 (0.63-0.94)	1.32	100.0	58.3	20.0	100.0
Pleural pH	0.76 (0.41-1.00)*	7.01	60.0	97.9	75.0	95.9

*Not different from random chance.
AUC, area under the curve; NPV, negative predictive value; PPV, positive predictive value; ROC, receiver operating characteristic.

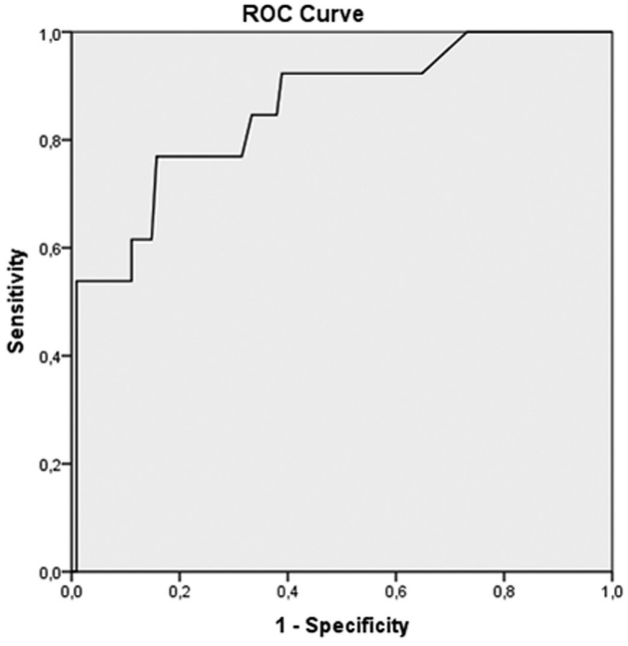


Figure 4. Receiver operating characteristic (ROC) analysis depicting the predictive value of the pleural fluid lactate for culture-positive parapneumonic effusions

first step, and Light's criteria have traditionally been used for this purpose.[11] Parapneumonic effusions are exudative effusions that can be detected in approximately 20% of hospitalized patients with pneumonia.[12] The prevalence of parapneumonic effusion increases when transthoracic ultrasonography is used.[13] The management of parapneumonic pleural effusions has gained more importance as it affects mortality in critically ill patients.[2,3] In the management of patients with parapneumonic pleural effusion, the primary decision is to drain the pleural space in addition to antibiotic therapy.[4,5]

An uncomplicated parapneumonic effusion is a sterile effusion that resolves with antibiotics alone.[14] On the other hand, frank pus in the pleural space (empyema) always requires chest tube drainage.[4,5] The main challenge is identifying patients whose fluids are not purulent but will eventually need drainage.[15] Pleural fluid pH <7.2 predicts a complicated clinical course, and this cutoff is used for the decision of the tube thoracostomy.[4,5] However, in the presence of pleural effusions, the pH of pleural fluid is affected by the pH of the blood.[9] In this study, we demonstrated that pleural fluid pH is affected by blood pH in critically ill populations. Since systemic acid-base disorders are common in critically ill patients,[10] pleural fluid pH <7.20 may not be a good indicator.

Pleural fluid lactic acid levels increase as a result of the increased metabolic activity of leukocytes and bacteria in the pleural fluid.[6] The use of increased lactate levels in detecting infectious pleural effusions has been investigated in various studies with conflicting results.[16-20] A small study of 57 patients with pleural effusions demonstrated that pleural fluid lactate elevation was not diagnostic for empyema.[16] Another study of 75 patients with pleural effusions showed that pleural fluid lactate can be used to distinguish bacterial

Table 4. Predictive Rates of Pleural pH <7.20 and Pleural Lactate >4.55 in Patients with Culture-Positive and Culture-Negative Parapneumonic Pleural Effusions

All Patients (n = 121)	**Culture-Positive Parapneumonic (n = 13)**	**Culture-Negative Parapneumonic (n = 61)**	***P***
Pleural pH <7.20	7 (53.8)	8 (13.1)	**.003**
Pleural lactate >4.55	10 (76.9)	10 (16.4)	**<.001**
Patients with Blood pH <7.35 (n = 53)	**Culture-Positive Parapneumonic (n = 5)**	**Culture-Negative Parapneumonic (n = 27)**	***P-***
Pleural pH <7.20	4 (80.0)	8 (29.6)	.053
Pleural lactate >4.55	4 (80.0)	4 (14.8)	**.009**
Patients with Blood pH ≥7.35 (n = 68)	**Culture-Positive Parapneumonic (n = 8)**	**Culture-Negative Parapneumonic (n = 34)**	***P***
Pleural pH <7.20	3 (37.5)	0 (0.0)	**.005**
Pleural lactate >4.55	6 (75.0)	6 (17.6)	**.004**

All values are expressed as numbers (percentages) or median (interquartile range). Bold values indicates statistical significance.

pleural inflammation from other types of pleural effusions, except malignant pleural effusions.[17] Two relatively large studies showed that lactate concentration can be used to distinguish infectious pleural effusions from other effusions.[18,19] In a recent study, pleural fluid lactate level was significantly elevated in complicated parapneumonic effusion compared with tuberculous pleural effusion.[20] Similar to the literature, we showed that pleural fluid lactate can be used to distinguish culture-positive parapneumonic effusions from other effusions. The population of our study consisted of critically ill patients and was different from these studies.[18-20] We think that the use of pleural fluid lactate to differentiate culture-positive parapneumonic effusions from other effusions is more valuable in critically ill patients as parapneumonic pleural effusions affect mortality, and a quick diagnosis and treatment are essential.[2,3]

This study has several limitations. The management of parapneumonic pleural effusions may be challenging in the ICU setting. There may be a delay in getting routine microscopy and culture results. Additionally, patients may already be on antimicrobial therapy, and cultures may result in a false negative. Measurement of pH may not guide the decision for tube thoracostomy. In these circumstances, lactate can be used as a quick and reliable aid for decisions. However, our results do not allow the clinician to use lactate as the only criterion for complicated parapneumonic effusions.

However, this study has strengths. We used culture-positive ones that more accurately demonstrate complicated parapneumonic pleural effusions, as pleural fluid cultures may give false-negative results.[21]

CONCLUSION

Pleural fluid pH is affected by blood pH in critically ill patients. Pleural fluid lactate levels can be measured quickly and easily in modern ICUs using blood gas analyzers. A cut-off of 4.55 mmol/L of pleural fluid lactate can be used as a useful tool to distinguish culture-positive parapneumonic effusions from other effusions. In addition to clinical, laboratory, and radiological assessment, lactate measurements can be particularly valuable in guiding early treatment.

Ethics Committee Approval: This study was approved by Ethics Committee of Dokuz Eylül University (approval No: 2020/16-07, date: July 13, 2020).

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – B.ERGÜN, M.K., M.N.Y., M.C.Ö., V.H., B.C., A.N.G., B.ERGAN; Design – B.ERGÜN, M.C.Ö., V.B., A.N.E., V.H., B.C., A.N.G., B.ERGAN; Supervision – B.ERGÜN, V.B., V.H., B.ERGAN; Data Collection and/or Processing – B.ERGÜN, M.K., M.N.Y., V.B.; Analysis and/or Interpretation – B.ERGÜN, M.K., M.N.Y., M.C.Ö., A.N.E., B.ERGAN; Literature Review – B.ERGÜN, M.N.Y., B.C., A.N.G.; Writing – B.ERGÜN, M.K., M.N.Y., M.C.Ö., V.B., A.N.E., V.H., B.ERGAN; Critical Review – B.ERGÜN, A.N.E., B.C., A.N.G., B.ERGAN.

Declaration of Interests: The authors have no conflict of interest to declare.

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Original Article

Correlation Between Daily PM_{10}, Nitrogen Dioxide, and Ozone Measurements with the Stringency Index in 15 Different Districts of a Big Metropolis

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Abstract

OBJECTIVE: Studies have investigated the effects of lockdowns on air quality around the world and found that fine particulate matter and nitrogen dioxide concentrations decreased due to reduced human activity, while ozone concentrations increased. In this study, we aimed to evaluate the correlation between daily stringency index values of our country and daily PM_{10}, nitrogen dioxide, and ozone measurements in different districts of Istanbul between March 1, 2020, and February 28, 2022.

MATERIAL AND METHODS: Ministry of Environment and Urbanization and National Air Quality Monitoring Network data on Istanbul air quality monitoring stations were used. The analysis included 15 stations that can monitor at least 75% of the days in a year. PM_{10}, nitrogen dioxide, and ozone were the main pollutants analyzed.

RESULTS: There was negative correlation between daily PM_{10} measurements and daily stringency index values in 3 stations; there was positive correlation in 6 stations. Between daily stringency index values and daily nitrogen dioxide measurements, there was a negative correlation in 3 stations and a positive correlation in 1 station. The daily measurements of 1 station showed a negative correlation with the daily values of stringency index for both PM_{10} and nitrogen dioxide. In 1 station, while PM_{10} measures were negatively correlated with stringency index, nitrogen dioxide measurements were positively correlated.

CONCLUSION: This study showed that pandemic limitations could not improve Istanbul's air quality everywhere. For adequate evaluation of impact of the limitations on air quality, it may be more relevant to study the socioeconomic infrastructure of each living area, the sociospatial inequality, industrial employment, the number of households, the density of employee class, and so on with all influencing factors that could have contributed to these various changes.

KEYWORDS: COVID-19, air pollution, stringency index, PM10, NO2, O3
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INTRODUCTION

On December 31, 2019, the Central Hubei Province in China's Wuhan region verified the finding of a novel coronavirus.[1,2] The novel coronavirus was given the name severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by the World Health Organization, and it was categorized as a new group within the family coronaviridae.[3] World Health Organization issued an official declaration on March 11, 2020, declaring the novel coronavirus [coronavirus disease 2019 (COVID-19)] outbreak a global pandemic.[4] This day coincided with the declaration by Turkey that it had identified its first case of COVID-19.

The lockdown measures implemented to prevent the spread of SARS-CoV-2 have significantly impacted human activities such as automobile use, public transportation, and economic activity.[5,6] In relation to this, the restrictions have improved air quality due to fewer human activities.[7,8] Since more than 55% of the global population lives in industrialized areas,[9] industrial air pollution is also a global threat in addition to transportation, heating, and other human activities.[5,10,11] Pollution-related illnesses caused approximately 9 million premature deaths, globally, in 2019, and 6.7 million of these deaths were related to outdoor and indoor air pollution.[12]

Air pollution is defined as "the contamination of the indoor or outdoor environment by any chemical, physical, or biological substance that alters the inherent qualities of the atmosphere. Particulate matter (PM), carbon monoxide, ozone (O_3), nitrogen dioxide (NO_2), and sulfur dioxide (SO_2) are the pollutants having the most evidence of endangering public health."[13,14] Particulate matter denotes inhalable particles made up of sulfate, nitrates, ammonium, sodium chloride, black carbon, mineral dust, or water. PM_{10} and $PM_{2.5}$ are related to well-known health hazards.[15] Both long-term and short-term exposures to PM are connected with cardiovascular and respiratory disease morbidity and mortality. Nitrogen dioxide

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is a key precursor of O_3, a pollutant closely associated with asthma and other respiratory problems. The primary source of NO_2 emissions into the atmosphere is the combustion of fuels for a variety of reasons, including but not limited to heating, transportation, and electricity generation.[13-15]

Many current studies have evaluated the effects of lockdown measures on air quality across the globe and showed that fine PM and NO_2 concentrations generally decreased during lockdowns.[16-18] The majority of studies found decreased background concentrations of pollutants and improved air quality indices during lockdowns, particularly for NO_2 because of its impact on reducing traffic movement.[16,18] In a study from our country, the effect of the lockdown on the air quality in Turkey from December 2019 to May 2020 was studied. $PM_{2.5}$ had a maximum reduction in most cities, while O_3 levels increased in most cities, including İstanbul.[19] The impact of COVID-19 measures on air pollutant concentrations measured in urban areas and traffic monitoring stations on both the European and Asian sides of İstanbul in March 2020 was analyzed in another study from our nation. Reductions of pollutants were estimated to range from 33% to 43% for PM_{10} and from 29% to 44% for NO_2. Nitrogen dioxide, which is mostly caused by vehicle emissions, decreased the greatest at the traffic monitoring sites.[20] Also, Aykaç et al[21] discovered that there were decreases of 33.4%, 59.6%, and 52.6% in the average concentrations of PM, NO_2, and O_3, respectively, in Istanbul during lockdowns between April 23 and 26, May 1 and 3, and May 23 and 26, in 2020; however, according to the findings of this study, there were significant variations in the rate of change of air quality among Istanbul districts. Aydın et al[19] found that O_3 levels were higher in April and May 2020 than 2019 in Istanbul. In this recent study, we tried to explore the correlations between pandemic restrictions and the change in air quality in accordance with the different areas of İstanbul in order to gain additional knowledge that would enable us to comment on these disparities.

MAIN POINTS

- Many studies have examined the effects of the pandemic on air quality and demonstrated that particulate matter (PM) and nitrogen dioxide (NO2) concentrations generally decrease during the pandemic, but we found in this study that there was no negative correlation between Stringency Index values and daily PM10 and NO2 measurements in some districts of İstanbul.
- Pandemic restrictions would not be able to achieve the same levels of success in reducing air pollution across all of the districts in a big metropol (like İstanbul).
- For adequate evaluation of impact of the limitations on air quality it may be more relevant to study the socio-economic infrastructure of each living area, socio-spatial inequality, industrial employment, the number of households, the density of employee class etc. with all influencing factors that could have contributed to these various changes.
- Only 15 of İstanbul's 39 stations met the criteria necessary to be declared genuine for this study. This is due to the fact that not all the stations could measure air pollution in accordance with the qualification definition of the European Environment Agency (the minimum percentage of days in a year that each station may monitor should be 75%).
- Studies monitoring pollutant concentrations with an increasing number of stations that are representative of the population everywhere need to be carried out.

There are several difficulties when assessing the impact of pandemic restrictions on air quality. One of them is the evaluation framework of restrictions. Gkatzelis et al[22] and Schneider et al[23] utilized the stringency index (SI) to examine the relationships between restrictive measures and air pollution. The SI is an indicator that identifies the stringency of government policies, considering the restrictive measures of the pandemic. They discovered substantial negative associations between the SI and variations in pollutant concentration, particularly that of NO_2. In this study, we aimed to evaluate the correlation between daily SI values of our country and daily PM_{10}, NO_2, and O_3 measurements at different stations in different districts of Istanbul between March 1, 2020, and February 28, 2022.

MATERIAL AND METHODS

Study Area

İstanbul is the most populated metropolitan in Turkey and serves as the center of the country's economy as well as its culture and history. Over 15 million people call the city home, making up 19% of Turkey's total population. With a total land area of 5712 km^2, the city is located on both the European and Asian sides of the Bosporus Strait. İstanbul has the highest population of any city in Europe and is the 15th largest metropolis in the world.[24]

The metropolis, which connects Europe and Asia and has a 647-km coastline, is the most commercially and consequential city in Turkey, with 2 airports, 1796 historical sites, 712 hotels, 57 universities, and 36 libraries. İstanbul, the main city in terms of trade, business, investment, banking, and tourism in Turkey, is home to 20.3% of the country's workforce, 50.6% of exports, and 54.6% of imports.[25]

There are 39 districts (962 neighborhoods) in Istanbul, and they each have their own unique demographic characteristics. Esenyurt, Küçükçekmece, and Bağcılar are the 3 districts in İstanbul that have the highest populations. The population of Esenyurt increased between 2017 and 2018, making it the district with the biggest population growth. The districts of Istanbul are shown in Figure 1, and the districts that have been dyed red are those that had the air quality station included in the study.

Air Pollution Data

In this cross-sectional study, publicly available data from the Ministry of Environment and Urbanization and the National Air Quality Monitoring Network[26] on air quality monitoring stations in the province of İstanbul were utilized. In accordance with the qualification definition of the European Environment Agency, the study included only those Istanbul stations whose percentage of the number of days they can monitor in a year was at least 75%. During the study period, 15 stations with this feature were included in the study. Each was assigned a number for this study. Two stations numbered

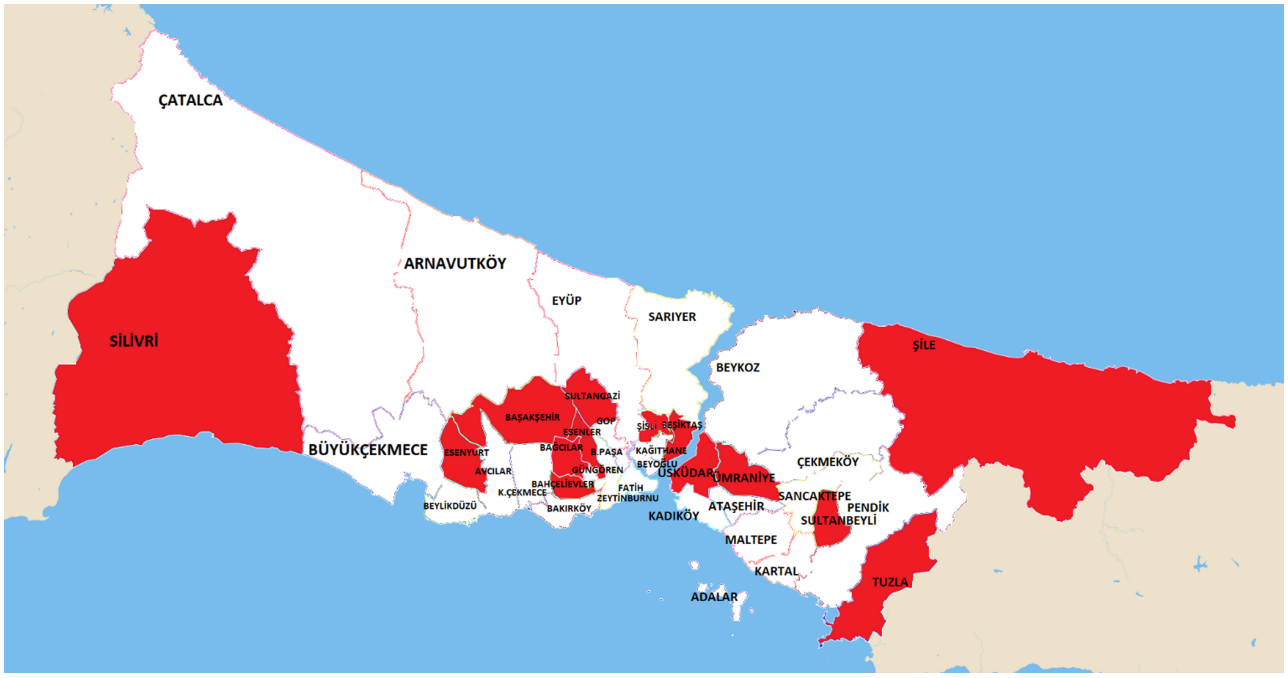


Figure 1. The districts of İstanbul (areas that have been dyed red are those that had air quality station included in the study).

11 and 15 were located in the same district (Bahçelievler). Table 1, shown in the "Results" section, displays the districts where the stations were located. Among the pollutants available from the database, PM_{10}, NO_2, and O_3 compounds were studied as the main pollutants. The daily data for these 2 compounds for the period between March 1, 2020, and February 28, 2022, were included in the correlation analysis.

Restriction Data

To analyze the correlation between the sociopolitical efforts taken to prevent pandemic transmission and the changes in air quality in Istanbul, the SI was utilized to reflect the change in preventative measures. It is crucial to note that this index just gauges the rigor of government regulations. It neither quantifies nor suggests the sufficiency or effectiveness of a nation's response. A higher score does not imply that a country's response is superior to the response of those with lower scores. The Oxford COVID-19 Government Response Tracker (OxCGRT) project computes the SI as "a weighted average of nine response criteria: school closures, workplace closures, cancellation of public events, restrictions on public gatherings, closures of public transportation, stay-at-home requirements, public information campaigns, internal movement restrictions, and international travel controls."[27,28]

The index is calculated on any given day as the mean score of 9 measures, each of which has a value between 0 and 100. A higher grade indicates stricter regulations. This implies that the value of the SI system increases when more measures are added. Stringency index is shared publicly on the website.[27,28] Stringency index values for Turkey between March 1, 2020, and February 28, 2022, were included in the correlation analysis as daily data.

Other Data

Population, surface area (km^2), and population density data of each district were reported besides SI and air pollution data. Also, the neighborhoods where the stations were located were categorized as trafficked areas, industrial areas, urban residential areas, and urban background areas. The stations in urban background areas monitor background concentrations of air polluting chemicals in a region for particularly long-term changes in atmospheric composition.[29] All these data were obtained from İstanbul Metropolitan Municipality, Governorship of İstanbul, and Turkish Statistical Institute websites.[30]

Statistical Analysis

Using IBM Statistical Package for the Social Sciences 28.0's (IBM Corp.; Armonk, NY, USA) Spearman correlation analysis, the correlation between daily SI data and daily pollutant (PM_{10}, NO_2, and O_3) measurements in different areas of Istanbul was analyzed. Any score from 0 to −1 indicates a negative correlation, which means that as one variable increases, the other decreases proportionally, and any score from 0 to +1 indicates a positive correlation, which means that they both increase at the same time, while the *P* was <.05.

Ethical Consideration

There was no need to get approval from an ethics committee for this study because it used publicly available data from the National Weather Monitoring Network run by the Ministry of Environment and Urbanization, and no special precautions were taken to protect individuals or communities that might be vulnerable.

RESULTS

There are 39 stations in İstanbul that measure the pollutants in the air. However, only 15 of those stations may be considered valid for this study because the percentage of days they can monitor in a year is at least 75%. Therefore, these findings are representative of 38.4% of the stations in İstanbul. Comparing the population of İstanbul to that of the districts in which the stations involved in this research were located, we find that the relevant population accounts for 42.4% of the

Table 1. The Characteristics and Demographical Properties of the Districts and Neighborhoods Where the Valid Stations for the Study Were Located

Number Assigned to the Stations for the Study	Name of the District Where the Station Is Placed	Area of the District (km^2)	Population of the District	Name of Neighborhood of the Station	Characteristics of the Neighborhood*	Population of the Neighborhood Where the Station Is Located	The area of the Neighborhood Where the Station Is Located (km^2)
1	Bağcılar	22.27	777 561	Kirazlı	Trafficked area	41 823	0.941
2	Başakşehir	104.49	481 900	Başakşehir	Urban residential area and industrial area	71 609	8.129
3	Beşiktaş	17.83	170 894	Yıldız	Urban background area	6552	1.119
4	Esenler	18.42	476 568	Yavuz Selim	Trafficked area	5482	0.241
5	Esenyurt	43.13	983 557	Mehterçeşme	Urban residential area	37 848	0.609
6	Şişli	10.72	261 595	Merkez	Trafficked area	13 738	1.131
7	Silivri	869.37	175 431	Alibey	Urban residential area	18 175	0.642
8	Sultanbeyli	29.10	361 702	Battalgazi	Urban residential area	36 341	3.131
9	Sultangazi	35.71	570 868	Uğur Mumcu	Trafficked area, urban residential area	41 937	1.433
10	Şile	781.72	37 290	Meşrutiyet	Urban background area	1909	3.243
11	Bahçelievler	16.59	596 374	Zafer	Trafficked area	86 758	1.085
12	Tuzla	124.51	269 798	Evliya Çelebi	Urban residential area	13 487	3.250
13	Ümraniye	45.38	711 395	Yukarı Dudullu	Trafficked area	21 532	1.786
14	Üsküdar	35.33	515 363	Selami Ali	Urban background area	13 286	0.447
15	Bahçelievler	16.59	596 374	Çobançeşme	Trafficked area	34 117	1.269
		Total = 2171.16	Total = 6 986 670			Total = 444 594	Total = 28.456

*Characteristics of the districts and neighborhoods were grouped as trafficked area, urban residential area, industrial area, and urban background area.

city's total population. The neighborhood population where the station was located accounted for 7% of the total population of the districts included in the study. The total area of the neighborhoods where the valid stations for the study were located accounted for 1.3% of the total area of the districts included in the study (Table 1).

Figure 2 depicts the trend of the SI for Turkey from January 2020 to March 2022, as a component of the OxCGRT project. Stringency index values for Turkey between March 1, 2020, and February 28, 2022, were included in the correlation analysis as daily data.

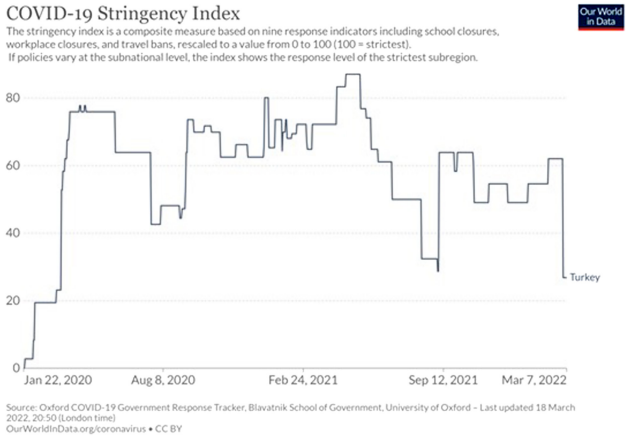


Figure 2. The trend of the stringency index (SI) for Turkey from January 2020 to March 2022, as a component of the Oxford COVID-19 Government Response Tracker (OxCGRT) project.

Table 2 displays averages of daily PM_{10}, NO_2, and O_3 measurements for 15 stations in Istanbul for the study period (March 1, 2020-February 28, 2022) and also during the first and second years of the pandemic separately; it also displays the data for PM_{10}, NO_2, and O_3 levels between March 1, 2018, and 29 February 2020, as a historical reference.

The result of the correlation analysis between daily SI values and daily PM_{10} and NO_2 measurements of these 15 stations in Istanbul between March 1, 2020, and February 28, 2022, is shown in Table 3. While there was a negative correlation between daily PM_{10} measurements and daily SI values in 3 of 15 stations (station numbers: 3, 5, and 9), there was a positive correlation between daily PM_{10} measurements and SI measurements in 6 stations (station numbers: 1, 7, 10, 12, 14, and 15). Evaluating the correlation between daily SI values and daily NO_2 measurements of stations, again for 3 stations but 2 different stations this time (station numbers: 2, 5, and 13), there was a negative correlation. But in 1 station (station number: 9), there was a positive correlation. The daily measurements of only 1 station (station number: 5) showed a negative correlation with the daily values of SI for both PM_{10} and NO_2. In 1 station

Table 2. Averages of Daily PM_{10}, NO_2, and Ozone Measurements for 15 Stations in Istanbul for the Study Period (March 1, 2020-February 28, 2022) and Also During the First and Second Years of the Pandemic

		Historical Reference March 1, 2018-29 February, 2020			During the First Year of the Pandemic *March 1, 2020-February 28, 2021			During the Second Year of the Pandemic **March 1, 2021-February 28, 2022			During the study period ***March 1, 2020-February 28, 2022		
Number Assigned to the Stations for the Study	Name of Districts Where the Stations Were Located	PM_{10} Median (Minimum–Maximum) ($\mu g/m^3$)	NO_2 Median (Minimum–Maximum) ($\mu g/m^3$)	Ozone Median (Minimum–Maximum) ($\mu g/m^3$)	PM_{10} Median (Minimum–Maximum) ($\mu g/m^3$)	NO_2 Median (Minimum–Maximum) ($\mu g/m^3$)	Ozone Median (Minimum–Maximum) ($\mu g/m^3$)	PM_{10} Median (Minimum–Maximum) ($\mu g/m^3$)	NO_2 Median (Minimum–Maximum) ($\mu g/m^3$)	Ozone Median (Minimum–Maximum) ($\mu g/m^3$)	PM_{10} Median (Minimum–Maximum) ($\mu g/m^3$)	NO_2 Median (Minimum–Maximum) ($\mu g/m^3$)	Ozone Median (Minimum–Maximum) ($\mu g/m^3$)
1	Bağcilar	—	—	—	34.1 (10.1-157.7)	35.8 (6-125)	38.2 (4.2-88.9)	30.8 (8.2-119.7)	42.0 (10-111)	37.6 (8.4-72.8)	32.5 (8.2-157.7)	39.3 (6-125)	37.7 (4.3-88.9)
2	Başakşehir	47.6 (7.2-204.2)	25 (4.1-110.4)	57.5 (3.14-110.6)	34.9 (6-163)	6.5 (1-58)	72.1 (16.7-119.8)	37.4 (8.6-127.5)	28.5 (8-90)	71.3 (12.8-129.9)	36.3 (6-163)	16.5 (1-90)	71.8 (12.8-129.8)
3	Beşiktaş	—	—	—	23.3 (4-82)	54.3 (9-137)	19.0 (1.2-146.9)	29.7 (8-86)	35.2 (10-62)	6.3 (1-108)	26.7 (4-86)	40.8 (9-137)	12.6 (1-146.4)
4	Esenler	—	—	—	28.8 (4.9-313.7)	53.3 (10-178)	—	28.7 (6.8-125.2)	49.5 (11-114)	—	28.8 (4.9-313.7)	51.7 (10-178)	—
5	Esenyurt	61.8 (18.2-228.5)	27.8 (7.3-78.3)	30.4 (1.5)-97.6	45.4 (20.6-174.2)	11.3 (2-33)	22.6 (5.2-52.8)	54.3 (21.5-161.1)	23.7 (1-70)	32.9 (3.6-100.3)	49.0 (20.6-174.2)	14.0 (1-70)	27.6 (3.6-100.3)
6	Mecidiyeköy	60.5 (17.9-178)	65.4 (24.5-131.9)	—	46.2 (10-184)	46.0 (15.1-106.8)	—	47.9 (20-128)	47.5 (13.1-113.6)	—	47.1 (10-184)	46.8 (13.1-113.6)	—
7	Silivri	29.4 (4.8-124.6)	22.1 (5.1-62.9)	61.7 (7.1-133.2)	23.8 (5.8-154.7)	14.3 (3.8-53.3)	66.5 (10.6-108.3)	29.2 (6.6-88.1)	16.2 (2.6-42.8)	55.2 (9.5-106.5)	26.8 (5.8-154.7)	15.3 (2.6-53.3)	61.7 (9.5-125.7)
8	Sultanbeyli	—	12.4 (1.3-60.26)	59.1 (6.7-121.6)	26.0 (5.1-130.7)	19.1 (1-176)	59.0 (3.3-106.4)	27.3 (7.5-138.7)	19.3 (2-65)	57.9 (9-106.5)	26.8 (5.1-138.7)	19.2 (1-176)	58.2 (3.3.-106.5)
9	Sultangazi	—	35.3 (8.1-100.7)	38.6 (0.5-98.5)	70.7 (8.1-162.3)	43.9 (16.9-275.8)	31.2 (7.6-103.6)	49.4 (11.3-105.2)	29.2 (9.3-98.4)	49.6 (8.4-120.5)	49.7 (8.1-162.3)	38.2 (9.3-275.8)	39.4 (7.6-120.5)
10	Şile	24.7 (6.1-116.4)	4.2 (0.1-31.6)	75.5 (18.6-129.2)	23.3 (7.7-90.3)	2.0 (0.1-20.9)	75.8 (22.3-118.2)	23.9 (9.6-86.6)	3.5 (0.6-24.7)	66.8 (19.8-97.7)	23.6 (7.7-90.3)	2.8 (0.1-24.7)	71.2 (19.8-118.3)
11	Şirinevler	46 (14.8-171.8)	67.5 (20.1-184.8)	—	38.2 (15.4-130.4)	46.4 (12.3-142.4)	—	37.2 (16.2-99.6)	46.4 (12.6-109.7)	—	37.6 (15.4-130.4)	46.4 (12.3-142.4)	—
12	Tuzla	—	—	—	33.9 (10-162)	36.9 (14-110)	25.9 (3-71)	34.5 (7-107)	45.2 (15-91)	33.4 (2.28-69.1)	34.1 (7-162)	41.7 (14-110)	31.2 (2.3-71.0)
13	Ümraniye	—	—	—	30.1 (6.5-127.9)	41.6 (14-86)	11.8 (8-62.8)	38.7 (12.3-126.3)	59.7 (15-104)	25.5 (3.8-80.1)	34.6 (6.5-127.9)	46.7 (14-104)	20.9 (3.8-80.1)
14	Üsküdar	—	—	—	25.0 (6.5-115.4)	31.9 (6-104)	—	22.9 (6.5-79.4)	40.0 (9-89)	—	23.9 (6.5-115.4)	37.2 (6-104)	—
15	Yenibosna	—	—	—	30.9 (2-173)	38.4 (9.2-132.4)	—	27.8 (3-129)	46.8 (8.0-134.9	—	29.1 (2-173)	43.5 (8.0-134.9)	—

NO_2, nitrogen dioxide; O_3, ozone; PM, particulate matter.

Table 3. The Result of the Correlation Analysis Between Daily PM_{10} and NO_2 Measurements and Daily Stringency Index Values of the Selected Stations in Istanbul Between March 1, 2020, and February 28, 2022

Number of Stations	Name of Districts Where the Stations Were Located	PM_{10} Correlation *r*	NO_2 Correlation *r*	O_3 Correlation *r*
1	Bağcılar	0.09*	−0.02	−0.16*
2	Başakşehir	0.06	−0.09*	0.007
3	Beşiktaş	−0.08*	0.003	0.27*
4	Esenler	−0.009	−0.03	—
5	Esenyurt	−0.09*	−0.5*	−0.31*
6	Mecidiyeköy	0.04	−0.02	—
7	Silivri	0.13*	0.01	0.08*
8	Sultanbeyli	0.02	−0.43	0.008
9	Sultangazi	−0.10*	0.35*	0.29*
10	Şile	0.11*	0.008	0.17*
11	Şirinevler	0.03	0.03	—
12	Tuzla	0.12*	0.002	−0.01
13	Ümraniye	−0.2	−0.49*	−0.18*
14	Üsküdar	0.15*	0.03	—
15	Yenibosna	0.15*	−0.06	—

PM, particulate matter; NO_2, nitrogen dioxide.
*Spearman correlation analysis $P < .05$.

(station number: 9), while the daily measurements of PM_{10} were correlated negatively with the daily values of SI, the daily measurements of NO_2 were correlated positively with the daily values of SI.

Evaluating the correlation between daily SI values and daily O_3 measurements of stations, for 3 stations (station numbers: 1, 5, and 13) there was a negative correlation, while for 4 stations (station numbers: 3, 7, 9, and 10) there was a positive correlation.

DISCUSSION

It is evident that the COVID-19-related lockdown has led to a significant drop in pollution levels, hence improving air quality across the majority of the world. Although many studies have examined the effects of the pandemic on air quality and demonstrated that PM and NO_2 concentrations generally decrease during the pandemic, we found in this study that there was no negative correlation between SI values and daily PM_{10} and NO_2 measurements in some districts of Istanbul. In addition, despite the pandemic restrictions, there was a positive correlation in some districts, indicating the increase of these pollutants. There may be several potential explanations for the results despite the lack of a proper approach to analyzing the causes in this study.

When a policy is enacted, the compliance of citizens is crucial, and there can be significant variation in its implementation. As the reason for our results differed according to the districts of Istanbul, implementation of pandemic restrictions may vary within Istanbul districts. El-Sayed et al[31] interpreted in their study that the stay-home orders were stricter in Miami as opposed to Orlando, hence the stronger reductions in levels of pollutants observed in Miami. In addition, the timing of restrictions, the method in which restrictions are applied, meteorological circumstances, and especially the physical characteristics of the districts, all may influence the effectiveness of air quality improvement. Lu et al[32] observed that the short-term emission control effect of lockdown ranged between 53.0% and 98.3% for all cities included in their study; however, the effect is much greater in southern cities than in northern cities ($P < .01$), while small and medium cities have a similar influence on NO_2 and SO_2 as megacities but a greater effect on $PM_{2.5}$ and PM_{10}. In a study from Myanmar, the researchers showed that during the COVID-19 pandemic, while restricting measures were in effect, the city's PM-related air quality improved from "unhealthy" to "good." However, the percent changes in PM concentrations varied among the 3 study sites, with the highest percent reduction in a semicommercial crowded area (84.8% for $PM_{2.5}$ and 88.6% for PM_{10}) and the lowest percent reduction in a residential quiet area (15.6% for $PM_{2.5}$ and 12.0% for PM_{10}). The percent reductions also varied among the different times during the COVID-19 pandemic that measurements were made.[33] In our study, the varying directions (positive or negative) of correlation between SI and daily measurements of PM_{10} and NO_2 in various districts were interpreted particularly as a result of district/neighborhood characteristics and variations in the enforcement of restrictions.

When describing the changes in PM concentrations during the COVID-19 pandemic, some studies have additionally accounted for seasonal variations. In the study described by Hashim et al,[5] the researchers compared the average PM concentrations in Baghdad, Iraq, throughout 5 time periods: the first period prior to the implementation of a lockdown and

the remaining 4 periods during a partial or complete lockdown. The concentrations of $PM_{2.5}$ and PM_{10} were found to be the lowest during the initial partial and total lockdowns compared to the other 4 periods. They hypothesized the following possible explanations for this result: the citizens' compliance with the lockdown measures during the first lockdown period contributed to the large decline of PM concentrations during that period, and the dry, hot climate during the summer led to the relative increase of PM concentrations in the subsequent lockdown periods. Chen et al[34] noted that other meteorological factors, such as the ambient temperature, relative humidity, wind speeds, precipitation, radiation, and ambient pressure, could also exert an influence on the ambient PM concentrations. We lacked data regarding meteorological parameters and seasonal variations, which was one of the limitations of our study. In actuality, the entire 2-year pandemic period was included in the evaluation of the correlation analysis for the study, as we hypothesized that this may reduce the shadowing effects of short-term factors such as seasonal and meteorological differences and the restriction and liberalization periods and permit evaluation over a longer period.

Lange et al[35] conducted a study in Pittsburgh, which, because of its industrial heritage and current sources of PM, provides a unique setting for assessing changes in air pollution during COVID-19 lockdowns. This study evaluated the premise that air pollution in Pittsburgh reduced during the lockdown—specifically, that NO_2 decreased greatly due to the decrease in traffic, whereas $PM_{2.5}$ did not fall or decreased very little due to the assumed continuation of industrial activity. Their study indicates that industrial sources contribute more PM to the atmosphere. In our study, there was a negative correlation between daily PM_{10} measurements and daily SI values in 3 of 15 stations (station numbers: 1, 5, and 9) located in 3 neighborhoods that were grouped as urban residential or urban background areas. Only 1 station's daily measurements (in the district of Esenyurt) demonstrated a negative correlation with the daily values of SI for both PM_{10} and NO_2. The Esenyurt district has a land area of 43.13 km^2 and a population of 983 557 people, and the station is located in the district's second most populous section. The pandemic limitations appear to have been useful in this area for improving air quality. On the other side, there was a positive correlation between daily PM_{10} measurements and SI measurements at 6 stations (station numbers: 1, 7, 10, 12, 14 and 15) located in the urban residential or urban background neighborhoods. Despite the restrictions, the increase in PM_{10} was a significant issue that required discussion with other affecting factors, such as the continuing industrial activity and others. The range of dates that we analyzed in our study (March 1, 2020-February 28, 2022) is extensive, and during this entire time period, the restrictions in Istanbul did not always include all aspects of society. In the study of Aykaç and Elbek,[36] it has been shown that especially at the beginning of the pandemic, the lockdown did not cover blue-collar workers. Continual population mobility and density during the pandemic in industrially populated districts such as Bağcılar, Bahçelievler, Esenler, Esenyurt, Sultangazi, and Tuzla have the potential to generate air pollution.[37] It may be possible to fully evaluate the impact of the SI reported for Turkey on the air quality in different living areas by assessing the socioeconomic infrastructure of each living area, the sociospatial inequality, industrial employment, the number of households, the employee class, and so on.

In some periods of pandemic, blue-collar workers were ordered to keep working. Their travel to the industrial zone from their residences made it harder to manage the pandemic and this contributed to the air pollution in these places. Consequently, examining districtional disparities and revealing the SI for each district could provide a more comprehensive view of the changes in air quality due to the pandemic restrictions.

Li et al[38] showed that the COVID-19 containment and closure policies did not significantly reduce NO_2 tropospheric NO_2 vertical column density (TVCD) in the mild or moderate clusters, but they did so in the poor cluster. They utilized the SI for monitoring pandemic restrictions like in our study and demonstrated that specifically, a rise of 1 SD (23.58) in the SI is associated with a drop of 3.2% NO_2 TVCD in the poor cluster (coefficient = −0.033, $P < .05$). In other words, these estimations imply that the most strict containment and closure policies (index score of 100) would reduce NO_2 TVCD by a maximum of 13.1%.[38] In the study of El-Sayed et al,[31] they found that differences observed in NO_2 between cities were likely due to the population differences among cities, leading to differences in mobile emissions. Dobson and Semple[39] showed that during the 2020 lockdown period, due to the effect of decreasing car journeys in Scotland, NO_2 values were considerably lower than those in the preceding 3 years. In Chen et al[40] study, they investigated the changes in private vehicle restriction policies and their impact on air pollution before and after the outbreak of COVID-19 using daily data from August 1, 2019, to February 7, 2020. They discovered that private car restrictions are a viable strategy for improving air quality. However, its impact is contingent on the city's economic development features. Various categories of the restriction (restrictions for private cars on traffic, distant working, distant education and total lockdown periods, etc.) may have different effects. Likewise, Gkatzelis et al[22] stated in a worldwide analysis that NO_2 level decreases were due to the stringency of lockdown measures. In our analysis, 3 stations (station numbers: 2, 5, and 13) exhibited a negative correlation between SI daily values and NO_2 levels. In particular, station number 13 was located in a densely trafficked area, and it appeared that the pandemic period improved NO_2 air quality in this region.

Although some criteria pollutants,[41] such as PM and NOx, decreased during closure periods, O_3 levels increased. In this respect, O_3 may be viewed as an exceptional pollutant in terms of COVID-19 measures and the relationship between air pollution and COVID-19. In our study, O_3 levels were measured at 10 of 15 stations, and in 4 of those stations, daily O_3 levels were positively correlated with SI values, whereas in 3 stations, the correlation coefficient was negative. Ozone has a complex structure and is a secondary pollutant. The levels of its precursors NOx and volatile organic compounds (VOCs) are crucial for O_3 formation. Due to the dependence

of O_3 levels on these precursors and photochemical reaction, levels of NOx and VCs and sunlight are O_3 level drivers.[19]

As an important matter, recent studies on COVID-19 in different countries have examined that improving air quality has been a component of reducing the risk of COVID-19 infection,[42] and geographical patterns of COVID-19 transmission and mortality among countries are linked with local levels of pollutants.[43-45] In their research, Baniasad et al[46] aimed to shed light on the COVID-19 pandemic and determine the relationship between the COVID-19 transmission rate, environmental factors (air pollution, weather, and mobility), and sociopolitical variables [government stringency index (GSI)]. In Russia, the United Arab Emirates, India, and the Philippines, it was observed that a higher SI was associated with a reduced incidence of COVID-19 cases. In spite of this, an increasing number of COVID-19 cases with greater GSI have been observed in a few nations. This increasing trend seen in Iran, Turkey, and Saudi Arabia suggests that the government has been slow to implement countermeasures against the COVID-19 pandemic.

There were some limitations to this study. First of all, only 15 among 39 stations in Istanbul were considered valid for this study because the percentage of days they can monitor in a year is at least 75%. Therefore, these findings are representative of 38.4% of the stations in Istanbul. Also, the total area of the neighborhoods where the valid stations for the study were located accounted for 1.3% of the total area of the districts included in the study. It has to have a greater number of valid stations monitoring the air quality in İstanbul in order to ensure that it is more representative. On the other hand, SI simply demonstrates the existence of restrictions but not their effectiveness. Adaptation of the population to the measures and seasonal and activity density variations during the study period may therefore influence the results. However, it should also be considered that these elements may not be similar among districts. The use of country-based values of the SI and the lack of data on the district-level specifics of the measures and their implementation may be significant limitations of our study. To analyze the effects of pandemic measures on air pollution levels in more detail, it would be advantageous to have access to pandemic data as well as environmental and sociopolitical variables.

In conclusion, the recent study looking at the correlation between SI and change in air quality in the districts of Istanbul determined that pandemic restrictions could not achieve the same improvements in air pollution in every district of İstanbul. We need to perform studies monitoring pollutant concentrations with an increasing representative number of stations while investigating all the influencing mechanisms and/or factors (e.g., meteorological conditions, changes in the behavior of population displacement, pollutant transportation, and implementation of government policies) that could have contributed to these changes in pollutant levels.

Ethics Committee Approval: There was no need to get approval from an ethics committee for this study because it used publicly available data from the National Weather Monitoring Network run by the Ministry of Environment and Urbanization, and no special precautions were taken to protect individuals or communities that might be vulnerable.

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Original Article

Adding Non-Invasive Positive Pressure Ventilation to Supplemental Oxygen During Exercise Training in Severe Chronic Obstructive Pulmonary Disease: A Randomized Controlled Study

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Abstract

OBJECTIVE: Chronic obstructive pulmonary disease is currently the fourth leading cause of death in the world. Pulmonary rehabilitation is recommended for chronic obstructive pulmonary disease.

MATERIAL AND METHODS: This study aimed to evaluate the effects of non-invasive ventilation, supplemental oxygen, and exercise training and supplemental oxygen during exercise training during pulmonary rehabilitation practice in comparison with only exercise training on lung functions, blood gases, lactate levels, respiratory muscle pressures, dyspnea, walking distances, quality of life, and depression in patients with severe chronic obstructive pulmonary disease. The main outcome measure is exercise capacity (6-minute walk test), and the secondary end-point included quality of life.

RESULTS: Thirty-five patients (mean ± SD age, 65.4 ± 6.5 years) with a mean bronchodilator forced expiratory volume in the first second of expiration of 39.4 ± 7%, undergoing an 8-week outpatient pulmonary rehabilitation, were randomized to either non-invasive ventilation, supplemental oxygen, and exercise training, supplemental oxygen during exercise training, or exercise training groups. The improvements in respiratory muscle strength were higher in non-invasive ventilation, supplemental oxygen, and exercise training patients than the moderate improvements in the exercise training group. Both non-invasive ventilation, supplemental oxygen, and exercise training and supplemental oxygen during exercise training groups showed significant increases in the 6-minute walk test and incremental shuttle walk test. However, the increase in walking distance was better in non-invasive ventilation, supplemental oxygen, and exercise training group (69.8 ± 53.2 m in 6-minute walk test and 66.6 ± 65.2 m in incremental shuttle walk test, $P = .001$ and $P = .005$, respectively) compared to supplemental oxygen during exercise training group (42.5 + 55.5 m in 6-minute walk test and 53.5 + 70.2 m in incremental shuttle walk test, $P = .01$ each, respectively). The total St. George's Respiratory Questionnaire score was similar in all study groups after the intervention. Symptoms of depression significantly improved only in non-invasive ventilation, supplemental oxygen, and exercise training group (−2.8 + 2.8, $P = .006$).

CONCLUSION: Non-invasive positive-pressure ventilation (NIPPV) added to supplemental oxygen during exercise training was associated with better physiological adaptations than other modalities.

KEYWORDS: COPD management, exercise training, non-invasive ventilation
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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is currently 1 of the 3 causes of death in the world. Chronic airway obstruction, expiratory flow limitation, and increased respiratory frequency result in end-expiratory lung volume, known as dynamic hyperinflation (DH) in patients with COPD. Even though DH is a compensatory mechanism that increases expiratory flow during exercise, it has some disadvantages such as loading the inspiratory muscles and increasing the work of breathing.[1,2] Dynamic hyperinflation causes breathlessness and diminished exercise tolerance. Exercise training (ET) which is a part of pulmonary rehabilitation (PR) leads to improve functional capacity, exercise tolerance, and quality of life (QoL).[3,4] Recently, there has been an increasing use of non-invasive ventilation (NIV) during exercise aiming to train patients at intensity levels higher than those allowed by their pathophysiological conditions.[2,5] It seems reasonable that the combination of the 2 interventional approaches, NIV, and ET may improve muscle strength and QoL in patients with COPD.[6]

Different modalities exist which can increase the effectiveness of ET such as heliox supplementation, intermittent exercise, and NIV. The use of NIV seems more practical compared to the other methods.[7] Another study showed that COPD

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patients with severe hyperinflation and exercise-induced desaturation benefit from NIV plus oxygen supplementation (O_2) during ET.[8] On the other hand, NIV performed during high-intensity exercise can modulate endothelial function and improve exercise tolerance in especially COPD heart failure.[9] However, there is no conclusive information in regard to NIV use during ET. There has not been a controlled trial designed to compare the benefits of PR in severe COPD carried out ET, NIV, and O_2 (ET + NIV + O_2), ET with oxygen (ET + O_2), and ET alone.

It was aimed to investigate the effects of 3 exercise modalities in severe COPD patients during an outpatient PR program in this study. It was hypothesized that ET + NIV + O_2 during exercise could promote optimal physiologic adaptations to ET in severe COPD.

MATERIAL AND METHODS

Design

The interventional study, designed as a prospective randomized controlled trial, composed of 61 patients, 35 of whom were randomized through computer-generated randomization into 1 of 3 groups: ET + NIV + O_2, ET + O_2, and ET (Figure 1). Ethical approval was obtained from the Institutional Review Board of Ege University, Faculty of Medicine for Human Studies and Ethics Committee (Approval Acceptance Number: 2020-KAEK-139) and was carried out in accordance with the principles of the Helsinki Declaration. A written informed consent was obtained from all patients. Stable patients with COPD (corresponding to GOLD Group D) were included in this study.[1]

Participants

All patients were receiving COPD optimal treatment according to the GOLD guideline (Long-Acting β-Agonist [LABA] + Long-Acting Muscarinic Antagonist [LAMA] + Inhaled Corticosteroids [ICS]), but there were no patients taking oral steroids or antibiotics. The patients with orthopedic, neurologic conditions, or malignant disorders that could prevent participation in an exercise program, in addition to unstable cardiovascular conditions such as arrhythmias, uncontrolled hypertension, severe pulmonary hypertension, diabetes mellitus, or other pulmonary diseases were ruled out. Patients who were already on long-term oxygen therapy (LTOT) and/or NIV due to chronic respiratory failure and exacerbation over the last month and during the ET sessions were also excluded.

MAIN POINTS

- Pulmonary rehabilitation has been proved beneficial effects in chronic obstructive pulmonary disease (COPD).
- Although the use of NIPPV added to supplemental oxygen during pulmonary rehabilitation requires equipment and expertise in implementation, it can be used to promote additional physiologic effects.
- Pulmonary rehabilitation can be performed in COPD regardless of the severity of the disease, on the condition that necessary equipments are provided.

All patients were delivered an 8-week supervised outpatient PR program and randomized to either ET + NIV + O_2, ET + O_2 groups, or only ET as a control group by drawing lots (opaque, shuffled, and coded envelopes that were opened before implementation). The variables were measured at baseline and after the program. The outcomes of all assessments were compared with the results of the control group. Education was also given to the patients. All patients were given information about NIV on a routine control visit.

PROCEDURES

Lung Functions, Lung Volumes, and Respiratory Muscle Strength Measurement

Forced vital capacity (FVC) and vital capacity (VC) measurements were carried out with a Spirometer (Sensor Medics 2400, Yorba Linda, Calif, USA) by following American Thoracic Society Guidelines[10] by using reference values of the Guidelines of European Respiratory Society.[11] Inspiratory and expiratory muscle strengths [Pimax and Pemax were measured during inspiration and expiration against closed airway at residual volume (RV)] were measured using microRPM (respiratory pressure meter) according to the method of Neder et al.[12] The patients were encouraged to give maximum effort. Residual volume and total lung capacity (TLC) were performed with a body plethysmography (Master Screen Body, Jaeger GmbH, Hoechberg, Germany).

Blood Gas Analysis and Lactate Levels

Arterial blood gases (PaO_2, $PaCO_2$, and pH) were analyzed in 100 µL arterialized blood sampled from the radial artery while lactic acid (LA) concentrations were measured in venous blood samples (Nova Biomedical Critical Care Xpress, Waltham, Mass, USA). Samplings were performed at rest and before and after ET sessions.

Exercise Capacity and Dyspnea

Dyspnea was evaluated by a modified BORG scale.[13] The 6-minute walk test (6MWT) and incremental and endurance shuttle walk tests (ISWT, ESWT, respectively) were performed in accordance with the references.[14-16] The minimal important significant changes for the 6MWT, ISWT, and ESWT were approximately 30 m (18), 47.5 m (16), and 45-85 seconds[16] respectively.

Health Status, Anxiety, and Depression

Quality of life was evaluated by the Turkish validated version of St. George's Respiratory Questionnaire (SGRQ).[17] The SGRQ is composed of 4 sub-categories; symptoms, activities, impact and total score and ranged from 0 to 100; as the score is getting increase, QqL is poorer. Four score changes in all subgroups are accepted as significant.[17,18]

Hospital anxiety and depression scale (HADS), each consisting of 7 items, was used to assess anxiety and depression. All patients were self-administered. Anxiety (HADSa) and depression (HADSd) using hospital anxiety and depression scale are evaluated as 2 separate columns. If the score was ≥8, it is defined as anxiety and/or depression.[19]

Exercise Training Protocol

An 8-week outpatient supervised PR was performed with a fixed protocol which was applied to all patients in our PR unit.

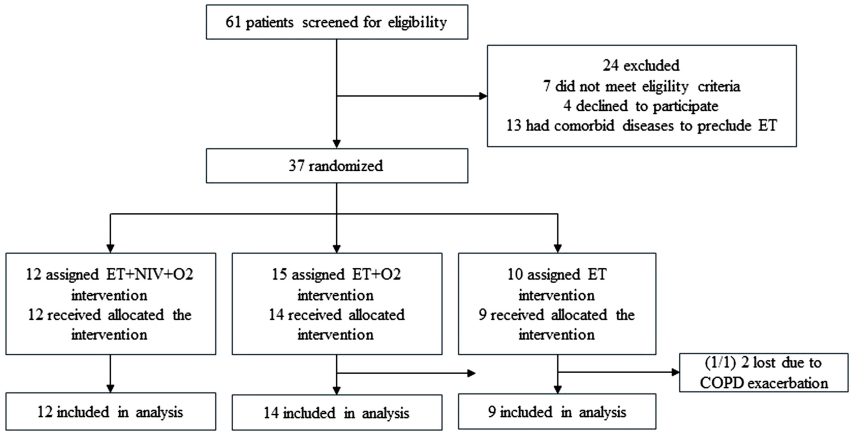


Figure 1. CONSORT diagram of the study.

The patients were delivered an ET program of cycle ergometer (15 minutes), treadmill (15 minutes), lower and upper extremity strength training (5-10 minutes), breathing and relaxation therapies (15-20 minutes, each), twice weekly for total 60-80 min/day, and home exercise program once a week. Breathing exercises were composed of glossopharyngeal, pursed lips, diaphragmatic, and segmental breathing. Relaxation exercises were administered in accordance with the Jacobson technique of progressive muscle relaxation. Exercise, first with a warm-up period, followed by workloads for walking and cycling speed for treadmill ergometer were calculated out of ISWT results. Patients were exercised at 50% of peak workload and 50%-80% of peak VO_2. Non-invasive ventilation was delivered with a bi-level ventilator (BIPAP-S, Respironics, Murrysville, Pa, USA) through a tight-fitting Silicon Gold Seal (Resipronics, Inc.) oro-nasal mask. The inspiratory pressure was started at 10 cmH_2O and increased 2 cmH_2O every minute according to the patient's tolerance.[20] The expiratory settings were started at 4 cmH_2O and increased 1 cmH_2O every minute. The expiratory and inspiratory pressures were slowly up-titrated to get the best ventilator support. Oxygen was inserted into the ventilator circuit at a flow rate (1-3 L/min) by dual-prong nasal cannulae for keeping the oxygen saturation during NIV at or above 90% during ET.

Statistical Analysis

Data were analyzed with Statistical Package for Social Sciences (SPSS) version 20.0 (IBM Corp.; Armonk, NY, USA), and data were presented as mean ± SD unless otherwise stated. Comparing categorical variables was performed with chi-square with Fisher's exact test (when appropriate). Normality test for numeric data was performed with Shapiro Will test. Statistical comparisons between the groups were calculated using 1-way analysis of variance for normally distributed data, and post hoc test was performed when the analysis of variance determined a significant effect. Kruskal–Wallis test was used for the data that were not distributed normally. The comparisons before and after rehabilitation within the groups were calculated using paired Student's *t*-test and Wilcoxon signed-rank tests when appropriate. $P < .05$ was accepted significant.

RESULTS

Thirty-five patients who were included in this study completed 16 ET sessions with individual home exercise programs. Significant differences were not detected in each group in terms of demographic features, body composition, comorbidities, lung functions, respiratory muscle strengths, blood lactate levels, 6MWT distances, and endurance time except BORG scale and ISWT (m) (2.6, 4.8, 2.8, for BORG scale and 360, 252, 345 m for ISWT, ET + NIV + O_2, ET + O_2, ET, respectively). Patients' demographics and characteristics were presented in Table 1. Twenty-four patients were excluded due to severe pulmonary hypertension, lumbar disc herniation, and declining participation. After randomization, 2 of the patients prematurely terminated the study because of an exacerbation of COPD (Figure 1).

Residual volume and total lung capacity decreased after the program (−305 ± 489 and −325 ± 524, both $P = .05$, respectively) in only ET + NIV + O_2 group. However, there were no changes in lung volumes in the ET + O_2 group, while there was a slight increase in FVC in the ET group after PR. The decrease in lung volumes in ET + NIV + O_2 group was not statistically significant in comparison with the ET alone patients ($P > .05$). It was detected that there was a significant increase in both Pimax (13.5 ± 12.1 cmH_2O, $P = .003$) and Pemax (15.5 ± 24.1 cmH_2O, $P = .04$) in ET + NIV + O_2 group, while it was determined a slight increase in only Pimax (8.7 ± 9.8 cmH_2O, $P = .02$) in the ET group.

The improvements in respiratory muscle strength were higher in ET + NIV + O_2 patients than the moderate improvements in the ET group. In the ET + O_2 group, it was detected that a decrease in Pimax (−5.07 ± 25.8 cmH_2O, $P = .47$) and the change in Pemax were not statistically significant (12.1 ± 41.4 cmH_2O, $P = .29$). Changes in blood gases were not detected at any time period in any of the groups. Patients who received ET + NIV + O_2 demonstrated a decrease in blood lactate level; however, it was not statistically significant ($P = .06$) (Tables 2 and 3).

BORG score decreased only in ET + O_2 group (−2.4 ± 2.7, $P = .005$) after the intervention. Both ET + NIV + O_2 and ET + O_2 groups showed significant increases in 6MWT and ISWT tests. However, the improvement in walking tests was better in ET + NIV + O_2 group (69.8 ± 53.2 m in 6MWT and 66.6 ± 65.2 m in ISWT, $P = .001$ and $P = .005$, respectively) compared to ET + O_2 group (42.5 + 55.5 m in 6MWT and 53.5 + 70.2 m in ISWT, $P = .01$ each, respectively). In

Table 1. Baseline Demographics and Characteristics of the Patients

Variables	ET + NIV + O_2 (n = 12)	ET + O_2 (n = 14)	ET (Control) (n = 9)	*P*
Age (years)	64.2 ± 7.3	65.9 ± 6.6	66.1 ± 5.4	.76
Gender (male) (n)	11	14	9	.37
BMI (kg/m²)	24.4 ± 4.2	23.4 ± 5.1	25.3 ± 3.1	.57
Smoking history (pack/year)	56.9 ± 41.6	37.5 ± 17.7	44.3 ± 16.5	.22
Post. FEV_1 (mL)	1180 ± 215	1060 ± 307	1188 ± 225	.39
Post. FEV_1 (predicted %)	41.4 ± 6.4	35.5 ± 8.5	41.5 ± 6.1	.08
FEV_1/FVC (%)	51.5 ± 7.0	45.9 ± 7.0	48.4 ± 6.6	.13
Initial BORG score	0.6 ± 1.3	2.2 ± 2.4	0.7 ± 1.0	.2
Comorbidities (n)				
Coronary artery disease	1	0	0	NS
Hypertension	1	5	0	
Diabetes mellitus	1	0	0	
FVC (mL)	1945 ± 739	2247 ± 603	2196 ± 328	.42
FVC (%)	59.4 ± 9.1	58.8 ± 14.5	59.2 ± 10.8	.98
FEV_1 (mL)	1076 ± 162	996 ± 269	1084 ± 270	.60
FEV_1 (%)	37.7 ± 3.9	33.5 ± 7.7	37.6 ± 7.5	.20
RV (mL)	4375 ± 1176	4602 ± 1339	4835 ± 1163	.70
TLC (mL)	6670 ± 1451	6767 ± 1559	7870 ± 2291	.24
RV/TLC (%)	65.0 ± 6.7	67.3 ± 7.4	62.8 ± 11.8	.43
IC (mL)	1476 ± 518	1432 ± 549	1772 ± 396	.27
IC/TLC (%)	22.8 ± 7.7	21.4 ± 7.4	24.0 ± 7.2	.71
Blood lactate level (mmo/L)	1.2 ± 0.7	1.1 ± 0.5	1.0 ± 0.9	.53
mMRC	2.5 ± 0.7	3.0 ± 0.9	2.4 ± 0.5	.06
BORG scale (exercise)	2.6 ± 1.4	4.8 ± 2.1	2.8 ± 1.6	**.007**
CAT score (n)	18.8 ± 9.6	21.6 ± 8.4	20.0 ± 18.0	.87
6MWT (m)	400.8 ± 57.4	345.3 ± 95.0	350.4 ± 81.2	.18
ISWT (m)	360.8 ± 100.8	252.1 ± 101.1	345.5 ± 105.8	.02
ESWT speed (km/h)	3.9 ± 0.7	3.4 ± 0.7	4.2 ± 0.7	.05
ESWT time (minutes)	18.0 ± 3.9	11.6 ± 7.5	15.4 ± 6.1	.19
SGRQ				
Symptoms	47.0 ± 22.6	42.8 ± 30.3	35.9 ± 15.0	.85
Activity	50.0 ± 24.6	60.7 ± 21.3	51.3 ± 21.5	.51
Impact	29.3 ± 19.4	41.9 ± 28.2	28.1 ± 19.6	.25
Total score	39.2 ± 17.6	47.7 ± 23.7	36.7 ± 15.9	.49
CRQ				
Dyspnea	3.4 ± 1.0	3.3 ± 1.1	4.3 ± 1.0	.24
Fatigue	4.1 ± 1.4	3.7 ± 1.5	5.5 ± 0.7	.40
Emotional	4.5 ± 1.5	4.7 ± 1.5	5.6 ± 1.1	.64
Mastery	4.6 ± 1.4	5.2 ± 1.4	5.7 ± 1.4	.50
HADs				
Anxiety	6.0 ± 4.1	5.6 ± 4.9	2.7 ± 2.7	.45
Depression	5.3 ± 3.0	5.2 ± 4.0	10.0 ± 13.5	.27

Results were reported as mean ± SD after testing for normal distribution. $P < .05$ values were statistically significant.
BMI, body mass index; CAT, Chronic obstructive pulmonary disease assessment test; CRQ, chronic respiratory disease questionnaire; ESWT, endurance shuttle walk test; FVC, forced vital capacity; HADS, hospital anxiety and depression scale; IC, inspiratory capacity; ISWT, incremental shuttle walk test; MEP, maximum expiratory pressure; MIP, maximum inspiratory pressure; mMRC, modified Medical Research Council dyspnea scale; 6MWT, 6-minute walk test; post-FEV1, post-bronchodilator forced expiratory volume in the first second of expiration; RV, residual volume; SGRQ, St. George's Respiratory Questionnaire; TLC, total lung capacity.

the ET group, increases in 6MWT and ISWT distance were 67.1 + 40.9 m and 51.1 + 33.7 m, $P = .01$ and $P = .02$, respectively. Symptom scores of SGRQ improved significantly only in the ET + NIV + O_2 group (−21.8 + 18.9, $P = .002$), whereas the total score improved in ET + O_2 patients (−12.2 + 20.1, $P = .04$). This finding may be associated with higher SGRQ baseline scores obtained in ET + O_2 group (47.7 ± 23.7). However, the total SGRQ score was similar in all study groups after the intervention. Symptoms of depression significantly improved only in ET + NIV + O_2 group (−2.8 + 2.8, $P = .006$) (Table 3).

DISCUSSION

The present study demonstrated that the addition of NIV as an adjunct to oxygen therapy during PR in severe COPD reduces DH and improves exercise capacity, respiratory muscle strength, symptom subgroup in SGRQ, and depression scores compared to ET + O_2 and ET groups. The intensity of ET during PR is important for achieving accurate physiologic effects. Exertional dyspnea and leg and respiratory muscle fatigue do not allow particularly severe COPD patients to maintain optimal intensity during training. Although the use of NIV has been proposed as another option to improve QoL, exercise tolerance, and respiratory performance, a similar effect between NIV and placebo was observed in the recent Cochrane review for the outcomes considered despite differences among studies. The authors concluded that due to a small number of available studies and sample sizes, the effects of adding NIV to conventional strategies are in need of further investigation.[21] A systemic review reported the results of the randomized controlled trials on oxygen during ET and found no beneficial effect on PR outcomes.[22] Another study concluded that patients with oxygen had longer exercise endurance but failed to improve maximal exercise capacity, walking distance, and QoL.[23] Borghi-Silva et al[24] made a comparison between the oxygen group and the NIV group in terms of similar physiologic outcomes and demonstrated that NIV was better than oxygen alone. Poor results in the oxygen group were related to the

Table 2. Changes in Lung Functions and Volumes, Respiratory Muscle Strength, Arterial Blood Gas Analysis, Quality of Life Scores, Walking Distances, Psychological Status Changes Before and After the Intervention in ET + NIV + O_2 Group, ET + O_2 Group, and ET Group

	ET + NIV + O_2 (n = 12)		ET + O_2 (n = 14)		ET (n = 9)	
Variables	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
Post-FVC (mL)	1945 ± 739	2236 ± 495	2247 ± 603	2305 ± 572	2196 ± 328	2483 ± 383
Post-FVC (%)	59.4 ± 9.1	60.6 ± 8.09	58.8 ± 14.5	60.7 ± 13.7	59.2 ± 10.8	68.0 ± 10.6
Post-FEV_1 (mL)	1076 ± 162	1116 ± 212	996 ± 269	1072 ± 298	1084 ± 270	1284 ± 255
Post-FEV_1 (%)	37.7 ± 3.9	39.4 ± 5.6	33.5 ± 7.7	36.4 ± 9.7	37.6 ± 7.5	45.1 ± 7.7
RV (mL)	4375 ± 1176	4070 ± 1101	4602 ± 1339	4564 ± 1319	4835 ± 1163	4426 ± 1054
TLC (mL)	6670 ± 1451	6345 ± 1386	6767 ± 1559	6795 ± 1522	7870 ± 2291	7023 ± 1009
RV/TLC (%)	65.0 ± 6.7	63.6 ± 6.9	67.3 ± 7.4	66.8 ± 8.2	62.8 ± 11.8	62.3 ± 7.6
IC (mL)	1476 ± 518	1488 ± 518	1432 ± 549	1505 ± 355	1772 ± 396	1806 ± 242
IC/TLC (%)	22.8 ± 7.7	23.6 ± 6.8	21.4 ± 7.4	22.4 ± 4.9	24.0 ± 7.2	26.1 ± 4.7
$Pimax_{peak}$ (cmH_2O)	67.0 ± 27.7	80.6 ± 25.9	76.7 ± 42.1	71.6 ± 27.5	63.5 ± 21.7	72.3 ± 21.9
$Pemax_{peak}$ (cmH_2O)	87.4 ± 32.9	101 ± 30.8	99.5 ± 41.8	112.1 ± 36.5	105 ± 32.8	124.5 ± 45.1
PaO_2 (mmHg)	77.4 ± 8.7	76.2 ± 5.6	72.6 ± 16.5	71.9 ± 11.8	73.1 ± 4.4	75.7 ± 10.1
$PaCO_2$ (mmHg)	36.4 ± 3.6	34.3 ± 2.8	35.6 ± 6.2	35.9 ± 5.4	36.0 ± 5.7	35.7 ± 4.2
SpO_2	95.7 ± 1.0	95.3 ± 0.9	93.7 ± 3.6	94.1 ± 2.9	95.4 ± 1.1	95.4 ± 1.5
Lactate (mmol/L)	1.2 ± 0.7	0.9 ± 0.6	1.1 ± 0.5	1.0 ± 0.3	0.9 ± 0.3	1.0 ± 0.9
BORG scale	2.6 ± 1.4	2.7 ± 1.5	4.8 ± 2.1	2.4 ± 1.6	2.8 ± 1.6	2.0 ± 1.3
CAT score	18.8 ± 9.6	7.4 ± 5.3	21.6 ± 8.4	12.1 ± 5.2	20.0 ± 18.0	10.7 ± 6.7
6MWT (m)	400 ± 57.4	470 ± 95.4	345 ± 95	387 ± 64	350 ± 81	417 ± 87
ISWT (m)	360 ± 100	427 ± 74	252 ± 101	305 ± 84	345 ± 105	396 ± 108
ESWT speed (km/h)	3.9 ± 0.7	4.7 ± 0.5	3.4 ± 0.7	3.9 ± 0.5	4.2 ± 0.7	4.5 ± 0.7*
ESWT time (min)	18.0 ± 3.9	19.4 ± 4.2	11.6 ± 7.5	16.0 ± 6.2*	15.4 ± 6.1	19.1 ± 4.9
SGRQ						
Symptom	47.0 ± 22.6	25.2 ± 18.2	42.8 ± 30.3	31.7 ± 23.7	48.7 ± 24.3	35.9 ± 15.0
Activity	50.0 ± 24.6	54.7 ± 22.8	60.7 ± 21.3	55.7 ± 20.3	55.7 ± 24.3	51.3 ± 21.5
Impact	29.3 ± 19.4	25.7 ± 19.8	41.9 ± 28.2	26.7 ± 20.7	26.3 ± 20.8	28.1 ± 19.6
Total score	39.2 ± 17.6	35.2 ± 17.9	47.7 ± 23.7	35.4 ± 18.4	38.9 ± 19.5	36.7 ± 15.9
CRQ						
Dyspnea	3.4 ± 1.0	3.8 ± 0.8	3.3 ± 1.1	3.3 ± 1.0	4.1 ± 1.2	4.3 ± 1.0
Fatigue	4.1 ± 1.4	4.6 ± 0.8	3.7 ± 1.5	4.7 ± 1.3	4.6 ± 1.4	5.5 ± 0.7
Emotional	4.5 ± 1.5	5.0 ± 0.9	4.7 ± 1.5	5.1 ± 1.0	5.2 ± 1.6	5.6 ± 1.1
Mastery	4.6 ± 1.4	5.2 ± 0.9	5.2 ± 1.4	5.6 ± 1.3	5.2 ± 1.6	5.7 ± 1.4
HADs						
Anxiety	6.0 ± 4.1	4.8 ± 3.0	5.6 ± 4.9	4.2 ± 4.4	3.7 ± 3.3	2.7 ± 2.7
Depression	5.3 ± 3.0	2.5 ± 1.9	5.2 ± 4.0	4.0 ± 4.0	10.0 ± 13.5	3.78 ± 2.58

Results were reported as mean ± SD after testing for normal distribution.
BMI, body mass index; CAT, COPD assessment test; CRQ, chronic respiratory disease questionnaire; ESWT, endurance shuttle walk test; FVC, forced vital capacity; HADS, hospital anxiety and depression scale; IC, inspiratory capacity; ISWT, incremental shuttle walk test; MEP, maximum expiratory pressure; MIP, maximum inspiratory pressure; mMRC, modified Medical Research Council dyspnea scale; 6MWT, 6-minute walk test; post-FEV1, post-bronchodilator forced expiratory volume in the first second of expiration; RV, residual volume; SGRQ, St. George's Respiratory Questionnaire; TLC, total lung capacity.

Table 3. Comparison of Differences Among ET + NIV + O_2 Group, ET + O_2 Group, and ET Group

	ET + NIV + O_2 (n = 12)		ET + O_2 (n = 14)		ET (n = 9)	
Variables	**Δ (Post-pre)**	***P***	**Δ (Post-pre)**	***P***	**Δ (Post-pre)**	***P***
Post-FVC (mL)	291 ± 754	.20	57 ± 221	.34	286 ± 283	.16
Post-FVC (%)	1.1 ± 7.5	.59	1.8 ± 5.3	.22	8.3 ± 8.04	**.01**
Post-FEV_1 (mL)	40 ± 134	.32	75 ± 146	.75	200 ± 191	.14
Post-FEV_1 (%)	1.7 ± 4.7	.23	2.9 ± 4.8	.44	7.4 ± 7.4	.18
RV (mL)	−305.0 ± 489.1	**.05**	−38 ± 747	.85	408 ± 689	.11
TLC (mL)	−325 ± 524	**.05**	28 ± 759	.89	−846 ± 1715	.17
RV/TLC (%)	−1.3 ± 3.0	.16	−0.5 ± 5.7	.74	−0.5 ± 10.3	.87
IC (mL)	11 ± 387	.91	72 ± 464	.57	34 ± 306	.74
IC/TLC (%)	0.8 ± 5.6	.61	10.0 ± 5.8	.53	2.1 ± 5.9	.32
$Pimax_{peak}$ (cmH_2O)	13.5 ± 12.1	**.003**	−5.07 ± 25.8	.47	8.7 ± 9.8	.02
$Pemax_{peak}$ (cmH_2O)	13.6 ± 26.7	**.025**	12.4 ± 43.2	.02	19.1 ± 27.2	.62
PaO_2 (mmHg)	−1.2 ± 10.2	.69	−0.6 ± 14.1	.86	2.5 ± 8.8	.4
$PaCO_2$ (mmHg)	−2.5 ± 4.3	.11	0.2 ± 5.2	.85	−0.2 ± 4.7	.88
SpO_2	−0.3 ± 1.1	.29	0.3 ± 2.2	.56	0.0 ± 1.6	.93
Lactate (mmol/L)	−0.3 ± 0.6	.06	−0.1 ± 0.5	.36	0.0 ± 0.3	.69
BORG scale	0.0 ± 1.8	.88	−2.4 ± 2.7	**.005**	−0.8 ± 1.2	.06
CAT score	−11.4 ± 8.6	**.002**	−9.5 ± 7.0	**.02**	−10.6 ± 15.9	.36
6MWT (m)	69 ± 53	**.001**	42 ± 55	**.01**	67 ± 40	**.001**
ISWT (m)	66 ± 65	**.005**	53 ± 70	**.01**	51 ± 33	**.002**
ESWT speed (km/h)	0.7 ± 0.7	**.005**	0.4 ± 0.5	**.007**	0.3 ± 0.2	**.002**
ESWT time (min)	1.3 ± 6.3	.15	4.4 ± 6.6	**.01**	3.6 ± 8.9	.12
SGRQ						
Symptom	−21.8 ± 18.9	**.002**	−11.1 ± 22.8	.09	−12.7 ± 19.5	.08
Activity	4.6 ± 31.3	.61	−4.9 ± 16.3	.27	−4.3 ± 8.7	.17
Impact	−3.6 ± 20.2	.18	−15.1 ± 25.7	.06	1.8 ± 9.3	.86
Total	−3.9 ± 19.5	.49	−12.2 ± 20.1	**.04**	−2.2 ± 6.8	.35
CRQ						
Dyspnea	0.3 ± 1.3	.33	−0.0 ± 1.1	1	0.1 ± 0.5	.47
Fatigue	0.5 ± 1.1	.15	0.9 ± 1.2	**.01**	0.9 ± 1.4	.08
Emotional	0.5 ± 1.0	.13	0.4 ± 0.9	.1	0.4 ± 0.7	.14
Mastery	0.6 ± 0.8	**.01**	0.4 ± 0.9	.1	0.5 ± 1.0	.17
HADs						
Anxiety	−1.2 ± 2.4	.1	−1.4 ± 2.7	.07	−1.0 ± 3.2	.38
Depression	−2.8 ± 2.8	**.006**	−1.1 ± 1.9	.052	−6.2 ± 14.4	.23

Results were reported as mean ± SD after testing for normal distribution.
BMI, body mass index; CAT, COPD assessment test; CRQ, chronic respiratory disease questionnaire; ESWT, endurance shuttle walk test; FVC, forced vital capacity; HADS, hospital anxiety and depression scale; IC, inspiratory capacity; ISWT, incremental shuttle walk test; MEP, maximum expiratory pressure; MIP, maximum inspiratory pressure; mMRC, modified Medical Research Council dyspnea scale; 6MWT, 6-minute walk test; post-FEV1, post-bronchodilator forced expiratory volume in the first second of expiration; RV, residual volume; SGRQ, St. George's Respiratory Questionnaire; TLC, total lung capacity.

dose delivered during ET. The mean flow of oxygen was 1.5 ± 0.8 L/min which corresponded to an FiO_2 of 0.24%-0.28%. In contrast to oxygen therapy, NIV was associated with better physiologic adaptations on submaximal performance, VO_2, dyspnea, and SpO_2. In the current study, an average of 2.0 ± 0.6 L/min oxygen with an FiO_2 of at least 28% was used. Despite delivering the optimal dose of oxygen, after exercise training, walking tests, dyspnea scores, and total score of SGRQ improved. However, adding NIV improved more parameters than ETO2. Therefore, the advantages of NIV in the physiologic adaptations may be superior to other adjuncts.

Costes et al[25] used BIPAP as an adjunct to a PR program. They assigned the patients to either NIV or spontaneous breathing. But they failed to report the inspiratory positive airway pressure (IPAP) settings used. The expiratory positive airway pressure (EPAP) is documented as 4-8 cmH_2O which may possibly lead to an increase in functional residual capacity as the EPAP is likely to exceed the intrinsic positive end-expiratory pressure (PEEP). In Menadue et al's[26] study, even though inspiratory pressure levels of ~10 cmH_2O were shown to be effective in reducing dyspnea, it was insufficient to adequately unload inspiratory muscles and thus increased exercise capacity. In the current study, inspiratory pressure levels of 12 ± 1.5 cmH_2O were effective as Pimax and Pemax were significantly increased when BIPAP was used. Only Pimax slightly increased in ET alone group. The mean EPAP was 5 ± 0.8 in this study, which is similar to previously reported levels. There was no significant effect of oxygen supplementation in terms of respiratory muscle strength in ET + O_2 group when compared with the ET group. This result may be due to several factors in the study. Baseline BORG was higher in the ET + O_2 group, which means that these patients were more dyspneic. This group included a higher number of very severe COPD patients; they had the worst bronchodilator forced expiratory volume in the first second of expiration and inspiratory capacity and also lower BMI than the other groups. With oxygen supplementation, the reduction in ventilation in submaximal workloads may be related to a slower increase in lactate level due to better oxygen delivery to peripheral muscles.

Another study found that NIV plus oxygen supplementation resulted in increased tidal volume (TV) and minute ventilation, decreased dyspnea intensity to compare with O_2 therapy at isotime (reduction of 1.0 ± 2.0 BORG units, $P < .05$), and a tendency but not significant changes in total dyspnea recovery time (326.2 ± 132.0s vs. 356.5 ± 156.9s, $P = .225$). Non-invasive ventilation has been effective in augmenting the effect of standard ET for exertional dyspnea in stable COPD with lower pulmonary function.[27] In the current study, pulmonary function tests of patients showed no change except for RV and TLC in ET + NIV + O_2 group. Dynamic hyperinflation improved in the participating patients in this study, but another study reported that this was not the case in patients with profound resting dynamic hyperinflation and ventilatory constraints during exercise.[7] Another study determined that COPD patients with severe static hyperinflation and exercise-induced desaturation significantly benefited from NIV adjunct to O_2 during exercise and recovery.[8]

Another study, which was similar to our study, investigated 88 elderly patients with severe COPD who were divided into 3 groups: control group (O_2 + regular treatment), interventional group A (plus NIV), and interventional group B (plus comprehensive PR). The improvement of mMRC, 6MWD, QoL scores, PaO_2, and $PaCO_2$ of intervention group B was better compared to intervention group A.[28] The patients in the current study showed improvement in exercise capacity (6MWT, ISWT, and ESWT) and QoL (BORG scale, CAT score, SGRQ, CRQ, and HADs). However, there was no change in the PaO_2 and $PaCO_2$ values of the participating patients.

In spite of promising results, the generalized use of NIV during exercise is unlikely to be adopted in routine PR settings. The use of NIV during exercise as a component of PR should be set aside in individual cases.[29] High-intensity NIV as an add-on tool during exercise is beneficial yet appropriate based on patient selection, and implementation is paramount in chronic hypercapnic respiratory failure.[30] A review proposed that NIV is an adjuvant intervention for ET in COPD as the intervention can improve exercise capacity and QoL.[31]

The sample size of the study is relatively small. Although 61 patients were screened, only 35 of them could be included. However, when considering patients' health status, especially the interventional group consisted of risky patients. Patients receiving NIV + PR + O_2 were taken to each session one by one. For that reason, this study took several years to complete.

CONCLUSION

It can be argued that although the use of NIPPV added to supplemental oxygen during PR requires equipment and expertise in implementation, it can be used to promote additional physiologic effects. Randomized clinical trials with larger sample sizes should aim to investigate the effect of training duration, intensity, ventilator modes, or settings in patients with severe COPD.

Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author.

Ethics Committee Approval: The study was approved by the Institutional Review Board of Ege University Faculty of Medicine (Approval Acceptance Number: 2020-KAEK-139) and was conducted in accordance with the principles of the Declaration of Helsinki.

Informed Consent: Informed consent was obtained from all individual participants included in the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – A.G.; Design – A.G.; Supervision – A.G.; Data Collection and/or Processing – S.D., Ş.T., F.E.; Analysis and/or Interpretation – S.D.; Literature Search – F.E.; Writing Manuscript – S.D.; Critical Review – S.D., A.G.

Declaration of Interests: The authors have no conflict of interest to declare.

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Original Article

Stereotactic Radiosurgery Results in Non-Small-Cell Lung Cancer Patients with Brain Metastases in the Era of Modern Systemic Treatment Agents

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Abstract

OBJECTIVE: This study reports the results of stereotactic radiosurgery and fractionated stereotactic radiosurgery treatment for brain metastasis in non-small cell lung cancer patients treated with modern systemic treatment methods (immunotherapy, targeted agents, and current chemotherapy agents).

MATERIAL AND METHODS: This study retrospectively analyzed patients diagnosed with non-small cell lung cancer and brain metastases who underwent stereotactic radiosurgery/fractionated stereotactic radiosurgery in the Radiation Oncology Clinic of Ankara Bilkent City Hospital between February 21, 2019, and August 15, 2022. The study's primary endpoint was accepted as the lesions' response status after stereotactic radiosurgery/fractionated stereotactic radiosurgery.The secondary endpoint was accepted as the patients' intracranial progression-free survival and overall survival.

RESULTS: This study included 85 patients treated for 174 lesions. Their median follow-up was 6.6 (range: 1-42) months.Their median intracranial progression-free survival after radiotherapy was 5.3 (range: 1-33) months, and their median overall survival was 6.6 (range: 1-42) months. Concurrent immunotherapy was administered to 10 (11%) patients and targeted therapy to 8 (9%). Magnetic resonance imaging indicated that 14 (6%) patients had a complete response, 62 (35.6%) had a partial response, 10 (5.7%) had stable disease, and 23 (13.2%) had progressive disease. The complete response rate was significantly higher in patients receiving targeted therapy ($P < .001$; odds ratio = 0.0025, 95% CI = 0.006-0.109). Intracranial recurrence was observed in 28 (32.9%) patients after stereotactic radiosurgery/fractionated stereotactic radiosurgery: 7 (8.2%) were inside the radiotherapy field, 13 (15.3%) were outside the radiotherapy field, and 8 (9.4%) overlapped the radiotherapy field. Intracranial progression-free survival was higher in patients receiving concomitant immunotherapy ($P = .028$; hazard ratio = 0.107, 95% CI = 0.015-0.783). However, overall survival was higher in patients receiving targeted therapy ($P = .035$; hazard ratio = 0.217, 95% CI = 0.053-0.897).

CONCLUSION: Using current systemic agents with radiotherapy for brain metastasis significantly affected post-radiotherapy intracranial progression-free survival.

KEYWORDS: Lung cancer, radiotherapy, stereotactic radiosurgery, immunotherapy
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INTRODUCTION

Lung cancer is the most common cause of cancer-related deaths worldwide, accounting for 18%.[1] Brain metastases (BMs) are present in 10% of patients with non-small-cell lung cancer (NSCLC) at diagnosis, increasing to 50% during disease progression.[2] Patients with BMs have a poor prognosis, with an average survival time of 3-6 months. However, some studies have reported survival in these patients of up to 2 years, depending on their extracranial disease status, number and prevalence of BMs, general condition, and administered targeted and immunological agents.[3,4]

Together with the historical process, the cornerstones for treating BMs are surgery, systemic therapy, and radiotherapy [RT; stereotactic radiosurgery (SRS) and fractionated SRS (fSRS)].[2,5] Stereotactic radiosurgery/fractionated stereotactic radiosurgery has begun to be used as first-line therapy for BMs, given concerns over neurocognitive decline after whole brain RT (WBRT).[6,7] Surgery, chemotherapy, and RT have been used to treat BMs in patients with NSCLC from the past to the present, but effective and curative treatment remains impossible in many patients. Immunotherapy (IT) has recently begun to be used as a first-line treatment approach in patients with lung cancer, with promising results reported.[8,9] However, there are limited published data on combining SRS/fSRS–IT to treat BMs in patients with lung cancer. It is important to assess the efficacy and safety of combining current systemic treatment agents with SRS/fSRS. Therefore, additional studies on this subject are needed.

This study analyzed the results of patients with NSCLC–BMs treated with SRS/fSRS. It aimed to report the toxicity results and survival data for SRS/fSRS in this patient group.

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MATERIAL AND METHODS

This study retrospectively analyzed patients diagnosed with NSCLC–BMs who underwent SRS/fSRS in the Radiation Oncology Clinic of Ankara Bilkent City Hospital. It examined patient interview information, patient files, and RT planning data. Based on this information, the following patient data were recorded: demographic status, tumor volume, SRS/fSRS total dose and fraction number, planning target volume (PTV), PTV margin, gradient index (GI), conformity index (CI), V12 of brain gross tumor volume (GTV) during treatment, IT agents used concurrently with SRS/fSRS, targeted therapy agents, steroid use and dose, magnetic resonance imaging (MRI)-based response evaluation of lesions, recurrence status and time, and final status.

Patients Selection

This study included patients aged >18 years with a pathologically confirmed NSCLC diagnosis who developed BMs at diagnosis or during follow-up, who received SRS/fSRS at the Ankara Bilkent City Hospital Radiation Oncology Clinic, had complete file information, and had an Eastern Cooperative Oncology Group status of 0-3. Patients without pathological evidence and missing file or follow-up data were excluded. Since the study is a retrospective study, informed consent was not obtained from the patients.

Treatment Planning and Follow-up

Planning computed tomography (CT) images were obtained without contrast with a 1.25 cross-section interval on the GE Discovery brand simulation CT device for the patients' treatment planning. A thermoplastic mask was used for fixation. The obtained images were transferred to the Varian-Aria planning system and fused with contrast-enhanced brain MRI images for GTV determination. For PTV, a 1-5 mm margin was given to the GTV. Treatment plans were made with volumetric modulated arc therapy (VMAT) or hyperarc techniques using the TrueBeam Varian software system. Radiotherapy was given to patients on Varian TrueBeam STX and EDGE devices. The patients' follow-up and RT response evaluations were based on contrast-enhanced, thin-section brain MRIs taken at 3-month intervals after RT. These control brain MRIs were evaluated by comparing them with MRIs at diagnosis. Brain MRI images of the patients at diagnosis and control were evaluated as complete response (CR), partial response (PR), and progressive disease (PD) according to the Response Assessment in Neuro-Oncolog (RANO) criteria.

Primary and Secondary Endpoints

The study's primary endpoint was the lesions' response status after SRS/fSRS. Its secondary endpoint was the patients' intracranial progression-free (iPFS) and overall (OS) survival. Overall survival was the time to death after RT. The RT start date was considered the start date for OS and iPFS. The endpoint for OS was the last control date for surviving patients and the date of death for deceased patients. The endpoint for DFS was the date of the first event for patients with relapse and the date of the last control for patients without recurrence.

Statistical Analysis

The data were analyzed using Statistical Package for Social Sciences (SPSS) version 26.0 (IBM Corp., Armonk, NY, USA). Continuous (quantitative) variables are expressed as mean, SD, minimum, and maximum values. Categorical variables are expressed as number (n) and ratio (%). The conformity of the variables to the normal distribution was assessed with Kolmogorov–Smirnov tests. The variables were compared using nonparametric tests because they were nonnormally distributed. The patients' categorical demographic characteristics were compared using chi-square and Fisher's exact tests. Univariate correlation analyses used Spearman's rank correlation coefficient (r_s). Kaplan Meier-log rank test were performed for univariate survival analysis. Cox regression analysis was used for multivariate survival analysis. The hazard ratio (HR) and 95% confidence interval (CI) values of the results that were significant in survival values were calculated.The hazard ratio (HR) and 95% confidence interval (CI) values of the results that were significant in survival values were calculated. for multivariate survival analysis.Cox regression analysis was for univariate survival analysis.Kaplan Meier-log rank test were An HR >1 denotes an increased risk relative to the reference category. The significance threshold of this study was set as .05.

Ethics Committee Approval

The study was conducted in accordance with the Declaration of Helsinki, and it was approved by the Ankara Bilkent City Hospital Ethics Committee 1 with the number E1-22-2874 on September 7, 2022.

MAIN POINTS

- In this study, patients with a diagnosis of non-small cell lung cancer and brain metastases were evaluated according to the Response Assessment in Neuro-Oncolog (RANO) criteria.
- This study is one of the few studies in which the response evaluation of stereotactic radiosurgery/fractionated stereotactic radiosurgery (SRS/fSRS) is according to the RANO criteria.
- It was found that the survival of the patient with a complete response to the RANO criteria was better.
- Intracranial progression-free survival has been observed to increase with SRS/fSRS and immunotherapy.
- Overall survival has been observed to increase with targeted therapies and radiotherapy.

RESULTS

This study included 85 patients who underwent SRS/fSRS in our clinic for lung cancer BMs between February 21, 2019, and August 15, 2022. The total number of BMs that underwent SRS/fSRS was 174. The study's median follow-up period from the start of RT was 6.6 (range: 1-42) months. The patients' median number of BMs was 2.[1-6] The patients' median age was 62 (36-85) years. Seventy-two (85%) patients were male, and 13 (15%) were female. Extracranial metastases were present in 35 (41%) patients and absent in 50 (59%). Concurrent IT was administered to 10 (11%) patients and targeted therapy to 8 (9%). The IT administration was as follows: 6 patients were given pembrolizumab, 3 nivolumab, and 1 atezolizumab. The targeted therapy administered was as follows: 2 patients were given erlotinib, 2 afatinib, 2 alectinib, 1 lorlatinib, and 1 trametinib-dabrafenib. Patient and treatment details are summarized in Table 1.

Table 1. Patient Characteristics and Treatment Parameters

Patient Characteristic		Median
Age		62 (36-85)
Sex	Female	13 (15%)
	Male	72 (85%)
Follow up		6.6 (1-42)
Brain metastases number		2 (1-6)
Systemic agent	Immunotherapy	10 (11%)
	Targeted therapy	8 (9%)
Total lesion		174
Total dose		27 (15-30)
Fraction		3 (1-5)
PTV margin	Yes	125 (71.8%)
	No	49 (28.2%)
WBRT treatment		15 (6.4%)
Tumor diameter and volume		11 mm (0.4-52) and 1 cc (0.1-56.9)
Target parameters	GI	4.61 (1.4-13)
	CI	1.04 (0.6-1.5)
Treatment technique	HA	81 (46.6%)
	VMAT	93 (53.4%)
First response in MRI	CR	14 (6%)
	PR	62 (35.6%)
	SD	10 (5.7%)
	PD	23 (13.2%)
iPFS		6.3 (1-33)
OS		6.6 (1-42)

CI, conformity index; CR, complete response; GI, gradient index; HA, hyperarc; iPFS, intracranial progression-free survival; MRI, magnetic resonance Imaging; OS, overall survival; PD, progressive disease; PR, partial response; PTV, planning tumor volume; SD, stabile disease; VMAT, volumetric arc therapy; WBRT, whole brain radiotherapy.

Stereotactic Radiosurgery/Fractionated Stereotactic Radiosurgery Treatment Parameters

The median total SRS/fSRS dose was 27 (15-30) Gy. The median fraction dose was 9 (5-24), and the median fraction number was 3 (1-5). Treatment was given to 16 (18.8%) patients every other day, and 36 (42.4%) had concomitant steroid use. WBRT was given to 5 (6.4%) patients. WBRT was administered as the primary treatment for 4 patients with multiple brain metastases. In the follow-up of these patients, SRS/fSRS was applied to the progressive lesion. The median time between WBRT and SRS/fSRS was 120 (0-630) days. In 1 patient with multiple brain metastases, SRS was applied to the larger lesion together with WBRT. WBRT was at 30 Gy in 3 (3.5%) patients, 25 Gy for 1 (1.2%), and 20 Gy for 1 (1.2%). Surgery was performed on only 6 (3.4%) lesions.

While SRS/fSRS was applied to 7 (70%) of 11 patients who received IT due to progression, 2 of them were applied SRS/fSRS for both progression and septum control, and 1 (10%) of them was considered as oligometastatic because of metastatic at the time of diagnosis. Stereotactic radiosurgery/fractionated stereotactic radiosurgery was applied to 7 (87%) of 8 patients who received targeted therapy due to progression, and 1 (13%) of them being metastatic at the time of diagnosis, which was accepted as oligometastatic.

In all patients who underwent surgical resection, SRS/fSRS was applied to the cavity after resection. The median long tumor diameter was 11 (0.4-52) mm. The median tumor volume was 1 (0.1-56.9) cc. The median GI was 4.61 (1.4-13). The median CI-Radiation Therapy Oncology Group was 1.04 (0.6-1.5). Hyperarc was used in 81 (46.6%) patients and VMAT in 93 (53.4%). Critical organs within 5 mm of each lesion were evaluated, finding 1 (0.6%) tumor chiasma and 11 (6.3%) tumors close to the brain stem (Table 1). When analyzed according to tumor size, tumors >0.5 cc had lower GIs than tumors ≤0.5 cc ($P < .001$; Z = −7944; Table 2**;** Figure 1).

Stereotactic Radiosurgery/Fractionated Stereotactic Radiosurgery Lesion Response Assessment

Response Assessment in Neuro-Oncolog–brain metastasis criteria are standardized across clinical studies involving BMs and are recommendations for assessing tumor response and progression. The RANO-BM criteria divide treatment responses into 4 groups [CR, PR, stable disease (SD), and PD] based on imaging (MRI or CT) and clinical features.[10] This study used the RANO criteria to evaluate the MRI response. Patients with a CR at their first follow-up after RT had a better OS. Evaluation based on these criteria can predict clinical outcomes.

Of the 174 lesions, 109 (62.6%) had initial MRI controls. According to RANO–BM criteria, 14 (6%) had a CR, 62 (35.6) had a PR, 10 (5.7%) showed SD, and 23 (13.2%) showed PD. The CR rate was higher for lesions in patients who received targeted therapy (Table 3; $P < .001$; odds ratio (OR) = 0.0025, 95% CI = 0.006-0.109). Intracranial recurrence was observed in 28 (32.9%) patients after SRS/fSRS, of which 7 (8.2%) were inside the RT field, 13 (15.3%) were outside the RT field, and

Table 2. Tumor Volume, Gradient Index

Tumor Volume	>0.5 cc	≤0.5 cc
GI_Mean	4.265	7.000
GI_Median	4.000	5.800

GI, gradient index.

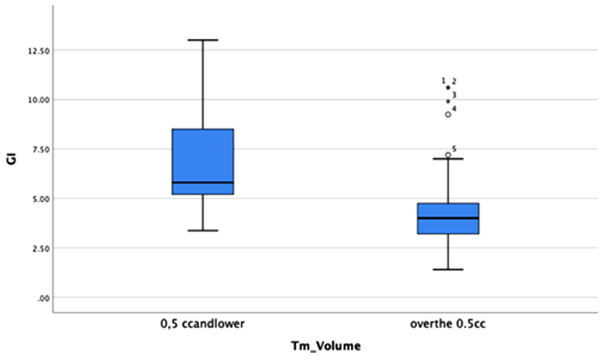


Figure 1. Gradient index and tumor volume box-blot image.

Table 3. Target Therapy and First Magnetic Resonance Imaging Response Relations

Target Therapy	First MRI Response		*P*	OR (95% CI)
	CR	Others		
No	3 (21.4%)	87 (91.6%)	<.001	0.0025 (0.006-0.109)
Yes	11 (78.6%)	8 (8.4%)		

CR, complete response; MRI, magnetic resonance imaging; OR, odds ratio.

8 (9.4%) overlapped the RT field. Patients with CR at their first follow-up had a significantly positive effect on OS compared to the other factors (Figure 2; *P* = .011; HR = 6.32, 95% CI = 1.53-26.01).

Intracranial Progression Free Survival Analysis

The relationships between the patients' response status at their initial control MRI and their OS and iPFS were analyzed. Patients with PD in their first control had a significantly negative effect on iPFS than the others (*P* < .001; HR = 0.116, 95% CI = 0.054-0.251; Figure 3), with a median iPFS of 5.3 (1-33) months. Intracranial recurrence was observed in 28 (32.9%) patients after SRS/fSRS, of which 7 (8.2%) were inside the RT field, 13 (15.3%) were outside the RT field, and 8 (9.4%) overlapped the RT field. Intracranial progression-free survival could be evaluated in 72 patients. While 10 patients who could not be evaluated died before the first control, 3 were excluded from the follow-up. Intracranial progression-free survival was not significantly affected by the number of metastases (*P* = .146), SRS/fSRS total dose (*P* = .576), SRS/fSRS fraction dose (*P* = .476), fraction number (*P* = .993), tumor volume (*P* = .637), longest tumor diameter (*P* = .420), GI (*P* = .878), CI (*P* = .662), RT technique (*P* = .086), sex (*P* = .956), extracranial metastases (*P* = .968), every-other-day treatment scheme (*P* = .361), steroid use (*P* = .348), age (*P* = .789), 5 mm adjacent critical organ (*P* = .554), targeted therapy (*P* = .425), or tumor bed RT status (*P* = .930). However, iPFS was significantly correlated with WBRT dose (*P* = .026; r_s = −0.866) and concurrent IT (*P* = .028; HR = 0.107, 95% CI = 0.015-0.783; Figure 4).

Overall Survival Analysis

Of the included patients, 53 (62.4%) were deceased, and 32 (37.6%) were alive. Their median OS was 6.6 (1-42) months. Overall survival was not significantly affected by the number of metastases (*P* = .900), SRS/fSRS total dose (*P* = .400), SRS/fSRS fraction dose (*P* = .278), fraction number (*P* = .284), tumor volume (*P* = .869), long tumor diameter (*P* = .266), GI (*P* = .751), CI (*P* = .518), WBRT total dose (*P* = .718), the time between WBRT and SRS/fSRS (*P* = .872), sex (*P* = .058), the presence of extracranial metastases (*P* = .9), treatment every other day (*P* = .965), steroid use (*P* = .528), age (*P* = .627), 5 mm adjacent to the critical organ (*P* = .655), concurrent IT status (*P* = .369), and WBRT status (*P* = .972). However, OS was significantly affected by the RT technique (*P* = .011; HR = 1.64, 95% CI = 1.119-2.414) and targeted therapy (*P* = .035; HR = 0.217, 95% CI = 0.053-0.897; Figure 5 and 6). Overall survival was significantly better in patients with CR at the first control than in the others (*P* = .011; HR = 6.32, 95% CI = 1.53-26.01; Figure 2).

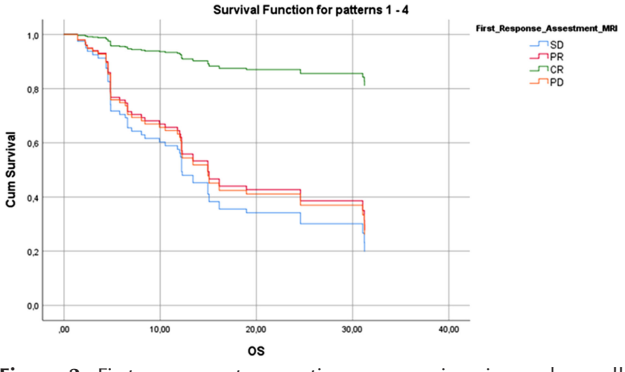


Figure 2. First assessment magnetic resonance imaging and overall survival Cox regression analysis image.

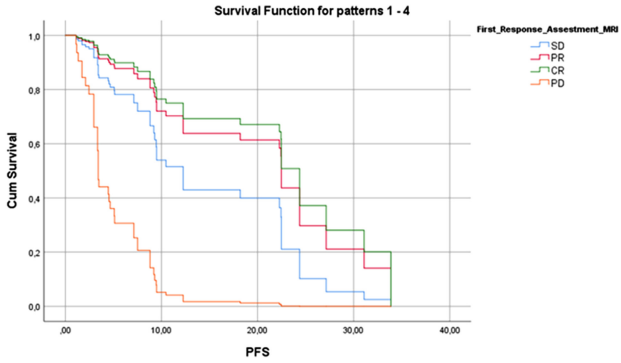


Figure 3. First assessment magnetic resonance imaging and intracranial progression-free survival Cox regression analysis image.

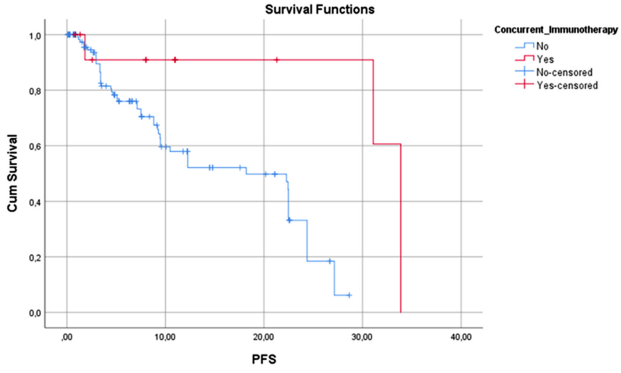


Figure 4. Images of intracranial progression free survival and concurrent immunotherapy Kaplan–Meier analysis images.

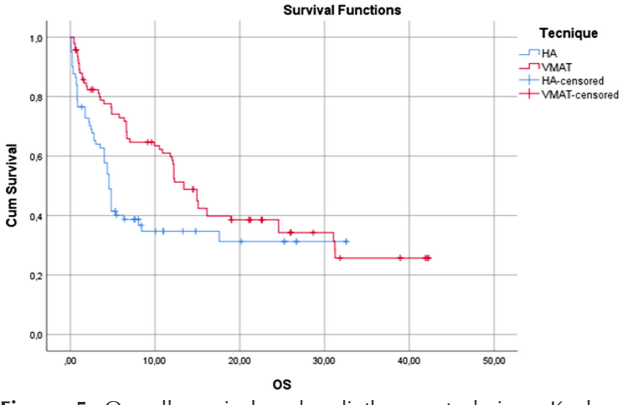


Figure 5. Overall survival and radiotherapy technique Kaplan–Meier analysis images.

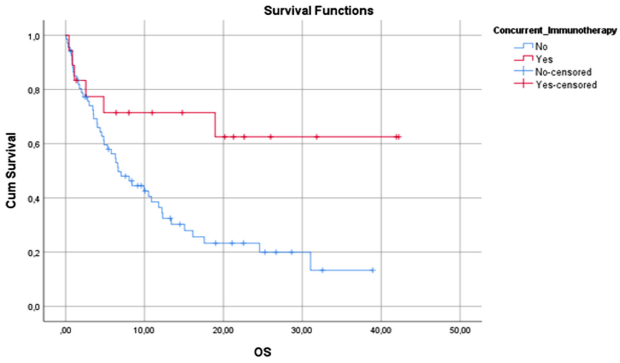


Figure 6. Overall survival and targeted therapy Kaplan–Meier analysis images.

DISCUSSION

This study examined 174 lesions in 85 patients with NSCLC–BM treated with SRS/fSRS. The CR rate was higher in patients receiving the targeted therapy than in others. Patients with a PD response at their first control had a significantly worse iPFS than the others. Patients with a CR response at their first control had a significantly better OS than the others.

In patients with BMs, the reported 7- to 14-month survival rates after SRS/fSRS are similar to surgical resection.[11] Although surgery is indicated for lesions >3 cm that cause a mass effect and are suitable for resection, SRS/fSRS is often preferred in current clinical practice because it is a less invasive and more cost-effective treatment option than resection. Leyrat et al evaluated SRS/fSRS in NSCLC–BM patients, finding a median follow-up period of 12 months and a median OS of 14 months.[12] Minitti et al reported that OS was 15.2 months after SRS/fSRS in NSCLC–BM patients with a median follow-up period of 12 months.[13] In our study, ablative RT doses were applied to lesions considered oligometastatic. Our follow-up period was 6 months, and our median OS was 6.6 months and the iPFS was 5.3 months, and we expect higher OS and iPFS could be obtained by prolonging the follow-up period.

The interactions between immune checkpoint inhibitors (ICIs) and SRS/fSRS must be investigated due to the increasing number of patients with metastatic cancer receiving ICIs. Stereotactic radiosurgery and fSRS act synergistically with immune regulators through many mechanisms, including tumor antigen release, increased antigen-presenting cell activation, increased blood–brain barrier permeability, and cell surface molecule upregulation.[14-16] Clinical data show that combining RT and ICIs increases OS if ICIs are started at least 30 days before and continued throughout RT therapy.[17,18] In our study, there was a significant relationship between IT use and iPFS, consistent with the literature, but not with OS. We believe that this may be due to our small number of patients.

While these combined therapies have survival benefits, there are concerns that combining SRS/fSRS and immune regulators may increase the risk of toxicity. In a retrospective study by Ahmed[19] et al, no additional toxicity was observed after co-administrating SRS/fSRS and anti-PD1/PDL1 treatment in NSCLC patients with BMs. Similarly, there is reassuring data on the safety profile and efficacy of combining anti-PD1/anti-PDL1 agents and various RT regimens (SRS/fSRS and WBRT).[20] There was only a potential warning of increased radionecrosis risk. Unlike these studies, other studies have shown that combined therapy increases side effects such as radionecrosis. A retrospective study evaluating 80 patients with melanoma showed that combining SRS/fSRS with an ICI increases symptomatic radionecrosis risk.[21] Another study by Martin et al[22] observed an increase in symptomatic radionecrosis after combining SRS/fSRS with an ICI in a patient population with NSCLC, melanoma, and renal cell carcinoma. However, most of this patient population comprised melanoma patients. In general practice, 50% of clinicians do not interrupt ICI when applying SRS/fSRS or WBRT to the brain.[23] In our study, no serious side effects were observed during patient follow-up.

The most important limitations of the study are its single-center and retrospective nature. The number of patients was small, the follow-up period was short, and long-term side effects could not be evaluated. Due to the lack of patient files, CT details such as the number of CT courses could not be reached for all patients.

CONCLUSION

This study examined patients who have undergone SRS/fSRS for diagnoses of NSCLC and BMs, evaluating the patients' treatment responses with the RANO criteria. Patients with CR according to the RANO criteria showed better survival. Intracranial progression-free survival increased with SRS/fSRS and IT, and OS increased with targeted agents and RT.

Ethics Committee Approval: This study was approved by Ethics Committee of Ankara Bilkent University City Hospital (Approval No: E1-22-2874, Date: 07.09.2022).

Informed Consent: Since the study is a retrospective study, informed consent was not obtained from the patients.

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Original Article

Clot Burden As a Predictor of Chronic Thromboembolic Pulmonary Hypertension After Acute Pulmonary Embolism: A Cohort Study

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Abstract

OBJECTIVE: A small percentage of acute pulmonary thromboembolisms (PTE) persist as chronic fibrin clots, potentially leading to chronic thromboembolic pulmonary hypertension (CTEPH). A scoring system for evaluating the burden of acute PTE based on computed tomography pulmonary angiogram (CTPA) findings was tested for its association with CTEPH within one year.

MATERIAL AND METHODS: In this retrospective cohort of 475 patients with a definitive diagnosis of acute PTE, the Qanadli score (QS) was calculated on the initial CTPA. Through regular follow-up over 1 year, symptomatic patients underwent extensive evaluation.

RESULTS: Of the 475 patients enrolled in the study [age 58.3 ± 16.6, 195 (41.1%) female, QS: 13.01 ± 7.37/40], 321 patients completed the study. A total of 22 (6.8%) patients were definitively diagnosed with CTEPH. In univariate analysis, the initial QS was significantly higher in patients with subsequent CTEPH than in patients without (17 ± 5.6 vs. 13 ± 7.6, $P = .009$). QS was directly associated with CTEPH (odds ratio: 1.08, 95% confidence interval: 1.0-1.16, $P = .042$). The evolution of CTEPH in men could be predicted with a sensitivity of 100% and a specificity of 54% when a cut-off point of 14.5 (43.5%) was set for QS. The area under the receiver operating characteristic curve in this setting was 0.74 with a *P*-value of .032. Qanadli score failed to predict CTEPH in women.

CONCLUSION: Scoring the clot burden in the pulmonary arteries through the Qanadli method can predict the evolution of CTEPH only in men 1 year after acute PTE. Women comprise most of the CTEPH patients. Thus, strict follow-up adherence seems to be even more important in women.

KEYWORDS: Pulmonary embolism, chronic thromboembolic pulmonary hypertension, computed tomography angiography, Qanadli index

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INTRODUCTION

Around 900 000 people are annually affected by venous thromboembolism in the United States.[1] Although signs and symptoms of acute pulmonary thromboembolism (PTE) depend on the size and location of the clot in the pulmonary arterial tree, it usually presents as acute-onset dyspnea.[2,3] Computed tomography pulmonary angiogram (CTPA) has proven to yield valuable information in the evaluation of acute PTE. Two commonly used indices of pulmonary arterial obstruction severity have been proposed by Qanadli et al[4] for CTPA and Miller et al[5] in angiography. Qanadli score (QS) closely correlates with the Miller index, oxygen saturation, and pulmonary artery pressure and helps distinguish massive PTEs.[6] Around 0.1%-11.8% of survivors of acute PTE eventually develop chronic thromboembolic pulmonary hypertension (CTEPH).[7] It is defined as a mean pulmonary artery pressure ≥25 mmHg and pulmonary artery wedge pressure ≤15 mmHg and a mismatch in perfusion–ventilation despite 3 months of optimal anticoagulation.[8] Although QS can aid in predicting the complications and outcomes of acute PTE, it is not clear if the clot burden is associated with the evolution of CTEPH in the future. It is noteworthy that about 30% of acute PTE patients have persistent perfusion defects after 6 months of anticoagulation, but only 10% of this population will develop CTEPH. Recurrent unprovoked VTEs, delayed onset of anticoagulation, the large size of the initial thrombus, and older age are risk factors for the evolution of chronic perfusion defects.[7,9] Early diagnosis of CTEPH is essential to prevent small vessel vasculopathy and right heart failure.[10] In this retrospective cohort study, the correlation between the initial QS and the evolution of CTEPH was assessed in a 1-year follow-up.

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MATERIAL AND METHODS

Study Material

The present study was conducted from January 2016 to October 2019. All patients received the standard of care based on the latest recommendations by the European Society of Cardiology. In this single-center retrospective cohort, all consecutive adult (≥18 years old) patients with a confirmed diagnosis of acute PTE were included. Patients diagnosed with modalities other than CTPA were excluded. Due to a paucity of evidence regarding the impact of fibrinolytics in the evolution of CTEPH and to avoid the inclusion of patients with additional interventions, those who received fibrinolytic were excluded from the study.

Follow-Up

The patients were followed for 1 year after the acute PTE. Patients who had remained symptomatic after 3 months of optimal anticoagulation underwent transthoracic echocardiography. If pulmonary hypertension was highly probable, based on the last PH guideline, a V/Q scan was performed for screening CTEPH. Patients with at least 1 large segmental perfusion defect were considered to have CTEPH. To rule out other diagnoses such as angiosarcoma or major vessel arteritis and evaluation for operability, CTPA was performed. All patients underwent right heart catheterization (RHC) for a definite diagnosis, hemodynamic examination, and determination of pulmonary vascular resistance (PVR), mean pulmonary artery pressure (mPAP), cardiac output (CO), and right atrial (RA) pressure. A Swan–Ganz catheter (Edwards Lifesciences company, Irvine, California, USA) was employed for all cases.

Computed Tomography Pulmonary Angiography and Qanadli Obstruction Index

Computed tomography pulmonary angiogram imaging was obtained using a 64-slice multi-detector computed tomography device (Somatom Sensation 64, Siemens, Munich, Bavaria, Germany). The procedure was set at 120 kV, 100 mAs, beam collimations of 0.6 mm, and a pitch of 1.22. Images were reconstructed in 1 mm thicknesses and 0.7 mm increments. Using an infusion pump (Ulrich Medical, Ulm, Baden-Württemberg, Germany), 80 mL of contrast media with an iodine concentration of 370 mg/mL was infused at a rate of 5 mL/sec through the antecubital vein. Before and after the infusion, 20 mL of normal saline was infused as an extravasation check and washout bolus. A test bolus in the lumen of the pulmonary trunk calculated the scan delay time, a method described by Wu et al.[11] The obstruction index was calculated according to the method proposed by Qanadli et al.[4] Each lung receives 10 segmental arteries (5 for the lower, 3 for the upper, and 2 for the middle lobe or lingula). The perfusion defect in a given artery is scored 1 if partially occluded and 2 if complete occlusion has occurred. The sum of scores from each involved arterial branch equals the Qanadli obstruction score (QS). Thus, the maximum score is 40. The obstruction index can then be calculated as a percent (Figure 1). Since PTE of the segmental and subsegmental arteries can be over-diagnosed, especially in patients with tachypnea and low pretest probability of acute PTE,[12,13] 2 radiologists evaluated the CTPA images separately. Eventually, patients with scores with higher inter-observer agreement were enrolled in the study.

Ventilation–Perfusion Scintigraphy

Patients with a high probability of pulmonary hypertension or low probability without any other reason better explaining the dyspnea underwent a V/Q scan. Scans were performed according to the European Association of Nuclear Medicine guidelines.[14] First, a perfusion scan using ^{99m}Tc-MAA was performed to rule out defects. If there was a suspicious defect(s), at least 24 hours later, a ventilation scan using ^{99m}Tc-DTPA nebulize was performed to check for any mismatches. The probability of persistent thrombus was evaluated according to modified PIOPED criteria. Patients with a high probability of chronic thrombus underwent RHC to investigate the right heart function and mechanics of pulmonary circulation.

Statistical Analysis

The fitness of the numerical variables to normal distribution was assessed via a 1-sample Kolmogorov–Smirnov test. Data was described as mean (SD) for numerical and frequency (percentage) for categorical variables. Comparisons between the 2 groups were performed by independent sample *t*-test for numerical and Pearson's chi-square or Fisher's exact test for categorical variables. Binary logistic regression models were applied for assessing adjusted associations between CTEPH and predictors. $P < .05$ was considered a statistically significant result. The accuracy of QS for diagnosis of CTEPH was assessed via the area under the receiver operating characteristic (ROC) curve (AUC). For interpretation, AUC was considered as no discrimination ability in 0.5-0.6, weak accuracy in 0.6-0.7, acceptable in 0.7-0.8, excellent in 0.8-0.9, and outstanding in 0.9-1. All measurements are presented with a confidence interval (CI) of 95%. The IBM Statistical Package for the Social Sciences Statistics version 22.0 for Windows (IBM Inc., Armonk, NY, USA) was applied for statistical analysis.

Ethics Committee Approval

The study protocol was approved by the ethics committee of the Tabriz University of Medical Sciences, Iran (reference number IR.TBZMED.REC.1396.1058). All patients were thoroughly informed about the study design and were assured that no identifiable data would be shared. All patients or their next of kin signed the informed consent form.

MAIN POINTS

- Early detection and treatment of chronic thromboembolic pulmonary hypertension (CTEPH) may prevent further pulmonary vasculopathy and right heart remodeling.
- In this cohort, 6.8% of all patients with acute pulmonary embolism (PTE) were complicated with CTEPH after a one-year follow-up.
- Burden of the initial clot, measured through Qanadli score, was aligned with evolution of CTEPH.
- Among male patients, Qanadli score was shown to predict he evolution of CTEPH with an area under the curve of 0.74 when a cut-off point of 14.5 (i.e. 43.5%) was set. However, among female patients, it failed to show statistical significance.

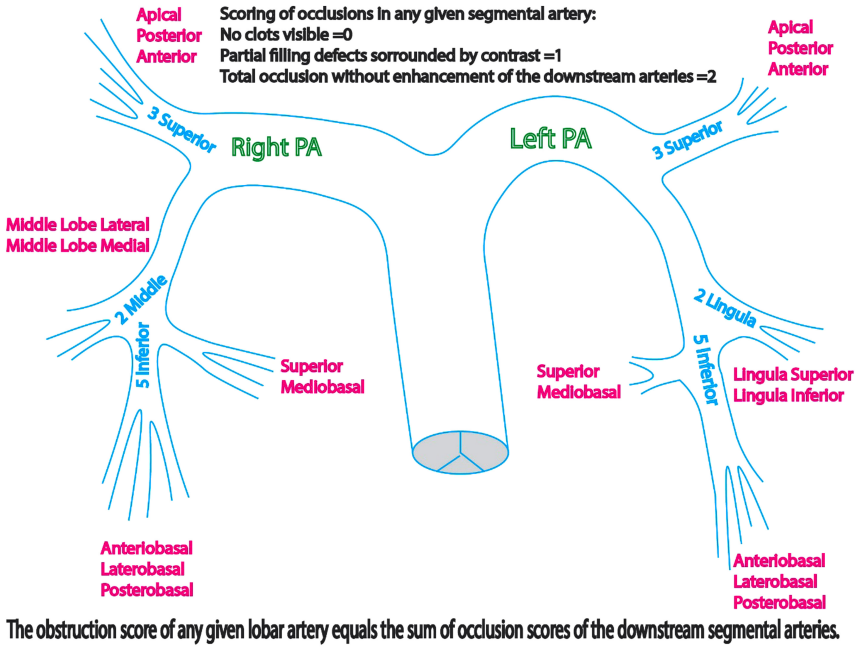


Figure 1. Calculation of the Qanadli obstruction score. The maximum possible score in this scoring system is 40. To report the index in percent, the score should be multiplied by 2.5. In our study, the original score was applied to the analysis. All rights reserved. Copyright for the image: The image in Figure 1 was created using Adobe Illustrator version 2022 by the authors of the present study. All rights for using the image are reserved.

RESULTS

Three hundred twenty-one patients (57% men, age 57 ± 16.3 years) were included in the analysis. Patients' baseline characteristics are described in Table 1.

Twenty-two patients (6.8%) were definitively diagnosed with CTEPH. Associations between the presence of CTEPH and patients' characteristics were assessed, and the results are presented in Table 2. More female patients and patients with higher QS at baseline were observed in the CTEPH group. Considering the potential effects of other relevant factors, including age, provoked versus unprovoked, surgery, and OCP, multivariable analysis was performed using binary logistic regression models.

Table 1. Baseline Demographic, Clinical, and Imaging Characteristics in the Study Population

Characteristics	
Age (years) mean (SD)	57 (16.3)
Sex, n (%)	
Male	184 (57%)
Female	137 (43%)
Surgery, n (%)	58 (18%)
Trauma with fracture, n (%)	31 (10%)
OCP*, n (%)	8 (3%)
Provoked PE, n (%)	192 (40%)
Baseline anatomy of pulmonary vasculature,† n (%)	
Right	56 (18%)
Left	26 (8%)
Bilateral	209 (65%)
Bifurcation	27 (8%)
Symptom, n (%)	107 (33%)
Qanadli score mean (SD), [minimum-maximum]	13 (7.5), [1-30]

Patients characteristics (n = 321).
*OCP, oral contraceptive pills that contain estrogen.
†Based on CT pulmonary angiogram.

Table 2. Baseline Demographic, Clinical, and Imaging Characteristics in the Study Population in Patients With and Without CTEPH During Follow-Up

Variable	CTEPH − (n = 299)	CTEPH + (n = 22)	*P*
Age (years) mean(SD)	57 (16.5)	53 (16.9)	.370
Gender, n (%)			.039
Male	176 (59%)	8 (36%)	
Female	123 (41%)	14 (64%)	
Surgery, n (%)	56 (19%)	2 (9%)	.257
Trauma, n (%)	30 (10%)	1 (5%)	.400
OCP, n (%)	7 (2%)	1 (5%)	.522
Provoke, n (%)	143 (48%)	8 (36%)	.299
Anatomy, n (%)			.124
Right	56 (19%)	0 (0%)	
Left	25 (8%)	1 (5%)	
Bilateral	192 (64%)	17 (90%)	
Bifurcation	26 (9%)	1 (5%)	
Qanadli score mean (SD)	13 (7.6)	17 (5.6)	.009

Univariable analysis, Comparisons between patients with and without CTEPH.
CTEPH, chronic thromboembolic pulmonary hypertension; OCP, oral contraceptive pills that contain estrogen.

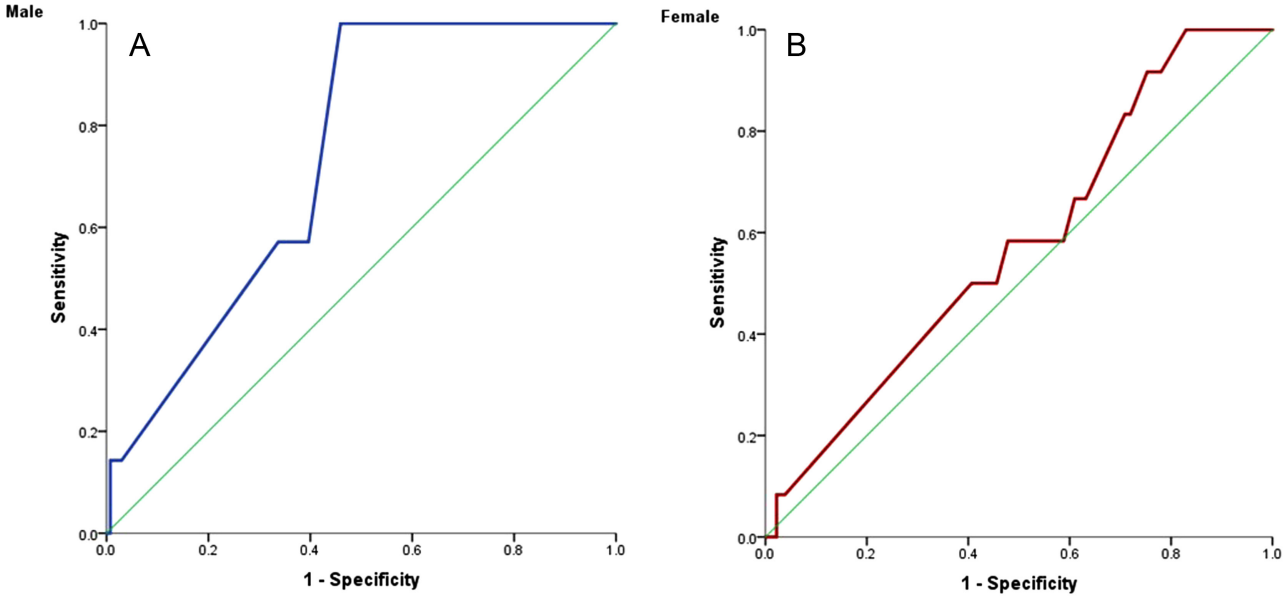


Figure 2. (A) Receiver operating characteristic curve of Qanadli score correlation with the evolution of CTEPH in men. (B) Receiver operating characteristic curve of Qanadli score correlation with the evolution of CTEPH in women. CTEPH, chronic thromboembolic pulmonary hypertension.

The accuracy of QS for diagnosis of CTEPH was assessed via the area under the ROC curve (AUC) (Figure 2). It was observed that only in men, QS had acceptable accuracy [AUC (95% CI): 0.74 (0.61-0.87) and can be used for diagnosis of CTEPH (Table 3).

In multivariable analysis, it was found that in the total population, QS had a statistically meaningful direct association with the presence of CTEPH. However, the correlation was weak [odds ratio (OR) 1.08, 95% CI: [1.00-1.16], *P* = .042] (Table 4, model 3). Besides, separate models were provided for male and female gender (Table 4, models 1 and 2). No significant associations were observed between CTEPH and the factors mentioned earlier in women. On the other hand, in men, CTEPH had a reverse association with unprovoked PTE [OR (95% CI): 0.04 (0.00-0.86), *P* = .040] and strong, direct association with the history of surgery [OR (95% CI): 17 (1.14-265), *P* = .040]. Also, borderline association was observed with QS and CTEPH [OR (95% CI): 1.15 (0.97-1.37), *P* = .102].

Table 3. Area Under the ROC Curve, Qanadli Score for Diagnosis of CTEPH

	AUC (95% CI)	*P*
Male*	0.74 (0.61-0.87)	.032
Female	0.58 (0.42-0.73)	.375

AUC, area under the curve; CTEPH, chronic thromboembolic pulmonary hypertension; ROC, receiver operating characteristic.
*Cut-off point for Qanadli Score: 14.5 (sensitivity = 1, specificity = 0.54).

DISCUSSION

Up to 12% of acute PTEs will eventually be complicated with CTEPH.[7] Before the introduction of pulmonary thromboendarterectomy (PEA), the 5-year survival for CTEPH patients was only 10%.[15] With PEA, the 5-year survival has improved to 72%.[16] Delayed diagnosis of CTEPH can lead to downstream small-vessel vasculopathy and right heart remodeling. Currently, there is 1-year delay in the diagnosis of CTEPH after acute PE.[17] By identification of patients at risk, this delay can be shortened. The incidence of CTEPH in this cohort was 6.8%. Women were found to be significantly predisposed to CTEPH after an acute PTE. Notably, about 25%

Table 4. Binary Logistic Regression Models

	Male (Model 1)		Female (Model 2)		Overall (Model 3)	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Score	1.15 (0.97-1.37)	.102	1.05 (0.95-1.14)	.298	1.08 (1.00-1.16)	.042
Provoke	0.04 (0.00-0.86)	.040	2.82 (0.78-10.22)	.115	0.99 (0.36-2.78)	.992
Age	0.99 (0.94-1.04)	.722	0.99 (0.95-1.02)	.577	0.99 (0.96-1.02)	.428
Surgery	17 (1.14-265)	.040	0	.998	.63 (0.12-3.28)	.464
OCP	-	-	0.49 (0.05-5.25)	.558	-	-
Gender*	-	-	-	-	2.45 (0.92-6.50)	.072

**P*-value for score–gender interaction = .157.
OCP, oral contraceptive pills that contain estrogen; OR, odds ratio.

of CTEPH patients do not have a history of diagnosed acute PTE.[18] Virchow's triad of endothelial injury, stasis, and prothrombotic state describes the favorable conditions for the DVT evolution.[19] However, these predisposing factors may not always be identifiable. These unprovoked VTEs carry a 7.4% per patient-year risk of recurrence.[20] Unlike other studies, unprovoked PTE was not significantly associated with CTEPH.

The Qanadli obstruction score is a semi-quantitative estimation of the clot burden which was proposed by Qanadli et al[4] in 2008. In a study of 60 patients with acute PTE, patients with adverse outcomes did not have a significantly different QS than those without. However, a Qanadli index >20% predicted adverse outcomes in ROC analysis.[21] In another study, this scoring model did not correlate well with right ventricular (RV) dysfunction.[22] The largest data available suggested that among CTPA parameters, only right/left ventricular diameter ratio >1.0 could predict death within 30 days, in multivariate analysis, while both Qanadli and Mastora indices failed.[23] The ineffectiveness of QS in predicting mortality was confirmed by the meta-analysis of pooled data from 19 studies.[21] Although QS is not a reliable predictor of short-term outcomes, it correlates closely with the pre-operative PVR and mPAP in CTEPH patients and can predict the response to pulmonary artery thromboendarterectomy.[24] In a previous study, a QS <16 was associated with complete resolution of thrombus.[25] The presence of endothelialized chronic fibrin clots is necessary but not sufficient for the evolution of CTEPH.[9] Our study focused on the evolution of CTEPH rather than unresolved thrombus, and in this regard, higher QSs was correlated with the evolution of CTEPH. In our study, higher obstruction scores were correlated with CTEPH evolution. Moreover, a QS of more than 14.5 (43.5%) had a sensitivity of 100% and specificity of 54% for predicting CTEPH in men. As high as 90% of patients with RV dysfunction (indicated as elevated RV/LV diameter ratio) have a QS >40%-43%.[4,26] Although higher QS was correlated with CTEPH in men, this was not the case in women.

Although we cannot positively explain the inability of QS in predicting CTEPH in the female gender, it might be due to the low statistical power of the study or some other unknown gender-related factor involved in the pathophysiology of CTEPH.

Limitations of this study include the retrospective methodology and a high rate of lost to follow-up. Future studies should use additional indices and more precise reconstruction methods to overcome the disadvantages of the present methods. Especially, QS failed to predict CTEPH in women, who comprise the majority of CTEPH patients.

CONCLUSION

Qanadli obstruction score has a direct association with the evolution of CTEPH in men within 1 year after acute PTE. The results for women were not statistically significant. Recognition of patients at risk would help in the early diagnosis of CTEPH and avoiding downstream vasculopathy and RV remodeling. Since most CTEPH patients are women, it is imperative to encourage them to adhere to follow-up strictly and have a low threshold for further investigation in female patients with persistent symptoms. All patients with V/Q mismatch should be referred to a CTEPH clinic for optimal management.

Ethics Committee Approval: The study protocol was approved by the ethics committee of the Tabriz University of Medical Sciences, Iran (approval number IR.TBZMED.REC.1396.1058).

Informed Consent: All patients were completely informed about the study design and were assured that no identifiable data would be shared. All patients or their next of kin signed the informed consent form.

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Letter to the Editor

Safety of Fiberoptic Bronchoscopy in Airway Pressure Release Ventilation Mode in Critically Ill Patients: Are These Results Safe?

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Dear Editor,

The current recommendations for performing bronchoscopies in intubated and mechanically ventilated patients indicate that the tidal volume (Vt) can be increased between 100 and 150 mL or the pressure limits/inspiratory pressures which guarantees an adequate Vt and ventilator setting should preferably be in mandatory mode.[1]

We have carefully read the recently published study titled, "The Safety of Fiberoptic Bronchoscopy in Airway Pressure Release Ventilation Mode in Critically Ill Patients with Severe Acute Respiratory Distress Syndrome: A Preliminary Study"[2] and have the following concerns regarding the methodology, validity, and recommendations made on the basis of the reported results.[3]

First, the authors describe a sample of 79 ventilated patients undergoing bronchoscopy, including 14 patients with severe acute respiratory distress syndrome (ARDS) with partial pressure of arterial oxygen (PaO_2)/fraction of inspired oxygen (FiO_2)142 (119-221). Four patients were excluded due to missing data, which could represent up to one-quarter of the patients undergoing bronchoscopy in the APRV mode (22% of missing data).

Second, the intensive care unit sedation protocol in this study included midazolam and fentanyl infusions with a neuromuscular relaxant rocuronium as needed during the procedure. However, the authors do not detail the need for relaxation. In daily practice, the use of muscle relaxants in critically ill patients requiring bronchoalveolar lavage (BAL) is generally due to bronchospasm, patient-ventilator maladjustment, or elevated airway pressure.[3] However, these factors should not be at play here as APRV encourages spontaneous breathing efforts to increase the final end-inspiratory transpulmonary pressure much higher than the set P-high of 30 cm H_2O.[4]

Third, the authors describe premature termination of the procedure, hypoxemia, and increased requirement for vasopressors within the first 24 hours in 3/14 patients, representing 21% of complications during the procedure. The high incidence of mortality (10/14, 71.4%) described in this series with the use of this ventilatory mode was striking as ARDS is characterized by a lower global mortality near 40%-60%.[5]

Fourth, despite the authors reporting that all procedures were performed by an intensivist-pulmonologist with >15 years of expertise in performing FB in critically ill patients. The mean values of pH 7.28 (7.21-7.37) 1 hour after the procedure are striking: during bronchoscopy in ventilated patients with severe ARDS, special attention should be paid to Vt drops and leak compensation during the performance of the procedure, particularly during the introduction of the bronchoscope into the airway.

The Evita Infinity V500 quickly recognizes and compensates for leakage by adjusting both the inspiratory trigger and termination points. There were no leak monitoring reports or the use of a compensation mechanism during the performance of these procedures.

Fifth, in this series, 35% of the patients had a diagnosis of severe ARDS secondary to pneumonia, and only 20% of the patients survived with some post-bronchoscopy antibiotic adjustment. In critically ill patients with severe ARDS, routine

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bronchoscopy-guided sampling for the diagnosis of ventilator-associated pneumonia is recommended in patients not responding to empirical antibiotic therapy.

In short, we believe that until further conclusive evidence is available, fiberoptic bronchoscopy in patients with biphasic APRV ventilation mode should be performed with utmost caution.

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Editor's Note: No response was received from Öztürk et al.

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