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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.

Journal History

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

Abstracting and indexing

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

Aims, Scope, and Audience

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

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

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

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

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Thoracic Research and Practice annually publishes an acknowledgement letter to thank all the reviewers of the previous year. Among the reviewers, some are distinguished with their performances and categorized as "Special Distinction in Reviewing". "Editor's Recognition Awards" category includes the reviewers who consistently provide top level service to Thoracic Research and Practice. Many thanks to all reviewers, authors, and section editors for their priceless contribution to our journal.

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Editorial

In Memoriam Friedrich Krause

Feyza Erkan
Department of Lung Diseases, Haliç University, İstanbul, Turkey

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Prof. Dr. Friedrich Krause passed away peacefully on October 27, 2023 at his home in İstanbul at the age of 94 years.

Born on January 7, 1929, Professor Krause studied medicine in different universities Bamberg, Erlangen, Innsbruck and obtained his MD degree at the University Würzburg in 1956. Afterwards, he worked in USA, UK, Sweden, Switzerland and as Red Cross Doctor in Kongo. He became a Specialist in General Surgery in the University Tübingen, where he was appointed Associated Professor in 1970. From 1970 to 1975 he worked as a Consultant in the University Ulm, where he became a Professor. He is one of the first thoracic surgeons of Germany in times, when this branch was not classified as a specialization category. From 1975 to 1987 he worked as the Head of the Department of Thoracic Surgery in the Clinic Lowenstein, 1987-89 as a Co-Chief in the Oncology Clinic Bad Rappenau, 1989-91 as the Head of the General Surgery Clinic in Najran Saudi Arabia.

1991 he came to İstanbul, married Dr. Feyza Erkan, a Turkish academician. First he worked in Marmara and İstanbul Universities by contract as a guest professor. There he taught many assistans how to perform the mediastinoscopy und contributed to the widespread use of this technic in Turkey. After he had acquired Turkish citizenship, he began to work as a surgeon in private clinics, as a consultant doctor of German Consulate in İstanbul and as a Chief of a Low Dose Laser Clinic. His main research interests were staging and treatment of lung cancer, diagnostic value of mediastinoscopy and medical thoracoscopy and tumor immunology. He produced more than 100 publications relating to different aspects of thoracic surgery.

He was a great teacher and mentor always encouraging his young assistants to learn and practice the necessary skills, technics and supported generously their career. He taught with great pleasure and patience. His humility, kindness and gentle approach to others will be a lifelong source of inspiration to all people who knew him. He had also committed himself to his patients with compassion. He saw not only the illness, but the human as a whole. Besides their diseases he was fully engaged in all other problems of his patients and tried to help them with all means. He had so much love for all humanbeings without any prejudice and was feeling himself responsible to help others whatever he could do.

He enjoyed to live in Turkey and had visited nearly all parts of this country. He was interested in nature, history and archeology.

He was always open to new knowledge and new ideas, tried to follow all scientific developments. Although he had some physical handicaps of his old body in his last years, he tried with strength and courage to overcome all the restrictions, continued to learn, contact people and share his wisdom till the end.

He was a dedicated member of Turkish Thoracic Society, took part in all congresses as long as his health permitted.

He will be always remembered as an example of a good person, an academican and a teacher.

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Original Article

What is the Optimal Treatment Regimen of Low-Molecular-Weight Heparin in Coronavirus Disease 2019 Pneumonia?

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Abstract

OBJECTIVE: The optimal anticoagulant treatment regimen in hospitalized coronavirus disease 2019 (COVID-19) patients is uncertain. This study aimed to compare the rates of disease progression and mortality in patients treated with low-molecular-weight heparin (LMWH) according to baseline D-dimer levels and in those who received a fixed-dose regimen irrespective of the D-dimer level.

MATERIAL AND METHODS: This was a retrospective analysis of all patients admitted to a university hospital for COVID-19 pneumonia during a 1-year period. The protocol for D-dimer-driven therapy (on-protocol) was as follows: prophylactic dose when the baseline level is <1000 ng/mL, intermediate dose when the level is between 1000 and 3000 ng/mL, and therapeutic dose when the level is >3000 ng/mL. We compared the progression and mortality rates between the on-protocol and off-protocol treatment groups. The off-protocol group consisted of patients that received a fixed-dose LMWH regimen, which was not in accordance with the defined protocol.

RESULTS: Of 384 patients (mean age 61.5 ± 15.9 years, 216 male), 294 patients with complete data composed the study group, and 174 patients were treated on-protocol and 120 patients were treated off-protocol. The on-protocol group had lower C-reactive protein (CRP), ferritin, lactate dehydrogenase (LDH), and D-dimer levels and higher SpO_2/FiO_2 levels at admission. Disease progression developed in 45/174 on-protocol patients (25.9%) vs. 53/120 off-protocol patients (44.2%) during the follow-up ($P = .001$), and mortality was 29 (16.7%) vs. 32 (26.7%), respectively ($P = .041$). Logistic regression analysis was performed and included age, presence of comorbidities, LMWH regimen, baseline SpO2/FiO2, CRP, and LDH levels as independent variables. The presence of cardiac comorbidity, age, CRP, and LDH levels, but not the LMWH treatment regimen, were associated with both disease progression and mortality.

CONCLUSION: A D-dimer-driven LMWH treatment protocol is not associated with better clinical outcomes in hospitalized COVID-19 patients.

KEYWORDS: Anticoagulants, COVID-19, D-dimer, embolism, treatments
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INTRODUCTION

Several studies and autopsy examinations have shown an elevated incidence of microvascular/macrovascular and venous/arterial thrombosis with embolic events.[1-4] It has been hypothesized that coagulopathy may be caused by the direct viral effect of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on the endothelium or by a strong inflammatory response resulting in sepsis.[5,6] In severe coronavirus disease 2019 (COVID-19) patients, the presence of new thromboembolism and elevated D-dimer levels have been reported to be risk factors associated with mortality.[3,4,7]

D-Dimer is a fibrin degradation product, and its levels are known to be elevated in COVID-19-associated coagulopathy.[8,9] Studies found that higher D-dimer levels are closely related to prognosis and mortality.[2-4,10,11] Although high D-dimer levels were reported to have a high sensitivity and specificity for diagnosing venous thromboembolism in 1 study.[12] This biomarker is considered primarily to be a marker of poor overall outcome rather than a specific predictor of thromboembolic disease in COVID-19.[13,14]

Studies have shown that prophylactic anticoagulants are associated with better clinical outcomes and that treatment at therapeutic doses does not provide any further improvements in outcomes.[12,15-17] Two studies suggest that in noncritically ill hospitalized patients, anticoagulation at the therapeutic dose was associated with better outcomes.[18,19] However, the bleeding risk is expected to be higher at therapeutic doses. In the study of Lopes et al,[15] the bleeding risk was 8% and 2% in the therapeutic and prophylactic anticoagulation groups, respectively [relative risk 3.64 (95% CI, 1.61-8.27), $P = .0010$]. Current guidelines thus recommend anticoagulant therapy at prophylactic doses in patients with moderate-to-severe COVID-19.[2,11] On the other hand, some studies showed that anticoagulation at therapeutic doses is associated with lower mortality in patients with high (sixfold of the upper limit of normal) D-dimer levels and that anticoagulant treatment dosed according to D-dimer levels is associated with improved survival in critically ill COVID-19 patients.[17,18,20] Two cutoff levels

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for D-dimer, 1000 and 3000 ng/mL, were used in previous studies and have also been used in this study. The 2 earlier studies showed that an admission D-dimer level above 1000 ng/mL was an independent risk factor for mortality[18] and that treatment with therapeutic-dose low-molecular-weight heparin (LMWH) was associated with improved survival only in patients with D-dimer levels sixfold above the upper limit of normal (3000 ng/mL in the case of our institution).[17]

In this study, we aimed to determine whether D-dimer-driven LMWH treatment or prophylactic LMWH treatment is more effective in preventing disease progression and mortality.

MATERIAL AND METHODS

This was a retrospective analysis of the hospital records of all patients admitted to a tertiary-care center of Ege University Faculty of Medicine with a diagnosis of COVID-19 pneumonia between May 2020 and April 2021. All patients presented with acute-onset fever and/or pulmonary symptoms and had radiographic evidence of pneumonia, i.e., presence of new pulmonary infiltrates, including ground-glass opacities, interstitial infiltrates, and consolidation. They all needed supplemental oxygen therapy. All relevant clinical data of the patients were retrieved from an electronic database, which was developed at the beginning of the pandemic and included data on patient demographics, symptoms, clinical, laboratory, and radiographic findings, treatment, and clinical outcomes.

The study protocol conforms to the ethical guidelines of the 1964 Declaration of Helsinki and its later amendments, and it was approved by Institutional Ethics Committee of Ege University Faculty of Medicine (20-5T/48). Written informed consent was obtained from all patients during the time they were hospitalized for their clinical data to be registered in the database and used anonymously for scientific purposes.

The Study Population

A total of 384 patients who were admitted to a single tertiary-care center with a diagnosis of COVID-19 pneumonia were initially included in the study. Of these, 36 patients whose initial or follow-up D-dimer levels were not recorded, 54 patients who were not treated with any anticoagulant agent, and 11 and 8 patients who were already receiving aspirin or an oral anticoagulant, respectively, were excluded. Thus, the data from 294 patients who received low-molecular-weight heparin treatment and for whom all relevant data were available were analyzed.

Anticoagulant Treatment Regimens

An anticoagulant treatment protocol was established in the department early in the pandemic following the publication of reports of coagulopathy associated with COVID-19. Thus, the prophylactic dose of enoxaparin was given to patients whose admission D-dimer level was below 1000 ng/mL, the intermediate (twice the prophylactic) dose was given to patients with D-dimer levels between 1000 and 3000 ng/mL, and the therapeutic dose was administered to patients when the initial D-dimer level exceeded 3000 ng/mL.

Main Points

- The presence of cardiac comorbidity, age, C-reactive protein, and lactate dehydrogenase levels were associated with both disease progression and mortality.
- Low-molecular-weight heparin treatment regimens were not associated with both disease progression and mortality.

The patients were treated according to this locally developed protocol (n = 174) or the enoxaparin dose was determined off-protocol at the discretion of the attending physicians (n = 120). The off-protocol group was divided into 2 subgroups: undertreatment group (n = 54)—patients with a D-dimer level higher than 1000 ng/mL who received the prophylactic dose, and overtreatment group (n = 66)—patients with a D-dimer level lower than 1000 ng/mL who received intermediate or therapeutic dose.

Assessment of Clinical Outcomes

We compared the clinical outcomes according to the LMWH treatment regimen. The 2 co-primary outcomes were inhospital mortality and disease progression. The disease progression was assessed using the Ordinal Scale for Clinical Improvement.[21] We also analyzed, as a secondary outcome, the safety of these regimens, namely bleeding events associated with LMWH treatment, by comparing the need for blood transfusions and hemoglobin levels at admission and discharge.

All relevant laboratory findings, including D-dimer, C-reactive protein (CRP), ferritin, lactate dehydrogenase (LDH), and SpO_2/FiO_2 levels at admission and follow-up (days 3-5 of hospitalization), were recorded and analyzed.

Statistical Analysis

Statistical analysis was performed with Statistical Package for the Social Sciences Statistics 23.0 for Windows packaged software (IBM Corp.; Armonk, NY, USA). Numerical variables were summarized with mean ± SD and categorical variables with frequency and percentage. The significance of differences among groups was assessed by the Student's *t*-test, Mann–Whitney *U-test*, 1-way analysis of variance, or Kruskal–Wallis *H* test for continuous variables and analysis of categorical variables was examined by the chi-square test. Pearson or Spearmen correlation analysis were used to determine the relationship between parameters. A value of $P < .05$ was considered significant for all statistical analyses.

As the 2 treatment groups were not similar in terms of baseline disease severity and inflammatory biomarkers, logistic regression analysis and propensity-matched analysis were performed to analyze the effect of different treatment regimens on mortality. To that end, receiver operating characteristic curves were first built for age, LDH, and CRP levels. With these analyses, threshold values were determined (62.5 years, 418.5 U/L, and 51.6 mg/dL for age, LDH, and CRP, respectively). Propensity score matching (PSM) was performed to avoid confounding bias in the analysis investigating the association between protocol adherence and mortality. The propensity score was calculated by using logistic regression to estimate the probability of mortality with the age, CRP, and cardiac morbidity-independent

Table 1. Demographic, Clinical Characteristics, and Laboratory Findings of the Study Population and the 2 Treatment Groups at Admission

	Total (n = 294)	On-Protocol (n = 174)	Off-Protocol (n = 120)	*P*
Male, n (%)	168 (57.1)	93 (53.4)	75 (46.6)	.15
Negative PCR, n (%)	52 (17.7)	31 (17.8)	21 (17.5)	1.0
Age, mean ± SD	62.4 ± 15.9	59.5 ± 16.6	66.7 ± 13.7	<.001
Cardiovascular comorbidity, n (%)	46 (15.6)	17 (9.8)	29 (24.2)	.001
SpO_2/FiO_2, mean ± SD	348.6 ± 113.8	364.0 ± 112.1	326.2 ± 112.9	<.001
CRP (mg/L), mean ± SD	88.0 ± 75.3	76.4 ± 69.1	104.9 ± 80.9	.001
Ferritin (µg/L), median (minimum–maximum)	464.0 (187.0-777.0)	426.0 (4.2-2891.0)	561.5 (43.8-10 265.0)	.08
LDH (U/L), mean ± SD	341.7 ± 191.5	310.8 ± 137.6	390.2 ± 247.0	.007
D-Dimer (µg/L), mean ± SD	1455.6 ± 1332.5	1182.9 ± 1044.7	1850.9 ± 1587.1	.001

CRP, C-reactive protein; LDH, lactate dehydrogenase; PCR, polymerase chain reaction.

variables. The 1 : 2 propensity matching without replacement was performed by using an optimal pair-matching algorithm. Standardized mean difference (SMD) was used for the assessment of balance after PSM. We assessed the balance of confounding between the matched data of the survivors and non-survivors according to the criterion of an SMD less than 0.1.

RESULTS

We collected data from 384 patients who were hospitalized in the ward or intensive care unit between May 2020 and April 2021. Of these, 294 patients who met the inclusion and exclusion criteria and had complete data composed the study group. The demographic features and admission values of relevant laboratory parameters are shown in Table 1. Of these patients, 97 (33%) had a progressive course during their follow-up in the hospital. The mortality rate was 20.7% (61 of 294 patients).

A total of 174 patients received LMWH according to the study protocol, and the remaining 120 patients were treated off-protocol. The CRP, ferritin, LDH, and D-dimer levels at admission were lower in the on-protocol group as compared to the off-protocol group. Similarly, SpO_2/FiO_2 levels were higher in the on-protocol group (Table 1).

The rate of clinical worsening was lower in patients who received on-protocol LMWH treatment (n = 45/174, 25.9%) as compared to patients treated off-protocol (n = 53/120, 44.2%) (*P* = .001). Similarly, fewer patients in the on-protocol group died (n = 29, 16.7%) as compared to the off-protocol group (n = 32, 26.7%) (*P* = .41) (Table 2). However, patients who had a progressive clinical course had higher follow-up D-dimer levels. Similarly, levels of CRP and ferritin at admission and follow-up were higher in patients whose clinical status worsened during the follow-up and in those who died, indicating that the difference in the 2 co-primary outcomes may be due to differences in the severity of disease in the 2 treatment groups (Table 3).

The mortality rates were similar in the overtreatment (n = 14/66, 21.2%) and undertreatment subgroups (n = 18/54, 33.3%) (*P* = .151). The rates of disease progression were also similar in the 2 subgroups (45.4% and 40.7%, respectively, *P* = .580) (Table 2).

Although on-protocol LMWH treatment appeared to be associated with better clinical outcomes, the severity of COVID-19 was not similar in the 2 treatment groups. In order to adjust for the confounding effect of less severe disease in the on-protocol group, 2 statistical analyses were performed. First, logistic regression analysis showed that mortality was associated with the presence of cardiac comorbidities, old age, high CRP, and LDH level but not with the dose of LMWH treatment (Table 4). Similarly, after PSM, there was no difference between the on-protocol and off-protocol groups in terms of mortality rate (n = 29/90, 32.2% vs. n = 31/90, 34.4%, respectively) (Table 5).

With regard to the safety of the different LMWH regimens, there was no difference in the percentage of patients who

Table 2. Progression and Mortality Rates Between On-Protocol and Off-Protocol Groups Together with the Overtreatment and Undertreatment Subgroups

	On-Protocol (n = 174)	Off-Protocol (n = 120)	*P*	Overtreatment (n = 66)	Undertreatment (n = 54)	*P*
Patients with a progressive course, n (%)	45 (25.9)	53 (44.2)	.001	30 (45.4)	22 (40.7)	.58
Patients who died, n (%)	29 (16.7)	32 (26.7)	.041	14 (21.2)	18 (33.3)	.15

Table 3. Laboratory Findings at Admission in Coronavirus Disease 2019 Patients According to Their Clinical Outcomes

	Patients with Progressive Course	Patients with Clinical Improvement	*P*
D-Dimer (mg/L), mean ± SD	1555.3 ± 1414.3	1301.0 ± 1233.4	.054
CRP (mg/L), mean ± SD	109.3 ± 77.8	69.3 ± 69.1	<.001
Ferritin (µg/L), median (minimum–maximum)	603.5 (32.9-10 265.0)	320 (4.2-4609.0)	<.001
	Patients Who Died	**Patients Who Survived**	
D-Dimer (mg/L), mean ± SD	1910.3 ± 1552.3	1254.1 ± 1195.7	<.001
CRP (mg/L), mean ± SD	115.8 ± 80.6	72.8 ± 70.0	<.001
Ferritin (µg/L), median (minimum–maximum)	618.0 (32.9-10 265.0)	353.0 (4.21-4609.0)	.001

CRP, C-reactive protein.

Table 4. Multivariate Logistic Regression Analysis for Mortality

	Odds Ratio	(95% CI)	*P*
Age > 62.5	5.3	2.5-11.1	<.001
LDH > 418.5	4.3	2.3-8.2	<.001
CRP > 51.645	3.4	1.7-6.9	<.001
Cardiac comorbidities	2.6	1.1-5.9	<.001

CRP, C-reactive protein; LDH, lactate dehydrogenase.

Table 5. Mortality Rates in the 2 Treatment Groups after Propensity Score Matching

	On-Protocol (n = 90)	Off-Protocol (n = 90)	*P*
Patients who died, n (%)	29 (32.2)	31 (34.4)	.87
Patients who survived, n (%)	61 (67.8)	59 (65.6)	

needed blood transfusions. The overtreatment subgroup showed a larger, but clinically modest decrease in hemoglobin levels (Table 6).

DISCUSSION

This study provides evidence that LMWH treatment at prophylactic doses results in similar clinical outcomes to D-dimer-driven doses in COVID-19 patients. This is an important finding as it may reduce the cost of treatment and the burden on healthcare systems. The study showed that LMWH at prophylactic doses resulted in similar rates of disease progression and mortality compared to D-dimer-driven doses. This suggests that there is no clinical benefit to higher D-dimer-driven doses and indicates that clinicians can safely reduce the dose of LMWH and still achieve the same clinical outcomes. The study also showed that the 2 treatment regimens resulted in similar rates of bleeding events, except that the use of higher doses was associated with larger decreases in hemoglobin levels. Even though this decrease was clinically modest, it must be taken into account in view of the lack of superiority in the clinical effectiveness of higher doses.

Adjustment of LMWH dosing according to D-dimer levels is legitimate as high D-dimer levels have been found to be associated with mortality[21] and shown in some studies to be related to the extent of pulmonary embolism.[22] The current study also found that D-dimer levels both at admission and at follow-up were related to the disease course. The cutoff level of 3000 ng/mL was chosen because levels above this threshold have been found to be associated with both the presence of pulmonary embolism and evidence of benefit from anticoagulant treatment at therapeutic doses.[17,23] The rationale for the cutoff level of 1000 ng/mL was that this was shown in early studies to be an independent predictor of mortality in COVID-19 patients.[24] Thus, D-dimer-driven dosing of LMWH appeared to be a more logical and personalized approach to deal with coagulopathy and its related consequences. In support of this view, an earlier study, which included critically

Table 6. Difference in Hemoglobin Levels Between Admission and Discharge and Need for Blood Transfusion in the Treatment Groups

	On-Protocol (n = 154)	Overtreatment (n = 53)	Undertreatment (n = 46)	*P*
The difference in hemoglobin levels between admission and discharge*, mean ± SD	−0.27 ± 1.11	−0.50 ± 1.3	−0.25 ± 1.0	.028
	On-Protocol (n = 174)	**Overtreatment (n = 66)**	**Undertreatment (n = 54)**	***P***
Patients who received blood transfusion, n (%)	20 (11.5)	13 (19.7)	8 (14.8)	.27

*Patients who received blood transfusions were excluded from the analysis.

ill COVID-19 patients only and which used the same cut-off levels and treatment doses, found that the D-dimer-driven regimen was associated with a lower rate of mortality.[18] In the current study, although the clinical outcomes, i.e., disease progression and mortality, appeared to be better with a D-dimer-driven LMWH treatment regimen, propensity-matched analysis of the data showed similar effectiveness compared to the prophylactic LMWH. Similarly, logistic regression analysis demonstrated that independent predictors of outcome were older age, cardiac comorbidity, and high levels of CRP and LDH at admission but not the LMWH treatment regimen. These findings differed from the previous study in ICU patients. This may be related to the differences in the severity of inflammation and coagulopathy in the 2 study populations.

The main strength of this study is that it included all patients who met the inclusion and exclusion criteria. This comprised a significant proportion of all patients admitted to the hospital for COVID-19. Thus, the findings should be generalizable. The main limitation, on the other hand, was that the 2 treatment groups were not similar in terms of laboratory findings (possibly reflecting disease severity) at admission. However, 2 separate statistical analyses were performed, namely propensity-matched analysis and logistic regression analysis, to account for these differences.

In conclusion, this study shows that prophylactic doses of LMWH result in similar clinical outcomes to D-dimer-driven doses in COVID-19 patients, with the added benefit of a lower risk of bleeding events.

Ethics Committee Approval: This study was approved by Ethics Committee of Ege University (Approval No: 20-5T/48, Date: 15.05.2020).

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

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Original Article

Evaluation of Patients with COVID-19 Followed Up in Intensive Care Units in the Second Year of the Pandemic: A Multicenter Point Prevalence Study

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Abstract

OBJECTIVE: A 1-day point prevalence study was planned to obtain country data by determining the clinical characteristics, follow-up and treatment methods of coronavirus disease 2019 (COVID-19) cases that required intensive care unit (ICU) treatment in the second year of the pandemic.

MATERIAL AND METHODS: All patients who were hospitalized in the ICUs due to COVID-19 between March 11, 2022, 08.00 AM, and March 12, 2022, 08.00 AM, were included in the study. Demographic characteristics, intensive care and laboratory data, radiological characteristics, and follow-up results of the patients were recorded.

RESULTS: A total of 811 patients from 59 centers were included in the study, 59% of the cases were male, and the mean age was 74 ± 14 years. At least one comorbid disease was present in 94% of the cases, and hypertension was the most common. When ICU weight scores were examined, Acute Physiology and Chronic Health Evaluation-II: 19 (15-27) and Sequential Organ Failure Assessment: 7 (4-10) were seen. Sepsis was present in 37% (n = 298) of cases. PaO_2/FiO_2 ratios of the patients were 190 the highest and 150 the lowest and 51% of the cases were followed via invasive mechanical ventilation. On the study day, 73% bilateral involvement was seen on chest x-ray, and ground-glass opacities (52%) were the most common on chest tomography. There was growth in culture in 40% (n = 318) of the cases, and the most common growth was in the tracheal aspirate (42%).

CONCLUSION: The clinical course of COVID-19 is variable, and ICU follow-up was required due to advanced age, comorbidity, presence of respiratory symptoms, and widespread radiological involvement. The need for respiratory support and the presence of secondary infection are important issues to be considered in the follow-up. Despite the end of the second year of the pandemic and vaccination, the high severity of the disease as well as the need for follow-up in ICUs has shown that COVID-19 is an important health problem.

KEYWORDS: COVID-19, intensive care, intensive care unit, pandemic, follow-up
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INTRODUCTION

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first described in December 2019 in China and rapidly spread to other countries.[1] As of March 11, 2022, nearly 602 million confirmed COVID-19 cases have been reported globally; of these cases, 576 million recovered from the disease, and 6 million people died.[2] Coronavirus disease 2019 presents with a wide clinical spectrum ranging from asymptomatic illness to respiratory failure, and patients were followed up in the intensive care unit (ICU) for different causes such as severe pneumonia, sepsis, and acute respiratory distress syndrome (ARDS). Epidemiological and clinicopathological features of disease were evaluated worldwide. Reportedly, COVID-19

cases include 14% of severe illnesses and 6% of critical illnesses that required intensive care; 2% of these cases underwent invasive mechanical ventilation (IMV).[3] The ICU mortality rate ranges from 4 to 11%.[4,5] In Turkey, the data about ICU follow-up are limited. This study aimed to describe demographical and clinical characteristics, ventilation settings, treatment regimens, and outcomes in patients with COVID-19 who were followed up in ICUs. Thus, to obtain data on different ICUs in our country in the second year of the pandemic, a 1-day point prevalence study was planned via the Turkish Thoracic Society (TTS) Respiratory Failure and Intensive Care Association.

MATERIAL AND METHODS

This descriptive cross-sectional research was designed as a 1-day point prevalence study. The study was announced to the members practicing in the ICUs via mail through the societies (TTS and the Turkish Society of Intensive Care). Consent forms were shared with the centers that participated in the study. All cases of initial real-time polymerase chain reaction (RT-PCR)-positive cases hospitalized in the ICUs due to COVID-19 between March 11, 2022, 8:00 AM, and March 12, 2022, 8:00 AM, were included. The data were collected via e-mail from each center. The study was approved by the ethical committee of Health Sciences University İzmir Dr. Suat Seren Chest Disease and Thoracic Surgery Training and Research Hospital (March 10, 2022/10-14) and was in accordance with the Declaration of Helsinki.

Patients

According to the COVID-19 guidelines of the Ministry of Health, patients in ICUs should be followed up based on the following conditions:[6]

- Dyspnea and respiratory distress.
- Respiratory rate ≥30/min.
- PaO_2/FiO_2 ratio <300.
- Increased oxygen recruitment.
- SaO_2 <90% or PaO_2 <70 mm Hg despite 5 L/min oxygen therapy.
- Hypotension (systolic blood pressure <90 mm Hg and more than 40 mm Hg decrease from usual systolic blood pressure and mean arterial pressure <65 mm Hg), tachycardia >100/min.

Main Points

- Coronavirus disease 2019 (COVID-19) patients were followed up in intensive care units for different causes, such as severe pneumonia, sepsis, and acute respiratory distress syndrome.
- The clinical features of the COVID-19 patients in the intensive care unit (ICU) during the second year of the pandemic were as follows: majority of the patients were over 65 years old and had comorbid diseases, ICU severity scores were high, and PaO_2/FiO_2 ratios were in lower limits.
- The clinical course of COVID-19 is variable, and ICU follow-up is required due to advanced age, comorbidity, the presence of respiratory symptoms, and radiological extensive involvement.

- Development of acute organ dysfunction such as acute kidney injury, impaired acute liver function tests, confusion, and acute bleeding diathesis.
- Patients with immunosuppression.
- Increased troponin levels and arrhythmia.
- Lactate >2 mmol.
- Presence of capillary return disorder and cutis marmorata.

Assessments

Data on case demographics (age and gender), COVID-19 PCR results, comorbidities, symptoms, ICU duration, chest x-ray and computed tomography (CT) features, Acute Physiology and Chronic Health Evaluation II (APACHE II) and Sequential Organ Failure Assessment (SOFA) scores, PaO_2/FiO_2 ratio, type of respiratory support therapy (nasal oxygen, mask oxygen, high flow oxygen, noninvasive ventilation [NIV], IMV), accompanying conditions (sepsis, septic shock, ARDS), complete blood count and CRP, types of medical treatment (antibiotics, corticosteroids, anticytokine), and follow-up results were obtained at study day.

Clinical suspicion of infection and an increase in inflammatory markers that were consistent with culture positivity (tracheal aspirate, blood, urine, and wound samples) were defined as non-COVID-19 secondary infections.

Statistical Analysis

The statistical analysis was performed using Statistical Package for the Social Sciences Statistics software for Windows, version 21.0 (IBM Corp., Armonk, NY, USA). Descriptive analyses were done for the patients' demographics and clinical data. Student's *t*-test was performed for continuous variables with normally distributed values, and the values were defined as the mean ± standard deviation (SD). The Mann–Whitney *U*-test was used for non-normally distributed continuous values, and the results were shown as median and 25%-75% as interquartile ratio (IQR). Counts and percentages were used when applicable.

RESULTS

A total of 811 cases from 59 centers were included in the study. Table 1 shows the demographic characteristics and radiologic features of patients on study day. Four hundred eighty-two (59%) of the cases were male, and the median age was 74 years. Nearly all of the cases had at least 1 comorbidity; hypertension (57%), diabetes mellitus (31%), coronary artery disease (26%), and chronic obstructive pulmonary disease (COPD) (20%), were the most frequent comorbidities. Of the cases, 73% were vaccinated for COVID-19, and on study day, 77% of the cases COVID PCR tests were positive. Of the patients, 780 (96%) had symptoms of COVID-19 at ICU admission, and dyspnea was the most common symptom. The laboratory data of the cases followed up in ICUs in the second year of the pandemic are shown in Table 1. Although most of the cases had bilateral involvement on the chest x-ray, the most common finding on the thorax CT was ground-glass opacities.

The ICU data and type of respiratory support of the cases followed up in the ICUs in the second year of the pandemic

Table 1. Demographic Characteristics and Initial Symptoms of Cases Followed in the Intensive Care Units (n = 811)

Age, year, mean ± SD	74 ± 14
Male, n (%)	482 (59)
Comorbidity, n (%)	763 (94)
COPD	164 (20)
HT	462 (57)
CVD	214 (26)
AF	109 (13)
CHF	161 (20)
DM	252 (31)
Alzheimer's	145 (18)
CVD	116 (14)
Malignancy	122 (15)
COVID vaccine, n (%)	591 (73)
Last COVID-19 PCR result, positive; n (%)	619 (77)
Presence of symptoms at admission, n (%)	780 (96)
Fever	161 (20)
Cough	362 (45)
Dyspnea	692 (85)
Leucocyte count, 10^9 L, median (25-75)	10205 (7100-14700)
Lymhocyte count, median (25-75)	710 (400-1150)
CRP (mg/dL), median (25-75)	108 (48-171)
Involvement on chest x-ray, n (%)	
Unilateral	161 (20)
Bilateral	590 (73)
Lesion on thorax CT, n (%)	
Ground-glass opacity	394 (52)
Consolidation	180 (24)
Fibrosis	19 (3)

AF, atrial fibrillation; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; CT, computed tomography; CVD, cardiovascular disease; DM, diabetes mellitus; HT, hypertension; PCR, polymerase chain reaction.

are shown in Table 2. On ICU admission, the APACHE-II and SOFA scores were 19 (15-27) and 5 (4-10), respectively. On study day, half of the cases were intubated and followed up with IMV for a median of 8 days, and 298 (37%) of cases had sepsis. Extracorporeal membrane oxygenation (ECMO) was applied to 1 of 811 patients, and 8 of the cases were in a prone position on the study day. Culture positivity was observed in 40% (318) of the cases; the most common positivity was detected in the tracheal aspirate specimen (42%), and *Acinetobacter baumanii* was identified frequently. On study day, 89 (11%) patients died in ICUs, 28 (4%) were discharged, and 693 (86%) were still in ICUs Table 2 shows the treatment procedures, infection status, and outcomes of the cases followed up in ICUs.

Table 2. Intensive Care Unit Data, Treatments and Outcomes of the Cases Followed in the Intensive Care Unit in the Second Year of the Pandemic (n = 811)

ICU duration, day, median (25-75)	9 (3-16)
APACHE II score, median (25-75)	19 (15-27)
SOFA score, median (25-75)	7 (4-10)
Lowest PaO_2/FiO_2, median (25-75)	150 (100-220)
Respiratory support therapies, n (%)	
Room air	12 (1)
Nasal O_2	109 (13)
Mask O_2	38 (5)
Reservoir oxygen mask	62 (8)
HFO	105 (13)
NIMV	70 (9)
IMV	415 (51)
HFO (day), median (25-75)	3 (2-6)
NIV (day), median (25-75)	2 (2-5)
IMV (day), median (25-75)	8 (3-18)
Tracheostomy, n (%)	63 (8)
Tracheostomy (day), median (25-75)	12 (6-21)
Sepsis, n (%)	298 (37)
Dialysis, n (%)	68 (8)
ECMO, n (%)	1 (0.1)
Prone position, n (%)	65 (8)
Anticytokine therapy (anakinra), n (%)	17 (2)
Pulse/mini pulse corticosteroid, n (%)	163 (20)
Anticoagulant, n (%)	753 (92)
Vasopressor, n (%)	283 (35)
Antibiotic therapy, n (%)	653 (82)
Antibiotic duration, median (25-75)	5 (3-9)
Culture positivity, n (%)	318 (40)
Source of infection, n (%)	
Tracheal aspirate	139 (42)
Blood	128 (38)
Urine	62 (19)
Wound	4 (1)
Pathogen, n (%)	
Acinetobacter baumanii	84 (10)
Klebsiella pneumoniae	50 (6)
Candida spp.	39 (5)
Pseudomonas aeruginosa	15 (2)
Result, n (%)	
Exitus	89 (11)
Discharge from ICU	28 (4)
Continued ICU stay	693 (86)

APACHE, acute physiology and chronic health evaluation; ECMO, extracorporeal membrane oxygenation; HFO, high-flow oxygen; ICU, intensive care unit; IMV, invasive mechanical ventilation; NIV, noninvasive ventilation; PaO_2/FiO_2, arterial oxygen tension/fraction of inspired oxygen; SOFA, sequential organ failure assessment.

DISCUSSION

The present study evaluated the clinical features of patients with COVID-19 in various ICUs during the second year of the pandemic. Most of the patients were over 65 years old and had comorbid diseases; their ICU severity scores were high, and PaO_2/FiO_2 ratios were in lower limits. The clinical course of COVID-19 is variable, and ICU follow-up is required owing to advanced age, comorbidity, the presence of respiratory symptoms, and extensive radiological involvement.

As reported in the ICU data of different countries, the cases followed up in ICUs due to severe COVID-19 were 60%-80% male, and the mean age was 60-70 years.[3,7,8] Consistent with these data, most of the patients hospitalized in the ICUs in our country were male and of elderly age. In a meta-analysis of 8 studies that involved 1816 patients,COPD, cardiovascular disease, and hypertension were found to be risk factors for severe illnesses and ICU admission.[9] Similarly, a prospective, multicentre cohort study, from 63 ICUs enrolled patients over 18 years old with RT-PCR-confirmed COVID-19 who were on IMV and showed hypertension and obesity as the main comorbidities.[10] Jain and Yuan[9] reported that the most prevalent symptoms of severe COVID-19 were cough, fever, and fatigue. Moreover, cough, fever, and dyspnea were common in ICU patients. Dyspnea was found to be the only symptom that is associated with both severe disease and ICU admission. Similarly, in our study, dyspnea was observed in most patients during ICU admission.

Chau et al's[11] study in 2004 showed the relationship between the initial chest radiograph and the clinical outcome of patients with severe acute respiratory syndrome (SARS). Their results showed that bilateral disease and involvement of more than 2 zones on the chest radiograph were associated with poor clinical outcomes. Patients with bilateral involvement had a higher rate of ICU admission, assisted ventilation, and mortality in comparison with those with unilateral involvement. Similarly, bilateral involvement in chest x-ray has been reported to be more common in patients in ICUs.[3,12,13] In our population, bilateral involvement in chest x-rays was detected frequently. Moreover, typical thorax CT features of COVID-19 were clearly defined as ground-glass opacities, with or without consolidations, in peripheral lung regions, and multifocal bilateral distribution. In most of the studies, such as ours, the common CT finding in ICU patients was ground-glass opacities.[13,14]

Based on the intensive care data from different countries, IMV support ranged from 28%-100%.[3,7,8,12,13,15] Patients included in our study were severe cases and half of them required IMV; thus, the APACHE II and SOFA scores of the present study were higher than the other studies.[3,8,13,16] This may be due to the clinical characteristics of the patients admitted to the ICUs and the differences in ICU capacities in various countries. Additionally, the lower rates of PaO_2/FiO_2 ratio also led to IMV support. A lower PaO_2/FiO_2 ratio at ICU admission was reported as an independent risk factor for mortality.[7] In previous studies, the use of NIV was reported to be 2%-11%, and the rate was similar in our data.[3,7,8,13] This might be related to the prevalent application of NIV in the ward and intermediate ICU.

The data about bacterial and fungal coinfection in patients with COVID-19 show that their number is increasing over time, and coinfections were associated with a high mortality rate and a longer course of ICU stay. Bardi et al[17] evaluated the epidemiological, clinical, and microbiological features and outcomes of ICU-acquired infections in their study which included 140 patients. The COVID-19-related nosocomial infection during ICU stay was defined as 41%. Furthermore, the nosocomial infections tended to be late complications occurring after 7 days of ICU stay.[17] Nosocomial infections in ICU patients vary across a wide spectrum comprising such as ventilator-associated pneumonia, tracheobronchitis, catheter-related bloodstream infections, and urinary tract infections. In the present study, the most common microbiological isolates were *A. baumannii* and *Klebsiella pneumonia*. Previous studies showed that immunomodulatory therapies, including tocilizumab and glucocorticoids, were associated with coinfections in patients with COVID-19.[18,19] Moreover, higher APACHE II score at ICU admission was associated with infection.[17] Interestingly, in our study, the rate of patients using antibiotics was higher than that of patients with culture positivity, i.e., 82% and 40%, respectively. This might be associated with the increased tendency to initiate empirical antibiotics by clinicians in ICUs.

Previous studies reported different ICU mortalities as follows: 16%-31%.[7,13,16] A multicenter retrospective study reported COVID-19 mortality rate of 4.5% in our country. This study defined that male patients with severe pneumonia, multiorgan dysfunction, malignancy, sepsis, and interstitial lung diseases were at increased risk of mortality.[20] The mortality rate was twice as high as in the present study, which might be related to the fact that our study included only patients in ICUs.

This study has some limitations. First, it is a cross-sectional 1-day point prevalence study and only shows the results on study day. It does not give information on the changing conditions in the follow-up of the patients. However, the results may be interpreted as a representation of severe COVID-19 and ICUs. Second, due to the multicenter nature of the study, the data may be heterogeneous due to the different structures of ICUs. However, considering that 59 different centers were evaluated, the results can provide important data on the ICUs in the whole country. To the best of our knowledge, this is the first and most widespread study that evaluates ICU patients with COVID-19.

In conclusion, this multicenter study showed that in the second year of the pandemic, the majority of the patients in ICUs were of elderly age and had comorbid diseases, high ICU severity scores, and high intubation rates. The clinical course of COVID-19 is variable, and ICU follow-up is required because of advanced age, comorbidity, the presence of respiratory symptoms, and extensive radiological involvement. Despite the end of the second year of the pandemic and vaccination, the severity of the disease is high enough to require follow-up in ICUs, which shows that COVID-19 continues to be an important health problem.

Ethics Committee Approval: The study was approved by the ethical committee of Health Sciences University Izmir Dr. Suat Seren

Chest Disease and Thoracic Surgery Training and Research Hospital (Approval No:10-14 Date: 10.03.2022).

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Original Article

Factors Associated with Increasing Costs in Severe Chronic Obstructive Pulmonary Disease Exacerbation: Turkish Thoracic Society Chronic Obstructive Pulmonary Disease Assembly

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Abstract

OBJECTIVE: Chronic obstructive pulmonary disease (COPD) that is the third leading cause of death in the world is one of the main economic burden. The cost is primarily due to COPD exacerbations and hospitalizations. We aimed to determine the factors associated with increasing costs in severe COPD exacerbation.

MATERIAL AND METHODS: It was a multicenter and prospective observational recording study. 294 patients who severe COPD exacerbation were included in the study. An amount of more than 429.58 euros was accepted as increasing costs (IC). Factors associated with IC were determined by regression analysis.

RESULTS: Mean age was 69.90 ± 9.79/years (minimum: 40 maximum: 95), mean costs were 594.9 ± 70.9 euros. About 83.7% of the patients were male, 24.1% (71) were active smokers, and 81% (238) had at least 1 comorbidity. Factors associated with IC in the regression analysis were delay of discharge (due to prolonged consultation), antibiotic use longer than 7 days, need to enteral/parenteral feeding, application of pulmonary rehabilitation (physiotherapy) at hospitalization, and refusal to be discharged.

CONCLUSION: The increasing costs in severe COPD exacerbation depends not only treatment but also the patient's social status and hospital-related factors. We think that the cost of severe COPD exacerbation can be reduced by interventions on interchangeable factors such as patient's social status and hospital-related factors.

KEYWORDS: COPD, severe exacerbation, costs, discharge, antibiotic, nutrition, pulmonary rehabilitation

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a multicausal global health crisis. According to World Health Organization (WHO), chronic obstructive pulmonary disease COPD is one of the most common noncommunicable diseases.[1] The prevalence of chronic pulmonary disease, which also includes COPD, increased by 40% from 1990 to 2017, and currently COPD is the third major cause of mortality.[1,2] The main cause of mortality is exacerbations. Every exacerbation is related to decrease in pulmonary function, deterioration in quality of life, and economic burden (increased cost).[3] Acute exacerbation of COPD (AECOPD) is defined as an acute event that worsens symptoms and is expressed as clinical instability.[3] Acute exacerbation of COPD can range in severity from the form that can be treated as an outpatient to the form that requires intensive care, and it is mainly triggered by airway infections or environmental exposure (dust and gases).[3] Although a definition of exacerbation has been made, it does not contain clear criteria. For this reason, the perception of the severity of exacerbation by both patients and healthcare providers varies. But the process of treatment in the hospital depends not only on the

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characteristics of the disease but also on the characteristics of the hospital and social environment. Therefore, all these components affect the cost associated with treatment. Acute exacerbation of COPDs account for a prominent amount of the direct costs associated with COPD.[4] In the United States, the direct cost of COPD is estimated at $29.5 billion, and the indirect cost is estimated at $20.4 billion.[5]

The cost varies from country to country. For example, in 2011, the cost per exacerbation was $269 in the United States, while in 2006 it was $649 in Canada.[6,7] The mean cost for hospitalized AECOPD was $3164 in Italy (2013), while it was $18.120 in the United States (2011).[6,8] The variability of costs among countries is remarkable, even if the currency and cost year are different.

In this study, we aimed to determine the factors associated with increased costs in severe COPD exacerbations.

MATERIAL AND METHODS

This was a multicenter prospective observational recording study that was approved by the Gazi University Faculty of Medicine Ethics Committee (Approval No: 687/2018, Date: 2018) with respect to the ethical standards specified in the 1964 Declaration of Helsinki. Informed consent was obtained from all patients.

Patient Selection

Between October 1, 2018, and September 30, 2019, all severe COPD exacerbation patients who were hospitalized in an emergency or outpatient clinic were enrolled. A total of 294 patients from 9 centers (7 university hospitals and 2 training and research hospitals) were included in the study.

Inclusion criteria were the patients who were aged >40 years, had COPD diagnosis (according to GOLD 2017)[9] of at least 1 year, had severe exacerbation,[9] and hospitalized from an emergency department or outpatient clinic. Exclusion criteria were patients who were aged <40 years, had no pulmonary function test in the last year, were hospitalized from the emergency department to the intensive care unit, and were transferred from the intensive care unit to the ward, with stable COPD, and hospitalized for another reason such as pneumonia, heart failure, and lung cancer.

In the study, GOLD 2017 was accepted as a reference for COPD diagnosis, staging, COPD exacerbation definition, exacerbation treatment, criteria for transfer to intensive care unit, and discharge criteria.[9]

Main Points

- When considering factors affecting cost, it is not enough to use only laboratory and clinical parameters.
- In particular, the total cost of patients with severe COPD exacerbation in the hospital was related to the treatment costs, as well as social situation of the patient and the facilities of the hospital.
- Therefore, this study revealed the necessity of multifactorial evaluation when it comes to total cost calculation.

The parameters in the recording form are shown in Figure 1. Hemogram, biochemistry, including liver and kidney functions, C-reactive protein, arterial blood gas, chest x-ray, and electrocardiogram were examined in all patients on the day of hospital admission and, if necessary, during follow-up. Patient declaration and used drugs were taken into account in comorbidity screening. The STOP-BANG questionnaire was applied to all patients for the risk assessment of obstructive sleep apnea. Vitamin D, cardiac enzymes, *N*-terminal pro-brain natriuretic peptide (NT-proBNP), echocardiography (ECO), and hemoglobin A1c (HbA1c) were examined in accordance with the conditions of each center and if necessary. If the clinician found it necessary, D-dimer, thorax computed tomography (CT), thorax CT angiography, bronchoscopy, and consultation (with other clinics) were performed. The follow-up of the patients ended in 4 ways: discharge, transfer to intensive care, transfer to another department, or exitus. The length of hospital stay was accepted as the total time in both the emergency room and the ward.

Total hospitalization costs were obtained from the data processing units of the centers participating in the study. Costs were recorded in Turkish lira, written down on the euro equivalent of that date. Because the cost ratios do not show a normal distribution, the median value corresponding to the 50% percentile is the limit. Values above 50% were accepted as increased cost. The cost calculation was made over the total cost. In order to determine the factors affecting the cost, the patients were examined under 2 groups. These are normal cost and increased cost groups.

Statistical Analysis

The statistical analyses were performed using the Statistical Package for the Social Sciences Statistics software, version 23.0 (IBM Corp.; Armonk, NY, USA). In the statistical analysis, categorical variables are given as numbers and percentages, and continuous variables are presented as mean ± standard deviation (SD) and as median (minimum–maximum value) for descriptive analyses. In the data that does not fits the normal distribution, the Mann–Whitney *U*-test was used for comparative analysis between the 2 independent groups, and the independent sample *t*-test was used for the data that fit the normal distribution. Comparison analyses for categorical variables between separate groups were done by the chi-square test. Logistic regression analysis was used to determine the factors affecting the increased cost. Variables with $P < .05$ in the univariate analysis were entered into multivariate logistic regression analysis.

RESULTS

This study included 294 COPD patients with the mean age of 69.90±9.79 (minimum: 40, maximum: 95) from 9 hospitals. About 246 (83.7%) of the patients were male, and 48 (16.3%) were female. 86 (30.4%) had low, 177 (62.5%) had medium, and 20 (7.1%) had high socioeconomic status. Among them, 21 (7.1%) never smoked, 190 (64.6%) were ex-smokers, 12 (4.1%) were passive smokers, and 71 (24.1%) were active smokers. 193 (65.6%) had biomass exposure. 56 (19%) patients had at least 1 comorbid disease. 171 (58.1%) patients had LTOT, and 227 (77.2%) patients were using bi-level positive airway pressure (BPAP) at home. Looking at STOP-BANG

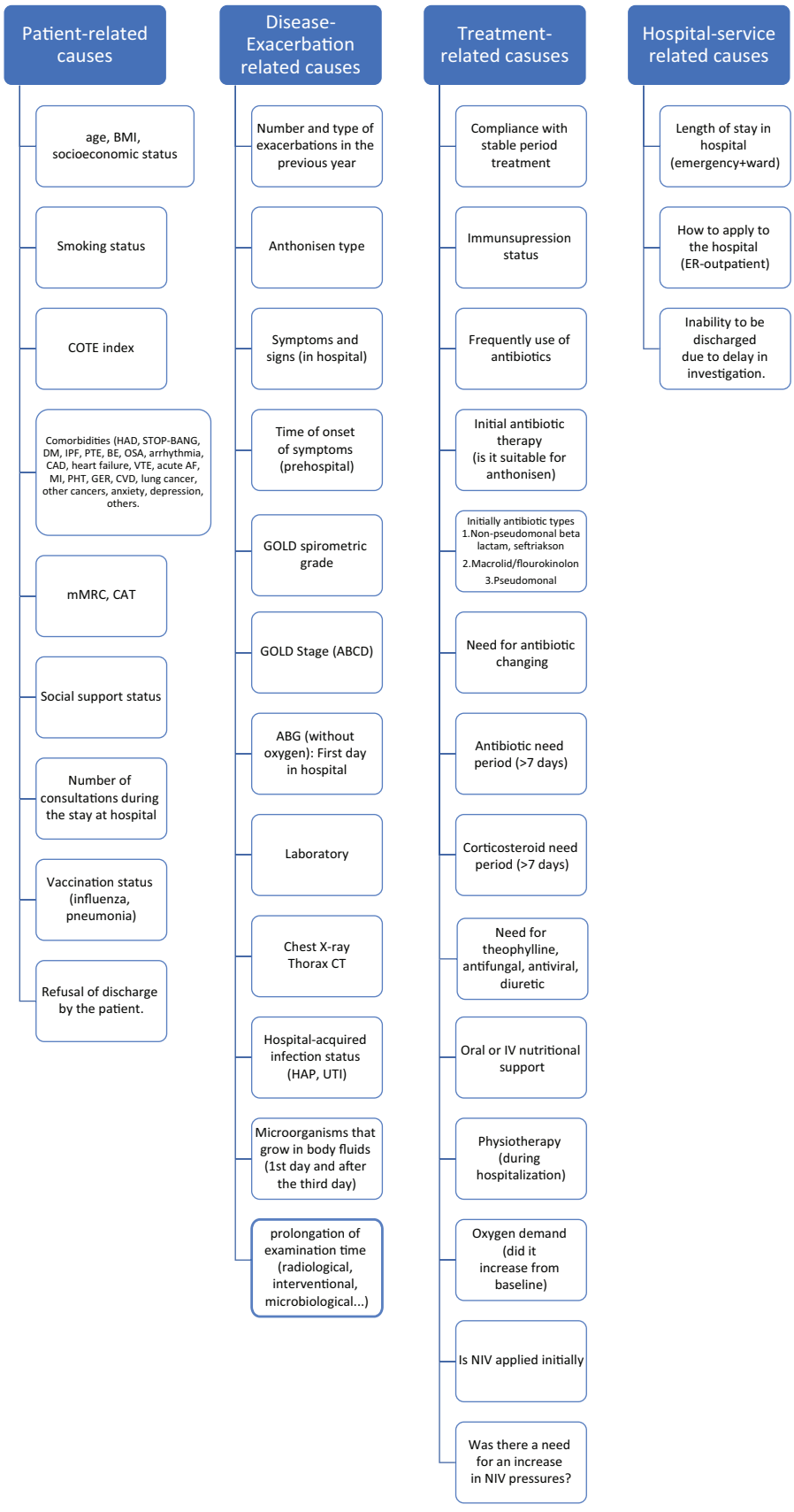


Figure 1. The parameters in the recording form. ABG, arterial blood gases; AF, atrial fibrillation; BE, bronchiectasis; BMI, body mass index; CAD, coronary artery disease; CAT, COPD Assessment Test; CT, computed tomography; CVD, cerebrovascular disease; DM, diabetes mellitus; ER, emergency room; GER, gastroesophageal reflux; HAD, Hospital Anxiety and Depression Scale; HAP, hospital-acquired pneumonia; IPF, idiopathic pulmonary fibrosis; IV, Intravenous; MI, myocardial infarction; mMRC; modified Medical Research Council; NIV, noninvasive ventilation, OSA, obstructive sleep apnea; PHT, pulmonary hypertension; PTE, pulmonary thromboembolism; UTI, urinary tract infection; VTE, venous thromboembolism.

Table 1. Relationship Between Main Demographic Characteristics of Patients and Increased Cost

Parameters	Total Patient*	Normal Cost Patient	Increased Cost Patient**	*P*
Age (years), n = 294 n(%)				
Mean ± SD	69.90 ± 9.79	n = 147	n = 147	.052[1]
Median (minimum–maximum)	69.00 (40-95)	68.18 ± 10.01	70.40 ± 9.47	
Age range, n = 294 n (%)				
<65 years old	88 (29.9)	52 (59.1)	36 (40.9)	**.042**[2]
>64 years old	206 (70.1)	95 (46.1)	111 (53.9)	
Sex, n = 294, n (%)				
Male	246 (83.7)	127(51.6)	119(48.4)	0.207[2]
Female	48 (16.3)	20(41.7)	28(58.3)	
BMI, n = 286, n (%)				
BMI <25	156 (54.5)	78 (50)	78 (50)	0.814[2]
BMI 25-30	75 (26.2)	38 (50.7)	37 (49.3)	
BMI >30	55 (19.2)	25 (45.5)	30 (54.5)	
SES n = 283				
Low	86 (30.4)	41 (47.7)	45 (52.3)	.370[2]
Medium	177 (62.5)	88 (49.7)	89 (50.3)	
High	20 (7.1)	13 (65)	7 (35)	
Cigarette n = 294 n (%)				
Never smoked	21 (7.1)	6 (28.6)	15 (71.4)	**<.001**[2]
Ex-smoker	190 (64.6)	83 (43.7)	107 (56.3)	
Passive smoker	12 (4.1)	5 (41.7)	7 (58.3)	
Active smoker	71 (24.1)	53 (74.6)	18 (25.4)	
Cigarette n = 294, n (%)				
Nonactive smoker	223 (75.9)	94 (42.2)	129 (57.8)	**<.001**[2]
Active smoker	71 (24.1)	53 (74.6)	18 (25.4)	
Biomass n = 294, n (%)				
None	193 (65.6)	104 (53.9)	89 (46.1)	.065[2]
Yes	101 (34.4)	43 (42.6)	58 (57.4)	
Comorbidity n = 294 n (%)				
None	56 (19)	34 (60.7)	22 (39.3)	.075[2]
Yes	238 (81)	113 (47.5)	125 (52.5)	
Influenza vaccine n = 294, n (%)				
None	230 (78.2)	126 (54.8)	104(45.2)	**.002**[2]
Yes	64 (21.8)	21 (32.8)	43(67.2)	
Pneumonia vaccine n = 294, n (%)				
None	228 (77.6)	121 (53.1)	107(46.9)	**.050**[2]
Yes	66 (22.4)	26 (39.4)	40 (60.4)	
LTOT n = 294, n (%)				
None	171 (58.1)	110 (64.3)	61(35.7)	**<.001**[2]
Yes	173 (41.9)	37 (30.1)	86 (69.9)	
BPAP n = 294, n (%)				
None	227 (77.2)	130 (57.3)	97 (42.7)	**<.001**[2]
Yes	67 (22.8)	17 (25.4)	50 (74.6)	
Stop-BANG n = 268, n (%)				
Low	40 (14.9)	21 (52.5)	19 (47.5)	**.015**[2]
Medium	134 (50)	74 (55.2)	60 (44.8)	
High	94 (35.1)	34 (36.2)	60 (63.8)	
Refusal to discharge n = 294, n (%)				
Yes	19 (6.4)	5 (26.3)	14 (73.7)	**.033**[2]
None	275 (93.6)	142 (51.6)	133 (48.4)	
Caregiver n = 294, n (%)				
None	95 (32.4)	58 (61.1)	37 (38.9)	**.009**[2]
Yes	199 (67.6)	89 (44.7)	110 (55.3)	

BMI, body mass index; BPAP, bi-level positive airway pressure; SES, socioeconomic status.
*Column percentage.**Line percentage.[1]Student's *t*-test.[2]Chi-square test.

scores, 40 (14.9%) patients had low scores, 134 (50%) had medium scores, and 94 (35.1%) patients had high scores. 64 (21.8%) patients had received the influenza vaccine within the last year. 66 (22.4%) patients had pneumococcal vaccination. 95 (32.4%) patients did not have a caregiver at home. Demographic characteristics are shown in Table 1.

The average cost per patient is 594.9 ± 70.9 euros (minimum: 22.4 euros, maximum: 7224.45 euros). Costs above 429.58 euros are classified as increased cost, and those below are classified as normal costs. Because the cost ratios do not show a normal distribution, the median value corresponding to 50% is the limit (Table 2).

Factors that increase the cost of hospitalization due to COPD exacerbation are examined under 4 main headings. These are patient-related factors, exacerbation-related factors, treatment-related factors, and hospital-related factors.

Patient-Related Factors

Patients of 65 years and over (P = .042), active smoking (P < .001), extrapulmonary malignancy (P = .02), LTOT at home (P < .001), BPAP at home (P < .001), not getting influenza vaccine (P = .002), not getting pneumococcal vaccine (P = .05), high risk in STOP-BANG (P = .015), refusing to be discharged (although the patient can be discharged) (P = .003), and lack of caregiver (P = .009) were the risk factors that related to increased cost.

Sex (P = .207), body mass index (BMI) (P = .814), biomass (P = .065), pulmonary embolism (PE) (P = .821), TB history (P = .515), bronchiectasia (P = .670), lung cancer (P = .077), and anemia (P = .409) vs. ejection fraction (EF) on the echocardiography lower than 40% (P = .774) were not related to increasing cost. Table 3 shows the logistic regression model of increased costs associated with patient-related factors. According to this, passive smoking was related to increased cost.

Exacerbation-Related Factors

History of 2 or more exacerbations in the last 1 year (P = .007), 1 or more severe exacerbations in the last 1 year (P < .001), GOLD-D (P < .001), FEV1 < 30% (P < .001), high procalcitonin (P < .001), low albumin/protein ratio (P = .04), pneumonia on chest x-ray (P < .001), pleural effusion on chest x-ray (P < .001), mass on chest x-ray (P = .019), pneumonia on thorax CT scan (P = .01), emphysema on thorax CT scan (P = .041), mass on thorax CT scan (P = .002), and hospital-acquired pneumonia (P = .006) were the risk factors that related to increased cost. Table 3 shows the logistic regression model of increased cost for associated exacerbation-related factors. Gold stage, procalcitonin, mass on chest x-ray, mass on thorax CT scan, and albumin/protein ratio variables were not included in the logistic regression model because they disturbed the model fit while creating the model.

Treatment-Related Factors

Frequently using antibiotic (P = .001), need to change antibiotics during hospitalization (P < .001), treatment antibiotics for more than 7 days (P < .001), use of corticosteroids for more than 7 days (P < .001), treatment combination of SABA/SAMA for more than 3 days (P < .001), need to antiviral treatment (P = .006), need to diuretic treatment (P < .001), increasing in oxygen demand during hospitalization (P < .001), need to NIMV during hospitalization (P < .001), need to increase NIV pressure during hospitalization (P < .001), need to Enteral/Parenteral feeding (P < .001) vs. applied of physiotherapy during hospitalization (P < .001) were the risk factors for increased cost. Table 3 shows the logistic regression model of increased costs associated with treatment-related factors.

Hospital-Related Factors

Hospitalization longer than 14 days (P < .001), hospitalization from the emergency department (P = .048), and delay in discharge (prolonged consultation) (P < .001) were associated with increased cost. Table 3 shows the logistic regression model of increased costs associated hospital-related factors.

The results of logistic regression analysis of all factors that have an effect on the increased cost are shown in Table 4. When the factors that were found to be significant here were modeled for the second time, it was found that the most effective factors on the increased cost were delay in discharge (due to prolonged consultation) [P = .001, OR (95% CI): 6.24 (2.09-18.59)], antibiotic use longer than 7 days [P < .001, OR (95% CI): 5.38 (2.99-9.68)], need for enteral/parenteral feeding [P = .001, OR (95% CI): 4.49 (1.88-10.72)], application of physiotherapy at hospitalization [P < .001, OR (95% CI): 2.94 (1.62-5.34)] and refusal to be discharged [P = .013, OR (95% CI): 4.57 (1.39-15.11)].

DISCUSSION

This study has shown that there are many factors related to increased cost for hospitalized patients with severe COPD exacerbation. The factors most associated with increased cost were delay of discharge (due to prolonged consultation), antibiotic use longer than 7 days, need for enteral/parenteral feeding, application of pulmonary rehabilitation (physiotherapy) at hospitalization, and refusal to be discharged.

In studies to date, the cost of AECOPD has been calculated, but the factors that increased cost have not been investigated in detail.

Table 2. Distribution Between Groups According to Cost

Cost Group	n	Mean	SS	Median	Minimum	Maximum
Normal cost	147	220.15 euros	106.74 euros	197.33 euros	22.4 euros	427.82 euros
Increased cost	147	969.58 euros	893.14 euros	668.67 euros	431.34 euros	7224.45 euros
Total	294	594.87 euros	737.60 euros	429.58 euros	22.4 euros	7224.45 euros

Table 3. Logistic Regression Model of Increased Cost Associated Patient-Related Factors, Exacerbation-Related Factors, Treatment-Related Factors, and Hospital-Related Factors

			OR (95% CI)	
Patient-Related Factors	***P***	**OR**	**Lower**	**Upper**
65 years and over (ref: <65 years)	.444	0.74	0.34	1.60
Caregiver (ref: none)	.363	1.44	0.66	3.14
Influenza vaccine (ref: none)	.898	1.07	0.39	2.95
Pneumococcal vaccine (ref: none)	.317	1.73	0.59	5.02
Extrapulmonary cancer (ref: none)	.951	1.04	0.29	3.78
Refusal to be discharged (ref: accept)	**.051**	4.61	0.99	21.42
Active smoker (ref)	.164	1		
Passive smoker	.038	5.24	1.10	25.03
Ex-smoker	.200	1.81	0.73	4.48
Never smoked	.227	3.07	0.50	18.98
LTOT (ref: none)	.090	2.09	0.89	4.89
BPAP (ref: none)	.277	1.85	0.61	5.59
Stop-BANG low	.091	1		
Stop-BANG middle	.296	0.57	0.19	1.65
Stop-BANG high	.653	1.30	0.42	4.08
EF (%)	.528	0.99	0.95	1.03
Exacerbation-Related Factors				
Average number of exacerbations in the last 1 year	.155	1.12	0.96	1.30
Average number of severe exacerbations in the last 1 year	.564	1.12	0.77	1.64
Pleural effusion on chest x-ray (ref: none)	.054	4.40	0.98	19.84
Pneumonia on chest x-ray (ref: none)	.638	0.76	0.23	2.44
Pneumonia (CT) (ref: none)	.217	2.13	0.64	7.04
Emphysema (CT) (ref: none)	.544	0.73	0.26	2.04
Hospital-acquired pneumonia (ref: none)	.217	2.14	0.64	7.14
GOLD spirometry grade 1	.078	1		
GOLD spirometry grade 2	.113	0.12	0.01	1.64
GOLD spirometry grade 3	.773	0.69	0.06	8.40
GOLD spirometry grade 4	.515	0.44	0.04	5.15
Treatment-Related Factors				
Frequently use of antibiotics (ref: none)	.220	1.48	0.79	2.74
Treatment antibiotics for more than 7 days (ref: none)	**<.001**	3.88	1.95	7.75
Treatment oral/IV corticosteroids for more than 7 days (ref: none)	.803	1.11	0.50	2.45
Treatment combination of SABA/SAMA for more than 3 days (ref: none)	.372	1.35	0.70	2.59
Antiviral treatment (ref: none)	.261	1.99	0.60	6.56
Diuretic treatment (ref: none)	.827	0.92	0.44	1.93
Increase in oxygen demand during hospitalization (ref: none)	.309	1.45	0.71	2.94
Need to NIV during hospitalization (ref: none)	.026	2.41	1.11	5.24
Need to increase NIV pressure during hospitalization (ref: none)	.209	2.24	0.64	7.88
Need to enteral/parenteral feeding (ref: none)	**.007**	3.87	1.45	10.31
Application of physiotherapy during hospitalization (ref: none)	**.003**	2.54	1.38	4.65
Hospital Related Factors				
Hospitalization from the emergency (ref: outpatient)	.054	1.70	0.99	2.91
Delay in discharge (due to consultation) (ref: none)	**<.001**	5.31	2.11	13.36

BPAP, bi-level positive airway pressure; CT, computed tomography; EF, ejection fraction; IV, intravenous; LTOT, long-term oxygen treatment; NIV, noninvasive ventilation; SABA, short-acting beta-agonists; SAMA, short-acting muscarinic antagonists; STOP-BANG, Score for Obstructive Sleep Apnea.

Table 4. Logistic Regression Analyses of the Most Effective Factors on the Increased Cost

	LR Model 1			LR Model 2			LR Model 3	
	OR (95% CI)	***P***		**OR (95% CI)**	***P***		**OR (95% CI)**	***P***
≥65 years	0.74 (0.34-0.60)	.444	Average Number of Exacerbations in the Last 1 Year	1.12 (0.96-1,.0)	.155	Frequently Using of Antibiotics (ref:none)	1.48 (0.9-2.74)	.22
Caregiver	1.44 (0.66-3.14)	.363	Average Number of Severe Exacerbations in the Last 1 Year	1.12 (0.77-1.64)	.564	Using oral/IV corticosteroids for more than 7 days (ref: none)	**3.88 (1.95-7.75)**	**<.001**
Influenza vaccination	1.07 (0.9-2.5)	.898	Pleural effusion (chest x-ray)	4.40 (0.98-19.84)	.054	Using oral/IV corticosteroids for more than 7 days (ref: none)	1.11 (0.50-2.45)	.803
Pneumococcal vaccination	1.73 (0.9-5.02)	.317	Pneumonia (chest x-ray)	0.76 (0.23-2.44)	.638	Using combination of SABA/ SAMA for more than 3 days (ref: none)	1.35 (0.70-2.59)	.372
Extrapulmonary malignancy	1.04 (0,.9-3.78)	.951	Pneumonia (CT)	2.13 (0.64-7,04)	.217	Antiviral treatment (ref: none)	1.99 (0.60-6.56)	.261
Refusal to be discharged	4,.1 (0.99-21.42)	.051	Emphysema (CT)	0,73 (0,26-2.04)	.544	Diuretic treatment (ref: none)	0.92 (0.44-1.93)	.827
Active smoker	1	.164	Hospital-acquired pneumonia	2.14 (0.64-7.14)	.217	increase in oxygen demand (ref: none)	1.45 (0.71-2.94)	.309
Passive smoker	5.24 (1,.0-25.03)	.038	GOLD spirometry grade 1		.078	Need to NIV (ref: none)	2.41 (1.11-5.24)	.026
Ex-smoker	1.81 (0.73-4.48)	.200	GOLD spirometry grade 2	0.12 (0.01-1.64)	.113	Need to increase NIV pressure (ref: none)	2,.4 (0.64-7.88)	.209
Never smoked	3.07 (0.50-18.98)	.227	GOLD S spirometry grade 3	0.69 (0.06-8.40)	.773	Need to enteral/Parenteral feeding (ref: none)	**3.87 (1.45-10.31)**	**.007**
LTOT	2.09 (0.89-4.89)	.090	GOLD spirometry grade 4	0.44 (0.04-5.15)	.515	Physiotherapy (ref: none)	**2.54 (1.38-4.65)**	**.003**
BPAP	1.85 (0.61-5.59)	.277				Hospitalization from the emergency (ref: outpatient)	1.70 (0.99-2.1)	.054
Stop-BANG low	1	.091				Delay in Discharge (due to consultation) (ref: none)	**5.31 (2.11-13.36)**	**<.001**
Stop-BANG middle	0.57 (0.19-1.65)	.296						
Stop-BANG high	1.30 (0.42-4.08)	.653						
EF (%)	0.99 (0.95-1.03)	.528						

BPAP, bi-level positive airway pressure; CT, computed tomography; EF, ejection fraction; LTOT, long-term oxygen therapy; NIV, noninvasive ventilation; STOP-BANG, Score for Obstructive Sleep Apnea.

Goossens et al showed that early discharge was cost effective than in hospital treatment for 7 days.[10] But degree of clinical improvement was greater in patients treated in hospital for 7 days. In conclusion of this study, the authors said that there is no clear evidence was found to decide that both of treatment was less costly or more effective.[10] Prolonged hospitalization is associated not only the existence of comorbidities[11] but also complicated discharge planning that requires additional home care or caregiver organizations.[12] The presence of comorbidity is important not only in terms of treatment management but also in terms of accessing other branches that will evaluate the comorbid condition. Just like in our country, in places where the number of patients is high, consultation services may be disrupted. In addition, factors such as the patient's problem of transportation to the hospital after discharge, unsuitable health condition to go out of the home, or difficulty reaching the doctor sometimes necessitate an elective consultation in the hospital.

However, if the consultation is delayed, possible investigations are delayed, and every hour spent in the hospital adds to the cost. In our study, delayed discharge due to prolonged/incomplete consultation was most associated with increased cost.

Antibiotics are generally used in the management for COPD during hospitalization, as infection is one of the main etiologic factors for AECOPD.[13] Li et al[14] reported that antibiotic use (0.086; 95% CI 0.131-0.178) were significantly (P = .001) associated with total hospitalization costs. In a study from Turkey, it was found that hospital antibiotic treatment ($111.6 ± 77.3; 86.6 ± 60.0) is one of the main reasons (P < .001) for increasing the cost.[15] Even under normal conditions, antibiotic treatment increases the cost. Therefore, if the duration of antibiotic use increases due to antibiotic resistance and/or hospital-acquired infections, the cost increases even more.

Nutrition is one of the important factors in COPD exacerbation management and has become popular in recent years. In the study of Zhang et al,[16] standard enteral nutrition significantly improved nutritional status and immunological functioning, reduced inflammatory markers, and improved cardiopulmonary function of AECOPD patients with respiratory failure. Wang et al[17] showed that enteral and/or parenteral nutrition support can successfully improve the pulmonary function of COPD patients who have respiratory failure and can reduce acute inflammation and oxidative stress. No data were available on the cost of enteral or parenteral nutrition administered to hospitalized patients with COPD exacerbations. In our study, enteral and parenteral nutrition were found to be associated with increased cost.

Pulmonary rehabilitation is stated to be a safe intervention during a COPD exacerbation.[18] Exercise, breathing techniques, education, and psychosocial support are essential components of rehabilitation.[18] Many studies have shown that rehabilitation interventions applied during hospitalization prevent a decrease in lower extremity muscle function, balance, and exercise performance and facilitate recovery afterward.[19-23] No data were available on the cost of pulmonary rehabilitation initiated during hospitalization. In our study, pulmonary rehabilitation practices initiated during hospitalization were associated with increased cost.

Early discharge is the main goal for all diseases requiring hospitalization because the longer the hospital stay, the higher the risk and cost of hospital-acquired infections. However, one of the factors affecting the discharge decision is the social status of the patient. Considering the relationship of COPD with poverty and poor socioeconomic status, we have to acknowledge the existence of a group of patients in underdeveloped and developing countries who have concerns about home care, nutrition, and heating. Patients with these and similar concerns refuse to be discharged, even though they are in the discharge state. However, considering that each day spent in the hospital increases the cost of hospitalization, we can conclude that refusing to be discharged also increases the cost. In our study, refusal to discharge was identified as one of the factors associated with increased cost.

The strengths of our work can be listed as follows: (1) It is a multicenter (representing a large part of the country) and prospective study. (2) The factors affecting the cost were not only limited to clinical and laboratory parameters but also the patient and hospital aspects of the event. The weaknesses of our study are as follows: (1) Since the access conditions for some laboratory tests are not standard in every hospital, there is a small amount of missing data. (2) Although the number of patients included in the study was large, the data here cannot be generalized to all COPD patients because the centers where the study was conducted are tertiary care hospitals. (3) The sociodemographic and administrative differences of each country, even the different regions within each country, may affect the results.

In this study, which is thought to represent a large part of the country, it was concluded that not only the laboratory or clinical parameters but also the social characteristics of the patients, the facilities of the hospital, and the working system affect the cost. Therefore, this study revealed the necessity of multifactorial evaluation when it comes to total cost calculation. Considering the occupancy of hospitals in densely populated areas, the delay of procedures such as consultation and radiological imaging due to in-hospital workload is a known but not documented fact. In order to find solutions to these issues, we think that pilot studies should be conducted for each region of the countries, and they should determine their own internal dynamics.

Ethics Committee Approval: This study was approved by Ethics Committee of Gazi University (Approval No: 687/2018, Date: 2018).

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

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Original Article

Recovery from Respiratory Failure in Patients with Coronavirus Disease 2019

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Abstract

OBJECTIVE: Coronavirus disease 2019 (COVID-19) can cause hypoxic respiratory failure; long-term oxygen therapy (LTOT) duration is unknown.

MATERIAL AND METHODS: The aim was to investigate which patients would need LTOT after COVID-19 pneumonia. This single-center, prospective study was conducted at the Ankara University Faculty of Medicine, Department of Chest Diseases, between May 2021 and December 2021. The 70 patients hospitalized for COVID-19 pneumonia and discharged with LTOT due to hypoxemic respiratory failure were included. Patients were divided into 2 groups as group I (LTOT requirement <3 months) and group II (LTOT requirement continued ≥3 months).

RESULTS: The mean age was 64.4 ± 13.5 years, and 44 (62.9%) of them were male. The most frequently encountered comorbidities were cardiovascular disease (57.1%) and lung disease (22.9%). While PaO_2 levels increased in both groups during the follow-up period, this increment was significantly higher in group I (PaO_2: 66.6 ± 9.9 mm Hg, $P < .001$). The factors affecting the LTOT requirement were evaluated using binary logistic regression. On multivariate analyses of lymphocytes, ferritin, C-reactive protein, PaO_2, SaO_2, subpleural reticulation, and number of lobes affected (≥3 lobes), the SaO_2 level and presence of subpleural reticulation were significantly different between the 2 groups [odds ratio (OR) (95% CI): 0.853 (0.749-0.971), $P = .016$] and [OR (95% CI): 0.171 (0.042-0.733), $P = .017$], respectively.

CONCLUSION: A significant proportion of patients who develop respiratory failure due to COVID-19 recover within the first 3 months. Factors determining the LTOT requirement for more than 3 months were SaO_2 and the presence of subpleural reticulation.

KEYWORDS: COVID-19, long-term oxygen therapy, post COVID, respiratory failure
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INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified as the cause of coronavirus disease 2019 (COVID-19) in December 2019. It spread dramatically from China to many other countries and was declared as a pandemic by World Health Organization (WHO).[1] Pneumonia and acute respiratory distress syndrome (ARDS) are severe manifestations of COVID-19, and patients develop various degrees of respiratory failure.[2] The coronavirus disease 2019 caused one-fifth of all long-term oxygen therapy (LTOT) starts during the pandemic.[3]

Low arterial oxygenation is the fundamental problem in severely ill patients with COVID-19 pneumonia.[4] Some patients with COVID-19 pneumonia recover from respiratory failure in a short time, while others require long-term supplemental oxygen therapy. The previous studies indicate that patients ≥50 years of age and having ≥3 comorbidities are at increased risk of LTOT requirement in COVID-19 after hospital discharge.[5] While radiological, clinical, and respiratory failure data are reported in patients with COVID-19 pneumonia in the first month after discharge, follow-up data after a longer period such as 3 months are rare.[6-8] Previous studies represent that the most common risk factors are higher age and preexisting chronic respiratory disease.[9] During our follow-up, a substantial proportion were able to quit LTOT. This study aims to identify risk factors for LTOT in patients hospitalized for COVID-19 pneumonia at a 3-month follow-up after hospital discharge.

MATERIAL AND METHODS

The study was approved by the Human Research Ethics Committee of Ankara University and numbered İ1-10-21. All patients provided written informed consent at the time of enrollment.

Study Participants

This study was conducted at the Ankara University Faculty of Medicine, Department of Chest Diseases between May 2021 and December 2021. In this single-center, prospective study, we enrolled 88 patients hospitalized for COVID-19

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pneumonia and discharged with LTOT due to hypoxemic respiratory failure. Patients in need of oxygen were hospitalized. Patients with hypoxemic respiratory failure who needed invasive/noninvasive mechanical ventilation (IMV/NIMV)/high-flow nasal oxygen (HFNO) and/or patients with hemodnamic instability were followed in the intensive care unit (ICU). Patients with oxygen saturation <92% and/or PaO_2 <60 mm Hg despite 4-5 L/min nasal oxygen support were admitted to the ICU. Noninvasive mechanical ventilation is used for hypoxemia and hypercapnia. High-flow nasal oxygen was used only for hypoxemia. Indications for IMV are apnea and respiratory failure that are unlikely to be successfully managed with noninvasive approaches (simple oxygen therapy, HFNO, or noninvasive ventilation) need for airway protection in unconscious patient. Hypoxemic respiratory failure was defined as partial pressure of arterial oxygen (PaO_2) <60 mm Hg of room air and normal or low partial pressure of carbon dioxide <45 mm Hg.[10]

In our country, due to legal issues, PaO_2 has to be <55 mm Hg and SaO_2 has to be <88% in room air to prescribe LTOT. The study patients used oxygen concentrators that provided oxygen at most 5 L/min at home.

Inclusion and exclusion criteria are summarized in Table 1.

Table 1. Inclusion and Exclusion Criteria

Inclusion Criteria
Age ≥18 years
Written informed consent
Diagnosis of SARS-CoV-2 infection by positive PCR on the nasopharyngeal swab
Presence of any radiological signs of COVID-19 pneumonia in thorax CT
Discharged with LTOT due to respiratory failure (PaO_2 <55 mm Hg)
To agree with follow-up after 3 months
Exclusion Criteria
Not eligible to follow up for 3 months
The patients with negative PCR results
Receiving LTOT before hospitalization

COVID-19, coronavirus disease 2019; CT, computed tomography; LTOT, long-term oxygen therapy; PaO_2, partial pressure of arterial oxygen; PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Data Collection

All patients' demographic features (age, gender, smoking history, and comorbid diseases), laboratory findings (lymphocyte, D-dimer, fibrinogen, ferritin, C-reactive protein, and neutrophil–lymphocyte ratio), arterial blood gas analysis (pH, PaO_2, $PaCO_2$, and SaO_2), thorax computed tomography (CT) findings (normal, ground-glass opacities, subpleural reticulations, fibrosis, and number of lobes affected), pharmacological therapy [corticosteroid, low-molecular-weight heparin, and acetylsalicylic acid (ASA)], and presence of ICU admission were recorded.

Patients were followed up for 3 months from discharge to evaluate the presence of LTOT need with an arterial blood gas sample at discharge and divided into 2 groups according to the duration of the LTOT requirement. Those with LTOT requirement <3 months were in group I and those with LTOT requirement continued ≥3 months were in group II. At the end of the 3-month follow-up period, these 2 groups were compared in terms of the laboratory (lymphocyte count, D-dimer, fibrinogen, ferritin, troponin, C-reactive protein, and neutrophil–lymphocyte ratio) and radiological findings, demographic features, smoking history, comorbid diseases, and medical treatment.

Main Points

- Coronavirus disease 2019 (COVID-19) can cause hypoxic respiratory failure; long-term oxygen therapy (LTOT) duration is important for follow-up.
- It is important to determine which patients would need LTOT after COVID-19 pneumonia. In this study, factors determining the LTOT requirement for more than 3 months were SaO_2 and the presence of subpleural reticulation.
- The presence of comorbidities, smoking history, and gender do not show any significant difference in terms of the LTOT requirement.

Thorax Computed Tomography Scan Examinations and Image Analysis

Patients were scanned using 4-slice CT scanner (Toshiba Asteion 4, Toshiba Medical System, Japan) and 16-slice multi detector CT scanner (GE Light Speed, GE Medical System, Milwaukee WI). The CT images were evaluated by the radiologist for the presence of the following characteristics: (1) normal; (2) ground-glass opacities; (3) subpleural reticulations; (4) fibrosis; (5) number of lobes affected by ground-glass opacities or subpleural reticulations or fibrosis. To quantify the severity of lung involvement, the number of affected lobes was recorded, and the involvement of 3 or more lobes was considered as severe.[11,12]

Primary and Secondary Endpoints

The primary endpoint of the study was improvement of respiratory failure at 3 months from hospital discharge. The secondary endpoint of the study was also assessed at 3 months from hospital discharge: alterations in laboratory values and radiological findings on thorax CT, and determining the factors that could impact the requirement for LTOT for more than 3 months.

Statistical Analysis

The data was analyzed using IBM StatisticalPackage for the Social Sciences Statistics software, version 22.0 (IBM Corp., Armonk, NY, USA).

Based on the findings of Ogata et al,[13] we estimate that about 66% of the study population would discontinue LTOT after follow-up duration. We calculated that 70 patients are required to reach the power of 90% with an ≥alpha level of 5%. The G*POWER 3.1.9.6 program was used to calculate the sample size. Continuous variables were described using mean with SD for parametric distributed variables, or median with 25th-75th percentiles/interquartile range (IQR) for nonparametric distributed variables. Pearson's chi-square test and Fisher's exact test were used to analyze categorical data as appropriate. Median scores of 2 groups were compared with

nonparametric Mann–Whitney *U*-test. The sStudent's *t*-test for unpaired data was used to compare parametric variables.

Binary logistic regression analysis was used in the univariate and multivariate analyses. The univariate analysis was first performed to identify any potential predictor variables, and variables with $P < .25$ were included in the multivariate analysis to determine any independent predictors of LTOT requirement for more than 3 months. The statistical significance of .05 was used for all analyses.

RESULTS

Study Population

In the study period, 88 patients with COVID-19 pneumonia were discharged from the hospital with LTOT. Median follow-up time for CT and laboratory findings is 88 (82-94) days. Eighteen patients were excluded for various reasons: 13 patients lost follow-up, 2 patients were on LTOT before COVID, and 3 patients have died in the first 3 months One of these patients had died due to hematologic malignancy; 1 of them had died due to cerebrovascular event; and 1 of them had died due to myocardial infarction. The remaining 70 patients were divided into 2 groups: LTOT requirement <3 months (group I, n = 42) and LTOT requirement ≥3 months (group II, n = 28) (Figure 1).

The baseline demographic and clinical features of the study population are shown in Table 2. The mean age of the study patients was 64.4 ± 13.5 years, and 44 (62.9%) of them were male. The most frequently encountered comorbidities were cardiovascular disease (57.1%) and lung disease (22.9%). The majority of patients had a smoking history, with no differences between previous and current smokers. Eight patients in group I and 6 patients in group II quit smoking during follow-up. The majority of patients had ≤1 comorbidity (68.7 %). There was no patient with venous thromboembolism during the discharge period. But at the follow-up period, we identified 4 patients with thromboembolism. All of them were part of group I. Since these patients were included in group I, we think that it did not affect the results of our study.

Concerning the treatments received during hospitalizations for COVID-19, ASA therapy for COVID-19 was significantly lower in group I ($P = .02$). These patients have used ASA treatment for comorbidities, not for COVID pneumonia. The LMWH treatment was used during hospitalization and has been continued 1 month after discharge. Ten patients underwent IMV, 14 patients NIMV, 14 patients HFNO, and 32 patients nasal oxygen treatment. In group I: IMV, n = 2; NIMV, n = 2; HFNO, n = 6; nasal oxygen, n = 32; and in group II: IMV, n = 8; NIMV, n = 12; HFNO, n = 8; nasal oxygen, n = 0. Thirty-eight (54.3%) patients were followed in the ICU; there were no differences between the groups in terms of ICU admission.

We observed lymphopenia, increased D-dimer, fibrinogen, ferritin, troponin, C-reactive protein, and neutrophil–lymphocyte ratio during the admission of the patients. In terms of laboratory findings on admission and follow-up, the groups were not significantly different, and all parameters returned to normal levels at the end of 3 months. On arterial blood gas analyses, mean PaO_2 was low in line with respiratory failure on admission (mean ± SD, 46.7 ± 5.2 mm Hg) (Table 3). The PaO_2 level increased to 60.8 ± 11.3 mm Hg (Table 4). During the admission period, PaO_2 level was significantly lower in group I ($P = .007$). While PaO_2 level increased in both groups during the follow-up period, this increment was significantly higher in group I (PaO_2 = 66.6 ± 9.9 mm Hg, $P < .001$).

Radiological Findings

Ground-glass opacities were the most common radiological finding in thorax CT (n = 68, 97.1%). This was followed by the presence of subpleural reticulation (n = 17, 24.3%). Fibrosis was observed in only 4 patients (5.7%) on admission (Table 3). At least 3 lobes have been affected with ground-glass opacities and/or subpleural reticulations and/or fibrosis in 61 (87.1%) of patients on admission. Regarding the presence of subpleural reticulation on thorax CT on admission, we observed a statistically significant difference between the 2 groups ($P = .022$), with the highest prevalence of subpleural reticulation in the group II (Table 4).

At the third-month follow-up visit, 3 (4.3%) patients in group I had normal thorax CT images. While the prevalence of ground-glass opacities decreased, distribution of subpleural

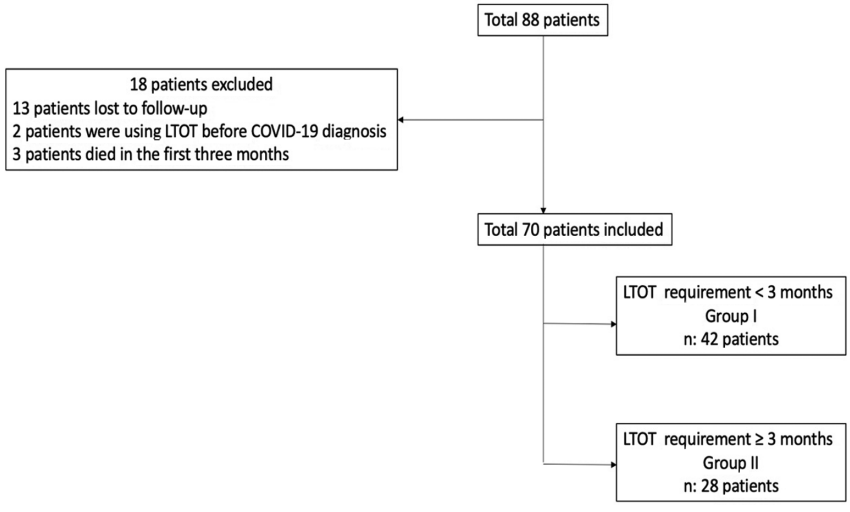


Figure 1. Flowchart of study patients. COVID-19, coronavirus disease 2019; LTOT, long-term oxygen therapy.

Table 2. Characteristics of Study Patients and Comparison of Parameters Between Groups I and II

	All Patients (n = 70)	Group I (n = 42)	Group II (n = 28)	*P*
Age (years) (mean ± SD)	64.4 ± 13.5	65.5 ± 13.4	64.8 ± 13.7	.414
Gender				
Male, n (%)	44 (62.9)	23 (54.8)	21 (75.0)	.086
Female, n (%)	26 (37.1)	19 (45.2)	7 (25.0)	.086
Smoking history (previous and current), n (%)	37 (52.9)	20 (47.6)	17 (60.7)	.509
Comorbid Diseases, n (%)				
Lung disease*	16 (22.9)	12 (28.6)	4 (14.3)	.163
Cardiovascular disease**	40 (57.1)	25 (59.59	15 (53.6)	.622
Malignancy#	5 (7.1)	4 (9.5)	1 (3.6)	.641
Immunosuppression##	7 (11.0)	5 (11.9)	2 (7.2)	1.000
Pharmacological Therapy				
Corticosteroid, n (%)	68 (97.1)	41 (97.6)	27 (96.4)	1.000
LMWH, n (%)	67 (95.7)	42 (100.0)	25 (89.3)	.060
Acetylsalicylic acid, n (%)	26 (37.1)	11 (26.2)	15 (53.6)	.020
ICU admission, n (%)	38 (54.3)	21 (50.0)	17 (60.7)	.378

ICU, intensive care unit; LMWH, low-molecular-weight heparin.
*Asthma, chronic obstructive pulmonary disease, interstitial lung disease, obstructive sleep apnea syndrome.
**Heart failure, coronary artery disease, hypertension.
#Lung cancer, leukemia, metastatic cancer.
##Solid-organ transplantation, bone marrow transplantation, chemotherapy.

Table 3. Laboratory and Radiological Findings on Admission and 3 Months After Discharge of All Patients

	Admission (n = 70)	Follow-Up (n = 70)
Laboratory parameters, median [IQR]		
Lymphocytes, × 10^3/μL	810.0 [597.5-958.7]	2070.0 [1637.5-2692.5]
D-dimer, ng/mL	698.5 [337.5-1972.0]	194.0 [123.0-412.7]
Fibrinogen, g/L	5.7 [4.8-6.7]	3.4 [2.9-3.9]
Ferritin, ng/mL	429.0 [217.1-1158.5]	141.0 [51.4-343.5]
Troponin, pg/mL	15.3 [8.3-29.1]	11.5 [5.9-28.0]
C-reactive protein, mg/L	118.7 [73.3-172.7]	5.0 [2.9-9.7]
Neutrophil–lymphocyte ratio	7.5 [4.9-11.0]	2.1 [1.6-2.9]
Arterial blood gas analysis		
pH	7.43 ± 0.05	7.43 ± 0.04
PaO_2, mm Hg (mean ± SD)	46.7 ± 5.2	60.8 ± 11.3
$PaCO_2$, mm Hg (mean ± SD)	36.9 ± 6.8	37.3 ± 6.3
SaO_2, % (mean ± SD)	82.0 ± 6.9	90.3 ±5.4
Thorax computed tomography findings		
Normal, n (%)	0	3 (4.3)
Ground-glass opacities, n (%)	68 (97.1)	50 (71.4)
Subpleural reticulation, n (%)	17 (24.3)	60 (85.7)
Fibrosis, n (%)	4 (5.7)	23 (32.9)
Number of lobes affected ≥3, n (%)	61 (87.1)	52 (74.3)

Cutoff points: Lymphocyte, 1500-4000 × 10^3/μL; D-dimer, 0-243 ng/mL; fibrinogen, 2-3.93 g/L; ferritin, 30-400 ng/mL; troponin, 0-14 pg/mL; C-reactive protein: 0-5 mg/L.
IQR, interquartile range; PaO_2, partial pressure of arterial oxygen; $PaCO_2$, partial pressure of carbon dioxide; SaO_2, oxygen saturation.

Table 4. Comparison of Parameters on Admission and Follow-Up between Groups I and II

	Admission			Follow-Up		
	Group I	**Group II**	***P****	**Group I**	**Group II**	***P****
Laboratory parameters, median [IQR]						
Lymphocyte, × 10^3/μL	775.0 [590.0-930]	845.0 [610.0-1117.5]	.335[#]	2140.0 [1740.0-2662.5]	1920.0 [1440.0-2837.5]	.385[#]
D-dimer, ng/mL	579.0 [314.2-1757.7]	899.5 [410.0-2614.5]	.491[#]	207.0 [114.5-459.7]	194.0 [129.2-406.0]	.719[#]
Fibrinogen, g/L	5.9 [5.0-7.0]	5.4 [4.3-6.6]	.162[#]	3.3 [2.9-3.8]	3.4 [2.7-4.7]	.415[#]
Ferritin, ng/mL	449.5 [232.4-1308.6]	429.0 [176.1-1067.0]	.378[#]	92.5 [37.2-291.8]	207.5 [91.5-347.7]	.051[#]
Troponin, pg/mL	15.3 [7.8-28.8]	16.3 [8.7-31.9]	.640[#]	10.9 [5.6-28.4]	11.9 [6.1-29.2]	.933[#]
C-reactive protein, mg/L	123.5 [86.8-175.3]	112.5 [46.7-171.7]	.350[#]	4.5 [2.9-9.4]	6.0 [2.9-18.3]	.319[#]
Neutrophil–lymphocyte ratio	7.7 [5.4-10.5]	7.3 [3.6-11.3]	.510[#]	2.3 [1.6-2.6]	1.9 [1.1-3.2]	.606[#]
Artery blood gas analysis						
pH (mean ± SD)	7.43 ± 0.05	7.43 ± 0.5	.957[δ]	7.43 ± 0.4	7.43 ± 0.3	.501[δ]
PaO_2, mm Hg (mean ± SD)	48.0 ± 5.2	44.7 ± 4.6	.009[δ]	66.6 ± 9.9	51.9 ± 6.7	<.001[δ]
$PaCO_2$, mm Hg, (mean ± SD)	35.5 ± 6.6	38.9 ± 6	.040[δ]	36.4 ± 5.9	38.6 ± 6.2	.148[δ]
SaO_2, % (mean ± SD)	84.0 ± 6.4	79.1 ± 6.6	.003[δ]	93.2 ± 2.3	86.1 ± 6.1	<.001[δ]
Thorax computed tomography findings						
Normal, n (%)	0	0		3 (7.1)	0	.270[γ]
Ground-glass opacities, n (%)	41 (97.6)	27 (96.4)	.643[γ]	27 (64.3)	23 (82.1)	.105[γ]
Subpleural reticulation, n (%)	7 (16.7)	10 (35.7)	.022[γ]	33 (78.6)	27 (96.4)	.036[γ]
Fibrosis, n (%)	0	4 (14.3)	.069[γ]	10 (23.8)	13 (46.4)	.048[γ]
Number of lobes affected ≥3, n (%)	35 (83.3)	26 (92.9)	.244[γ]	25 (59.5)	27 (96.4)	<.001[γ]

IQR, interquartile range; PaO_2, partial pressure of arterial oxygen; $PaCO_2$, partial pressure of carbon dioxide; SaO_2, oxygen saturation.
*Comparison of admission parameters between groups I and II.
**Comparison of follow-up parameters between groups I and II.
[δ]Student *t*-test was used for the comparison of parametric values between groups I and II.
[#]Mann–Whitney *U*-test was used for the comparison of nonparametric values between groups I and II.
[γ]Chi-square was used for the comparison of categorical values between groups I and II.

reticulations and fibrosis rose on follow-up in both study groups, 60 (85.7%) and 23 (32.9%), respectively (Table 3). In terms of the presence of ground-glass opacities on admission, while there was no difference at admission, there was a statistically significant difference in terms of the presence of subpleural reticulation and fibrosis between the groups at follow-up, and it is shown in Table 4 (Figure 2 and 3).

While the number of affected lobes decreased in both groups in the follow-up, a statistically significant difference was found between the groups during the follow-up ($P < .001$) (Table 4).

The admission parameters were evaluated for the factors affecting the LTOT requirement using binary logistic regression. On univariate analysis, PaO_2 and SaO_2 levels on follow-up were significantly different between 2 groups [odds ratio (OR) (95% CI): 0.876 (0.789-0.972), $P = .013$] and [OR (95% CI): 1.892 (0.822-0.968), $P = .006$], respectively. On multivariate analysis of lymphocyte, ferritin, C-reactive protein (CRP), SaO_2, subpleural reticulation, and number of lobes affected (≥3 lobes); SaO_2 level and presence of subpleural reticulation were significantly assoociated with the requirement of LTOT [OR (95% CI): 0.843 (0.759-0.936), $P = .001$] and [OR (95% CI): 5.084 (1.306-19.788), $P = .019$], respectively (Table 5).

DISCUSSION

In this study, we report the prevalence and severity of respiratory failure and factors, which affect the LTOT requirement after 3 months of hospital discharge in COVID-19 patients. We observed a considerable improvement in respiratory failure at 3 months from hospital discharge.

In this study, males (44, 62.9%) were affected more than females (26, 37.1%), with an M : F ratio of 1.6 : 1. This male gender dominance has also been observed in previous studies for various coronavirus infections.[5,14] In a study by Martin et al,[15] the vast majority of patients with respiratory failure who were admitted to the ICU due to COVID-19 pneumonia were male and they had at least 1 comorbidity.

Female sex hormones are thought to be responsible for a better immune response to respiratory virus infections such as SARS-CoV-2 infection.[16] In our study, most of the female patients had continued LTOT requirements less than 3 months after discharge, compared to males; however, this was not statistically significant.

Age is an important host factor in the host response to infections; elderly have a poor prognosis.[17] In a study evaluating the relationship between the course of COVID-19 and age, laboratory findings revealed that disease severity and inflammation were directly related to increased ferritin levels in all age groups and increased CRP in the elderly.[18] In the same study, the ground-glass opacities on chest CT were more frequent among the elderly.[18] In our study, we observed that age has no effect on the requirements for LTOT, according to multivariate logistic regression analysis.

The association between smoking status and severe COVID-19 remains controversial. Smoking has been associated with

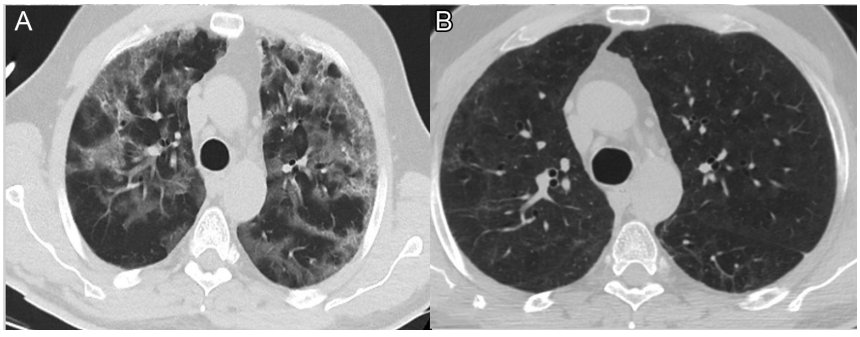


Figure 2. Fifty-eight-year-old male patient with coronavirus disease 2019 pneumonia in Group I has no smoking history and no comorbidities. (A) Thorax computed tomography (CT) scan at admission includes bilateral ground-glass opacities. (B) Thorax CT scan at follow-up period includes decreasing range of ground-glass opacities.

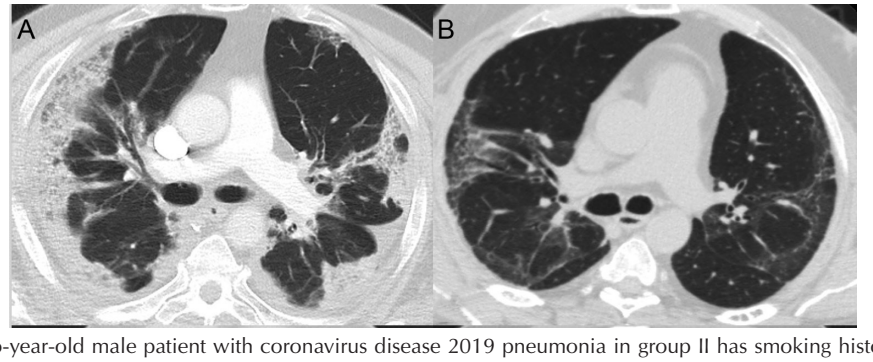


Figure 3. Seventy-two-year-old male patient with coronavirus disease 2019 pneumonia in group II has smoking history and comorbidities such as hypertension and diabetes mellitus. (A) Thorax computed tomography (CT) scan at admission includes bilateral ground-glass opacities, consolidations, and subpleural reticulations. (B) Thorax CT scan at follow-up period showed decreasing range of ground-glass opacities and consolidations, increasing subpleural reticulations.

Table 5. Binary Logistic Regression Analysis of Coronavirus Disease 2019 Patients Who Had Long-Term Oxygen Therapy Requirement for More Than 3 Months

	Univariate Analysis		Multivariate Analysis	
	Odds Ratio (95% CI)	***P***	**Odds Ratio (95% CI)**	***P***
Age, years	1.015 (0.980-1.052)	.408		
Gender, male	2.478 (0.868-7.077)	.090		
Smoking	1.700 (0.644-4.487)	.284		
Lymphocytes	1.001 (1.000-1.002)	.111	1.001 (1.000-1.002)	.094
D-dimer	1.000 (1.000-1.000)	.463		
Fibrinogen	0.829 (0.601-1.143)	.253		
Ferritin	1.000 (0.999-1.000)	.202	0.999 (0.998-1.000)	.143
C-reactive protein	0.996 (0.990-1.009)	.280	0.999 (0.990-1.007)	.737
PaO_2	0.876 (0.789-0.972)	.013		
SaO_2	1.892 (0.822-0.968)	.006	0.843 (0.759-0.936)	.001
Ground-glass opacities	1.519 (0.091-25.325)	.771		
Subpleural reticulation	2.778 (0.906-8.520)	.074	5.084 (1.306-19.788)	.019
Number of lobes affected ≥3	0.385 (0.074-2.005)	.257	0.297 (0.039-2.249)	.240

PaO_2, partial pressure of arterial oxygen; SaO_2, oxygen saturation.

an increased risk of infection and poor outcomes for bacterial and viral pathogens.[19] However, some studies reported a low prevalence of current smokers among people hospitalized due to COVID-19.[20,21] In a meta-analysis comparing non-smokers with current smokers, former smokers appear to be at increased risk of hospitalization, severe disease, and mortality, while current smokers appear to be at reduced risk of SARS-CoV-2 infection.[22] In our study, smoking history did not differ between the groups and was not a factor affecting the requirement for LTOT.

The presence of comorbidities is an important risk factor for severe COVID-19 and possesses a greater risk of mortality due to COVID-19.[19] The most common comorbidities associated with severe COVID-19 are coronary artery disease, congestive heart failure, cardiac arrhythmia, chronic obstructive pulmonary disease, diabetes mellitus, cancer, chronic kidney disease, and obesity.[21,23,24] In previous studies, it has been reported that recovery is delayed in patients with comorbidities and aged >50 years.[5,25] In our study, lung disease, cardiovascular disease, malignancy, and immunosuppression were evaluated in the groups. Cardiovascular and lung diseases were the most common comorbidities but in contrast to previous studies did not affect the course of the disease after discharge.

In a study, abnormal CRP results and lymphocyte count have been observed as prognostic factors in COVID-19 patients.[15] In another study, admission oxygen saturation of <88%, troponin level >1 pg/mL, C-reactive protein level >200 mg/L, and D-dimer level >2500 ng/mL were strongly associated with critical illness than age or comorbidities.[26] In terms of laboratory findings, there were no significant differences between the groups at the admission and follow-up periods in our study. In a study, researchers have explored relationships between the severity of acute respiratory failure, and they considered that patients recovering from ARDS from any cause may have persistent functional impairment 1 year after hospital discharge; therefore, these findings might not be COVID-19-specific.[27] In another study, decreased P/F ratio (PaO_2 divided by the inspired oxygen concentration) during the early discharge period was associated with severe COVID-19 pneumonia and fibrosis.[28] In our study, we observed that PaO_2 and SpO_2 levels significantly affected the need for LTOT for at least 3 months.

Persisting abnormalities in radiology at discharge may be continued despite the absence of symptoms in patients with COVID-19 pneumonia. To assess enduring CT findings, it is advisable to conduct CT scans at both three and six months to determine the frequency of radiological abnormalities. In a previous study, 3 months after hospital discharge, pulmonary structural abnormalities and functional impairment were observed to be highly prevalent in patients with ARDS secondary to COVID-19 who required an ICU stay.[1] In our study, while the most frequent finding was ground-glass opacities on admission CT, subpleural reticulation was observed as the most common finding at 3-month CT, followed by ground-glass opacities and fibrosis. The CT features of lung fibrosis were seen in 32.8% of all study patients and in 46.4% of the patients in group II. Fibrosis and subpleural reticulation were more common among Group II patients (Table 4). Although fibrosis occurs in such a large proportion of subjects in patients with COVID-19 pneumonia, most of those "fibrotic-like" changes, such as subpleural reticulations, are reversible.[5]

In RECOVERY Collaborative Group's randomized controlled study, 14892 patients were evaluated for ASA usage in COVID-19 pneumonia.[29] In this study, 1222 (17%) of 7351 patients allocated to aspirin and 1299 (17%) of 7541 patients

allocated to usual care died within 28 days. Patients allocated to aspirin had a slightly shorter duration of hospitalization (median 8 days, IQR 5 to >28 vs. 9 days, IQR 5 to >28), and a higher proportion were discharged from hospital alive within 28 days (75% vs. 74%; rate ratio 1.06, 95% CI: 1.02-1.10; *P* = .0062). Among patients not on IMV at baseline, there was no significant difference in the proportion meeting the composite endpoint of IMV or death (21% vs. 22%; risk ratio 0.96, 95% CI: 0·90-1·03; *P* = .23). In patients hospitalized with COVID-19, ASA was not associated with reductions in 28-day mortality or in the risk of progressing to IMV or death, but was associated with a small increase in the rate of being discharged alive within 28 days. In our study, ASA use was higher in patients who required LTOT for 3 months, and this was statistically significant. It was observed that the use of ASA did not contribute to the early termination of oxygen therapy. When compared to the RECOVERY study, it can be said that the patients using ASA in our study had similar discharge results.

In the light of the data obtained from our study, it is not possible to determine at the beginning which group of patients would need LTOT after 3 months. It may be recommended that patients be followed up at regular intervals after COVID-19 pneumonia. In this regard, it is crucial to establish follow-up criteria to assess the clinical and radiological sequelae that may arise in patients after experiencing COVID-19 pneumonia.

In a study, patients were divided into 2 groups: as early recovery and refractory groups, in terms of respiratory support time. In the refractory group, it was determined that oxygen support could not be stopped within 6 months after the COVID-19 diagnosis.[13] Similarly, in our study, patients who required LTOT were more likely to be hospitalized in the ICU, and their radiological pathological findings continued in the follow-ups.

As seen in previous studies, it is thought that the radiological findings of patients will regress in longer follow-ups.

We think that subpleural reticulation, which persists for a long time, is a radiological finding similar to fibrosis and may transform into fibrosis in the future. Therefore, patients with continued subpleural reticulations should be followed. However, it is not yet clear whether there will be a decrease in oxygen demand as the radiological findings regress. We think that it is important for future studies to investigate the presence of COVID-19-related underlying vascular pathologies in patient groups who require oxygen therapy for more than 3 months and whose radiological findings regress, and to investigate whether there is an underlying interstitial lung disease in patients whose radiological findings last longer than 3 months.

Our study had some limitations. It was a single-center study with a small sample size. Study observation was limited to the follow-up period, lacking longer follow-up. In terms of the requirement of LTOT, long-term follow-up of patients with COVID-19 pneumonia would be more reliable to estimate the development of chronic respiratory failure.

In conclusion, our findings reveal that a significant proportion of patients who develop acute respiratory failure due to COVID-19 recover within the first 3 months. Since chronic respiratory failure after COVID-19 recovery is an emerging threat to global health, advances in post-COVID-19 management are important. Since patients whose radiological findings continue after COVID-19 pneumonia may require LTOT, we recommend planning thoracic CT controls in appropriate cases to follow-up the formation of fibrosis. Whether subpleural reticulation will regress or turn into fibrosis can be determined by longer follow-ups. Another important finding of the study is that the number of involved lobes at follow-up is associated with respiratory failure. Although it is not possible to say which patients need oxygen therapy for a long time, it can be said that patients whose radiological findings continue in the follow-ups need oxygen support for a longer period of time. More studies are needed to determine the necessity of LTOT in the diagnosis and to identify treatment options that will enable the discontinuation of oxygen therapy in the early period.

Ethics Committee Approval: This study was approved by Ethics Committee of Ankara University (Approval No: İ1-10-21).

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

Peer-review: Externally peer-reviewed.

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

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Original Article

Survival Effect of Surgery in Patients with Stage IIIB/N2 Non-small Cell Lung Cancer: A Comparative Study with Definitive Chemoradiotherapy

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Abstract

OBJECTIVE: We compared the survival outcomes of surgery within multimodality treatment regimens with the outcomes of definitive chemoradiation treatments in patients diagnosed with clinical (c) IIIB/N2 non-small cell lung cancer (NSCLC). We investigated whether surgery within multimodality treatment provides a survival advantage at this stage.

MATERIAL AND METHODS: Data from 79 patients with cIIIB/N2 between 2009 and 2016 were analyzed retrospectively. While the surgery was performed after neoadjuvant therapy in 51 cases (IIIB/Surgery Group), definitive chemotherapy ± radiotherapy was applied in 28 cases (IIIB/Definitive Group).

RESULTS: In cIIIB/N2 cases, the 5-year overall survival (OS) was 27.4%, with a median OS of 24.6 months. The 5-year OS of the IIIB/Surgery Group was 27.3% (median survival 22.5 months), while it was 28.6% (median survival 29.1 months) in the IIIB/Definitive Group (P = .387, HR = 0.798, 95% CI, 0.485-1.313). Although there was a survival advantage in the group with a pathological complete response (PCR) after surgery (n = 14) compared to the group that did not (n = 37), the observed difference was not statistically significant. (5-year OS; 42.9% vs. 18.5%, P = .104). Additionally, there was no statistically significant difference between the survival of PCR patients and the IIIB/Definitive Group in terms of OS (P = .488).

CONCLUSION: Surgery performed within multimodality treatment regimens in selected cIIIB/N2 cases did not provide a survival advantage over definitive chemoradiation treatments.

KEYWORDS: Stage IIIB, N2, neoadjuvant treatment, definitive therapy, lung cancer
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INTRODUCTION

Approximately 20%-30% of NSCLC cases are diagnosed at stage III.[1] In the eighth edition of tumor-node-metastasis (TNM), stage III, non-small cell lung cancer (NSCLC) is divided into 3 different stages. Stage IIIB constitutes a highly heterogeneous group, as T3-4/N2 and T1-2/N3 cases are represented at this stage. In contrast to N3 cases, surgery can be considered as an option in multimodal treatments in highly selective T3-4/N2 cases.[2] It is recommended that neoadjuvant chemotherapy (CT) or concomitant chemoradiotherapy (CRT) is followed by surgery in stage IIIA/N2 cases with single and non-bulky (<3 cm) N2 lymph node (LN) involvement, for which complete resection is feasible.[2] Although the current treatment approach in stage IIIB/N2 cases is immunotherapy and CRT, surgery is offered as a treatment option within multimodal regimens in very highly selected cases such as non-invasive T3/N2.[2] As durvalumab treatment is not routinely used in many countries, surgery is widely preferred in stage IIIB/N2 cases, and very promising survival results have been reported with multimodal treatment regimens, including surgery in selected stage IIIB/N2 cases where complete resection is possible.[3]

There are not many studies on the outcomes of surgery in stage IIIB/N2 NSCLC cases classified according to the eighth edition of TNM staging system. In this study, we compared the survival outcomes of stage IIIB/N2 patients not receiving immunotherapy and receiving only definitive CT ± radiotherapy (RT) treatment with the survival outcomes of selected cIIIB/N2 patients undergoing surgical treatment. We aimed to investigate whether surgery provides a survival advantage in selected clinical (c) IIIB/N2 NSCLC patients.

MATERIAL AND METHODS

The study received approval from the Ethics Committee at Yedikule Hospital with the number 329-5 on August 24, 2022 and was conducted following the principles outlined in the Declaration of Helsinki. Informed consent was obtained from the patients.

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The data of 79 patients included in the study with a diagnosis of cIIIB/N2 between 2009 and 2016 were evaluated retrospectively. The patients' staging was determined based on the eighth edition of TNM staging. Patients were divided into 2 groups: those who underwent surgery within multimodality treatment regimens (IIIB/Surgery Group) and those who received definitive treatment only (IIIB/Definite Group).

In all cIIIB/N2 patients, involvement of mediastinal LNs was proven by endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) and/or cervical mediastinoscopy. Extent mediastinoscopy or video-assisted thoracoscopic surgery was performed for a biopsy of aortopulmonary window (APW) LNs. The clinical diagnosis of T3-T4 was made by positron emission chemotherapy (PET-CT) and/or contrast-enhanced thorax CT. Patients with pathological involvement of a second nodule in the same lobe in PET-CT examination (confirmed preoperative or postoperative pathological examination), cases with tumor diameter between 5 cm and 7 cm, and cases with the suspected invasion of the chest wall, mediastinum, or pericardium were evaluated as T3.

Cases with suspected carina, vena cava superior, and atrium invasion, and cases >7 cm without invasion in which complete resection could be achieved, were considered selected T4 cases. Patients that were deemed unresectable due to invasion of the heart, great vessels, recurrent laryngeal nerve, esophagus, and vertebral body, as well as cases with cN3, bulky N2, multiple N2, and persistent N2 after neoadjuvant therapy, were excluded from the study and referred to oncology clinics for definitive treatment. Cases with incomplete resection (R1-2) were also not included.

In the PET-CT examination, mediastinal LN with a high standardized uptake volume-maximum (SUVmax) value before neoadjuvant therapy, a value of <2.5 after induction therapy was evaluated as radiological mediastinal downstage. In clinical restaging, mediastinoscopy was used to reevaluate the mediastinum after neoadjuvant therapy in cases diagnosed with N2 by EBUS, while re-evaluation was generally performed with PET-CT in cases undergoing mediastinoscopy in the initial staging. Endobronchial ultrasound and/or mediastinoscopy were used for restaging in cases with mediastinal LN >2.5.

When choosing a multimodality treatment regimen, including surgery or definitive CRT in stage IIIB/N2 cases where complete resection can be achieved, the patient's age, general condition, accompanying comorbidities, unfitness for multimodality treatment, insufficiency in respiratory function capacity, or cardiac risk were evaluated at the multidisciplinary tumor board conference. Moreover, patient preference was one of the most important selection criteria. Multidisciplinary councils consisted of a thoracic surgeon, radiation/medical oncologist, and pulmonologist, as recommended in the guidelines of the American Society of Clinical Oncology.[4] Surgery was performed in patients with mediastinal downstage after neoadjuvant CT or CRT in the IIIB/Surgery Group. In the IIIB/Definitive Group, where complete resection could be achieved but no resection decision was made, definitive CT ± RT was performed.

Platinum-based agents are preferred as neoadjuvant CT, and although there is no standardization, we applied them in the form of at least 2 cycles. There is currently no established standardization for deciding whether to perform CRT (60-66 Gray, 30-33 days) or CT alone for neoadjuvant therapy.

Posterolateral or anterolateral thoracotomy approaches were applied to the surgical group of patients. Although lobe-specific LN dissection/sampling may be preferred in the early stages, we en bloc remove the LNs in the ipsilateral mediastinum along with the surrounding adipose tissue in patients who have received neoadjuvant therapy for N2 disease. Therefore, in all patients, regardless of tumor size and location, systematic mediastinal nodal dissection was performed. Mediastinal LN stations (5-6-7-8-9 on the left side and 2R-4R-7-8-9 on the right side) and hilar LN stations (stations 10 and 11) were dissected en bloc as determined intraoperatively by the surgeon. The number of N2 stations dissected intraoperatively was 3.2 ± 1.2 (range: 3-5 stations), and the overall reported total N2+N1 stations were 6.5 ± 1.1 (range: 5-10 LNs). The resected tissues and lymph nodes were histopathologically evaluated by the same pathologists. In pathological reports, the overall N2+N1 LNs were reported as 18.5 ± 8.1 (10-75 LNs) (Table 1).

As a definitive chemoradiation treatment regimen, 6 cycles of platinum-based agents were given together with concomitant RT (60-66, Gray 30-33 days).

Clinical follow-up was conducted once every 3 months during the first year and once every 6 months between the first and fifth years. Patients were evaluated with a non-contrast chest CT every 6 months. In cases of suspected recurrences

Table 1. Description of Lymph Node Stations and Nodes Reported

Assessed and reported	Lymph Node Stations and Lymph Nodes ± SD (minimum–maximum)
Number of N2 station dissected	3.2 ± 1.2 (3-5)
Number of N1 station reported	3.0 ± 1.1 (2-5)
Number of N2 lymph nodes	9.3 ± 5.0 (6-33)
Number of N1 lymph nodes	10.6 ± 5.7 (6-54)
Overall total N2+N1 stations reported	6.5 ± 1.1 (5-10)
Overall total N2+N1 lymph nodes reported	18.5 ± 8.1 (10-75)

Main Points

- Treatment strategies are controversial in patients with stage IIIB/N2 non-small cell lung cancer.
- In selected stage IIIB/N2 cases where complete resection is possible, multimodality treatment regimens including surgery can be applied.
- Surgery performed within multimodality treatment regimens in selected cIIIB/N2 cases did not provide a survival advantage over definitive chemoradiotherapy treatments.

or metastases, PET-CT was requested, and cranial magnetic resonance imaging was conducted when deemed necessary.

Overall survival (OS) was defined as the duration from the date of surgery to the date of death from any cause.

Statistical Analysis

The data were inputted into the Statistical Package for the Social Sciences Statistics for Windows, Version 23.0 (IBM Inc., Armonk, NY, USA) software for analysis. Descriptive statistics were employed to characterize the variables, utilizing measures such as mean, maximum, and minimum values, while percentages were utilized for qualitative variables. By Kolmogorov–Smirnov analysis, whether the distributions were normal or not was determined. For variables that followed a normal distribution, the mean was reported, and to compare groups, the Student's *t*-test was utilized. The analysis of qualitative variables was conducted using the Pearson chi-squared test. However, if the sample size of a group was small, the Fisher's exact test was used instead. Nonparametric continuous variables were documented as the median and assessed using Mann–Whitney *U*-tests for comparison. Survival was estimated using the Kaplan–Meier method, and survival was compared between the groups with a log-rank analysis. A *P*-value less than .05 was considered to be statistically significant.

RESULTS

There were 79 patients included in the study with a diagnosis of cIIIB/N2. Surgery was performed in 51 (64.5%) patients within the multimodality treatment regimens (IIIB/Surgery Group). In 28 cases (35.5%), surgical resection was not performed, and definitive CT ± RT was administered (IIIB/Definite Group).

Demographic and clinicopathological characteristics of the patients are summarized in Table 2. There were 51 patients in the IIIB/Surgical Group and 28 patients in the IIIB/Definitive Group. There was no statistical difference between the groups in terms of age, gender, side, radiological tumor diameter, anatomical localization of positive LN, and clinical T subtype. There was a trend toward statistical significance in terms of histological tumor type ($P = .06$). A statistical difference was found between the 2 groups in terms of the mediastinal staging method ($P = .02$). In mediastinal staging, EBUS was performed at a statistically higher rate in the IIIB/Surgery Group (31.4% vs. 7.1%).

Lobectomy was performed in 41 patients in the IIIB/Surgery Group and pneumonectomy in 10. Chest wall resection was performed in 7 of them. While PET-CT was used most frequently for restaging of the patients (n = 32, 62.7%), mediastinoscopy was performed in 16.5% (n = 13) of the remaining patients and EBUS (n = 6) in 7.6%.

In the IIIB/Surgery Group, pathological complete response (IIIB/Surgery-PCR) was detected in 14 cases (27.4%), while viable tumors were present in 37 cases (72.6%) (IIIB/Surgery-non-PCR). Considering the postoperative pathology results, 40 (78.4%) of the patients developed downstage of N2 (IIIB/Surgery-Non persistent N2), while 11 patients (21.6%) had persistent N2 (IIIB/Surgery-Persistent N2).

Survival Analysis

The 5-year OS rate for all patients was 27.4%. (median survival time: 24.6 months, 95% CI, 18.2-30.9). The 5-year OS rate for the IIIB/Surgery Group was 27.3% (median survival time 22.5 months, 95% CI, 11.8-33.1), while it was 28.6% (median survival time 29.1 months, 95% CI, 18.9-39.2) for the IIIB/Definitive Group. The observed difference was not statistically significant ($P = .387$, HR = 0.798, 95% CI, 0.485-1.313) (Figure 1).

Subgroup Analysis

Among the patients in the IIIB/Surgery Group, the 5-year OS was 42.9% (median survival time: 27.0 months, 95% CI, 0-116.4) in patients with pathological complete response (n = 14), while it was 18.5% (median survival time: 15.6 months, 95% CI, 3.6-27.5) in non- or partial responders (n = 37). However, the observed difference was not statistically significant. ($P = .104$) (Figure 2).

There was also no statistical difference in terms of survival between patients with the pathological complete response and the IIIB/Definitive Group ($P = .488$).

Among the patients in the IIIB/Surgery Group, the 5-year OS was 29.8% (median survival time 23.1 months, 95% CI, 18.6-27.7) in those with downstage mediastinal LN (n = 40), while the 3-year survival rate in those with persistent N2 was 18.2% (median survival time 13.9 months, 95% CI, 3.3-24.5). Nonetheless, this difference was not statistically significant ($P = .113$, Figure 3).

The 5-year OS was also not affected by age ($P = .083$), gender ($P = .842$), histological type ($P = .978$), tumor diameter (0.866), whether surgery was within the treatment protocol ($P = .387$), mediastinal staging methods ($P = .294$), location of N2 ($P = .232$), and resection type ($P = .589$).

Comparisons of variables that may affect survival are listed in Table 3.

DISCUSSION

Lung cancer is one of the most important causes of cancer-related death in both genders worldwide.[5] In early-stage NSCLC cases, direct surgery option is a generally accepted approach. However, treatment strategies change significantly as the stage progresses, and the indication for surgery and its impact on survival become controversial. In current guidelines, surgery is not recommended in stage IIIB/N2, except for T3N2 patients who do not have clinical and radiological signs of an invasion.[2] The results of the phase III PACIFIC trial on nonsurgical stage III patients were striking. Cases that did not show progression after CRT were administered the PD-L1 antibody durvalumab, and the 5-year OS rate was reported to be 42.9%.[6] On the other hand, since immunotherapy is still an expensive treatment in many countries, its use in routine practice is limited.[7] The treatment strategy in cases at this stage may be, therefore, limited to definitive CRT. The sociocultural and economic conditions of the patients affect the treatment choice.[8] The patients included in our study were patients receiving treatment between 2009 and 2016, and none of these patients had a chance for definitive treatment, including

Table 2. Demographic and Clinicopathological Characteristics of the Patients

Variable	Total (n = 79)	Stage IIIB/Surgery (n = 51)	Stage IIIB/Definitive (n = 28)	*P*
Age, mean ± SD	57.6 ± 0.7	57.3 ± 0.9	58.0 ± 1.3	.825
Gender, n (%)			5 (17.9)	.180
Female	9 (11.4)	4 (7.8)	23 (82.1)	
Male	70 (88.6)	47 (92.2)		
Side, n (%)				.219
Left	35 (44.3)	20 (39.2)	15 (53.6)	
Right	44 (55.7)	31 (60.8)	13 (46.4)	
Histological subtype, n (%)				.067
Squamous cell	32 (40.5)	24 (47.1)	8 (28.6)	
Adenocarcinoma	34 (43.0)	22 (43.1)	12 (42.9)	
Other[#]	13 (16.5)	5 (9.8)	8 (28.6)	
Radiological tumor diameter, median cm, (IQR)	6.0 (1.9)	6 (1.7)	6.1 (2.2)	.955
Mediastinal staging type, n (%)				.02
Mediastinoscopy	61 (77.2)	35 (68.6)	26 (92.9)	
EBUS	18 (22.8)	16 (31.4)	2 (7.1)	
Positive LN, n (%)				.486
4R	33 (41.8)	22 (43.1)	11 (39.3)	
7	20 (25.3)	15 (29.4)	5 (17.9)	
4L	19 (24.1)	9 (17.6)	10 (35.7)	
APW	7 (8.9)	5 (9.8)	2 (7.1)	
Clinical T subtype, n (%)				.120
T3	55 (69.6)	36 (70.6)	19 (67.9)	
T4	24 (30.4)	15 (29.4)	9 (32.1)	
Resection type, n (%)*			—	N/A
Lobectomy	41 (80.4)	41 (80.4)		
Pneumonectomy	10 (19.6)	10 (19.6)		
ypN status, n (%)*			—	N/A
ypN0	35 (68.6)	35 (68.6)		
ypN1γ	5 (9.8)	5 (9.8)		
ypN2α	11 (21.6)	11 (21.6)		
ypT status, n (%)*			—	N/A
T0	14 (27.5)	14 (27.5)		
T1	13 (16.5)	13 (16.5)		
T2	18 (22.8)	18 (22.8)		
T3	4 (5.1)	4 (5.1)		
T4	2 (2.5)	2 (2.5)		

APW, aortopulmonary window; EBUS, endobronchial ultrasound; IQR, interquartile range; LN, lymph node; n, number; na, nonapplicable; yp, new pathological stage.
*These ratios were based on 51 patients undergoing surgery after neoadjuvant therapy. Unblock chest wall resection was also performed in 7 (13.7%) of these patients. While four of the patients with ypN1 were N1a, one patient was found to be N1b. While three of the patients with α ypN2 were found N2a1, five were ypN2a2, and three of them were N2b.
[#]Adenosquamous cell carcinoma and large cell carcinoma.

immunotherapy. Nevertheless, in our study, even in highly selective cIIIB/N2 patients who can achieve complete resection, surgery within multimodality regimens was found not to provide a survival advantage compared to definitive CRT.

In terms of survival outcomes of stage IIIB/N2 cases, quite different results are presented in the literature. These differences may be due to the use of different editions of TNM.

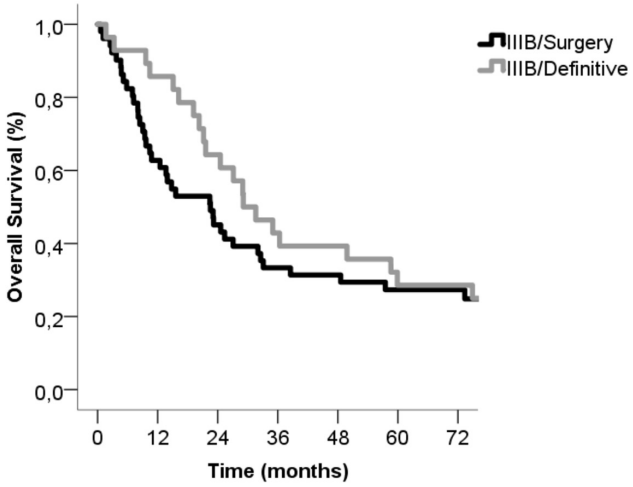


Figure 1. Overall survival of IIIB/Surgery Group and IIIB/Definitive Group.

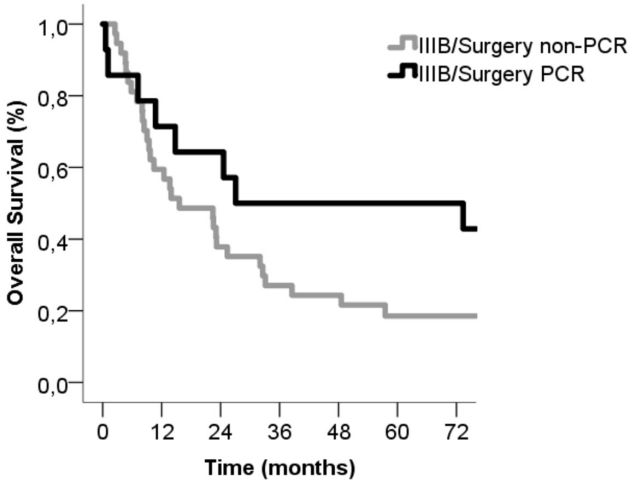


Figure 2. Overall survival of the IIIB/Surgery-nonPCR Group and the IIIB/Surgery-PCR group. PCR, pathological complete response.

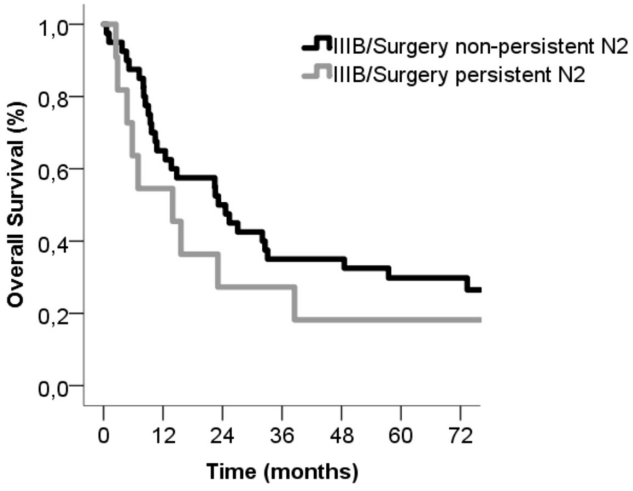


Figure 3. Overall survival of IIIB/Surgery-non Persistent N2 Group and IIIB/Surgery-Persistent N2.

The 5-year survival rate was reported as 25% in cN0-1 pathological (p) IIIB/N2 (unexpected N2) patients who were staged according to the eighth8th edition of the TNM system, and did not receive neoadjuvant therapy, whereas it was reported as 39% in cN2/N3 stage IIIB cases staged considering the seventh7th edition of the TNM system.[3,9] The authors attributed successful survival outcomes obtained from IIIB/N2-N3 patients, above the literature rates, to the selection of optimal surgical candidates and low postoperative mortality.[3]

The largest study on this subject is the ESPATURE Phase III study.[10] In selected IIIB NSCLC and resectable stage IIIA/N2 patients, according to the sixth edition of TNM staging,

Table 3. Comparison of Variables that May Affect Survival

Variable	5-year Overall Survival (%)	Median Survival Time (Months)	*P*
Age, n (%)			.083
<65	30.1	27.1	
≥65	15.4	15.6	
Gender, n (%)			.842
Female	26.9	24.5	
Male	33.3*	29	
Histological type			.978
Adenocarcinoma	30.9	22.4	
Non-adenocarcinoma	25.5	29	
Tumor diameter,			.866
≤7 cm	27	24.5	
>7 cm	25	25.3	
Treatment type, n (%)			.387
Neoadj+S ± Adj	27.3	22.5	
Adj	28.6	29.1	
Mediastinal staging type, n (%)			.294
Mediastinoscopy	30.9	24.5	
EBUS	16.7	24.6	
Mediastinal LN metastasis location			.232
Subcarinal	15	15.1	
Paratracheal or APW	32	24.6	
Resection type, n (%)			.589
Lobectomy	29.1	22.4	
Pneumonectomy	20.0*	23.1	
Response to treatment			.104
Pathological complete response	42.9	27	
Partial response or no response	18.5	15.6	
ypN status			.113
Downstage	29.8	23.1	
Persistent	18.2	13.9	

APW, aortopulmonary window; Adj, adjuvant treatment; EBUS, endobronchial ultrasound; LN, lymph node; Neoadj, neoadjuvant treatment; n, number; S, surgery; yp, new pathological stage.
*Three-year survival results.

surgeries after induction treatment regimens were compared with definitive treatment modalities, and there was no difference in survival between the groups. However, a survival advantage was seen in the surgical group, T3N2 cases, and T4N0-1 subgroups. Contrary to this study, in the analysis of the National Cancer Database data, including T4/N2 and N3 patients, patients treated with radiotherapy, chemotherapy, and surgery in any sequence group showed a statistically significant survival advantage compared to the definitive chemoradiation treatment group.[11]

The most important point to be considered in similar studies in the literature is the use of different editions of the TNM, and this probably affects survival outcomes.[12,13]

Using the eighth TNM staging system instead of the sixth and seventh editions of TNM and focusing only on the IIIB/N2 (T3-T4/N2) patient group in our study were thought to make our study a more successful design in questioning the role of surgery regarding the IIIB/N2 patient group.

We think that the 5-year survival rate of patients in the cIIIB/N2 group is similar to the latest International Association for the Study of Lung Cancer (IASLC) group data, which is a valuable parameter for our selection of appropriate patients (IASCL vs. the current study; cIIIB 5-year OS: 26%, median 19 months vs. 27.3%, median 22.5 months).[14] It was stated that the patients who would prefer surgery among the multimodality regimens in N2 cases should be patients in whom complete resection is feasible and whose 90-day perioperative mortality expectation should be ≤5%. Another point underlined in the same guidelines is that patients and their relatives should be included in the treatment decision process and that a surgical opinion must be received in non-surgical treatment decisions.[14] In the cases included in the study, the final decisions were evaluated in multidisciplinary tumor councils, and the preferences of the patients and their relatives were taken into account.

The mediastinal downstage after neoadjuvant therapy and the complete pathological response in the postoperative examination are known to be associated with good survival.[15,16] Conversely, 5-year survival rates of 30-47.3% have been reported in persistent single N2 cases that cannot achieve mediastinal downstage.[17] In our IIIB/Surgery Group, although the median survival difference was 10 months between persistent N2 cases and those with mediastinal downstage, this difference could not reach statistical significance (5-year OS: 29.8% vs. 18.2%). Likewise, although there was a median survival difference of approximately 11 months in the patient group with a complete response compared to the group with a non-complete response, this difference did not reach statistical significance against both the non-complete response and definitive treatment groups.

Mediastinal downstage can also be evaluated with EBUS and PET-CT, but mediastinoscopy is still the gold standard.[2,18] All 3 methods were used for restaging in the cIIIB/N2 patient group. In evaluating the best staging algorithms, EBUS is recommended as the minimally invasive method in the first step, and mediastinoscopy is for restaging.[2]

The PACIFIC study has led to the questioning of the surgery to be performed at this stage. Although surgery does not provide any survival advantage at this stage among multimodal treatment strategies, we think that applications for cancer immunotherapy in IIIB/N2/N3 patients bring new surgical indications. In the following years, surgery may have a new indication within neoadjuvant CT + immunotherapy and definitive CRT + immunotherapy regimens in stage IIIB/N2 cases.[19,20] Again, salvage surgery is a new indication in stage IIIB patients receiving definitive CRT + durvalumab and being completely respected with good condition, and there is not enough data on this subject yet.[21]

The current study has some limitations, primarily attributed to its retrospective design. It does not claim to determine treatment strategies in stage IIIB/N2 due to the limited sample size and limited single-center setting, which reduces generalizability to broader clinical practice. Therefore, the view that surgery does not provide a survival advantage at this stage should be interpreted with caution as it is a single-center study. However, our study is one of the largest studies in the IIIB/N2 patient group using only the eighth TNM staging system. We think that our similarity with IASLC survival results is indicative of our selection of the clinically appropriate stage IIIB patient group. Currently, EBUS/endoscopic ultrasound (EUS)-guided fine needle aspiration is the first-choice method for sampling mediastinal lymph nodes due to its minimally invasive nature and high diagnostic value. However, we could not apply for EUS because there was no equipment in our center during the years of the study. Therefore, we could not sample stations 8 and 9. Since the diagnosis of T3-4 disease is made only based on radiological findings, there may be disagreements among radiologists. The T4 patient group within the cIIIB/Surgery Group consists of a highly selected group of patients. In addition, the number of patients with PCR and mediastinal downstage is very small and may affect the outcomes of the study in terms of statistical significance. Therefore, the results of this study should be interpreted with caution in terms of surgical outcomes in stage IIIB/N2 NSCLC patients.

Complete resections performed within multimodality treatment regimens in highly selective cIIIB/N2 patients did not provide an advantage over definitive chemoradiation treatments in terms of OS. Although a survival advantage was observed in cases with a complete response to induction treatment regimens, this difference did not reach statistical significance compared to the definitive treatment group. Even though there was a difference in survival between cases with and without mediastinal downstage after induction treatment regimens, it was not statistically significant. Large phase III studies are needed on the application and benefit of surgery after neoadjuvant chemotherapy + immunotherapy or salvage surgery after definitive treatment in stage IIIB/N2 cases.

Ethics Committee Approval: This study was approved by Ethics Committee of Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital (Approval No: 329-5, Date: August 24, 2022).

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

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Review

A Narrative Review of the Clinical Trials in Sleep-Related Breathing Disorders from 2022 to Present

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Abstract

Sleep-related breathing disorders (SRBD) comprise obstructive sleep apnea (OSA), central sleep apnea (CSA), obesity-hypoventilation syndrome (OHS), as well as isolated sleep-related hypoxemia (ISRH), according to the recent International Classification of Sleep Disorders 3. During the last decades, there have been cumulative research reports indicating an association between the SRBD and increased cardiometabolic illness and death, as well as decreased quality of life. Notwithstanding, the results have been inconclusive, and the evidence level was not high regarding the effect of treatment for the SRBD on adverse outcomes. In the current work, we aim to give a comprehensive review of the clinical trials published from January 2022 to August 31, 2023. We highlight the heterogeneity of cardiometabolic disorders among adults with SRBD and particularly emphasize OSA management, drug therapy for OSA, positive airway pressure (PAP) therapy and cardiovascular outcomes, other effects of PAP in pregnancy and neurocognitive function, as well as the effects of surgical treatment and oral appliances. We also underline future directions in OSA management, telemonitoring, and drug-induced sleep endoscopy in managing the SRBD, especially OSA. We ascertain that more studies are needed within the CSA, OHS, and ISRH research fields.

KEYWORDS: Sleep-related breathing disorders, obstructive sleep apnea, cardiovascular, drug therapy, telemedicine
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INTRODUCTION

The current narrative review aims to summarize the recent research articles regarding the clinical trials within the sleep-related breathing disorders (SRBD) research field from January 2022 to August 31, 2023. According to the International Classification of Sleep Disorders (ICSD) 3, SRBD comprise obstructive sleep apnea (OSA; defined as an apnea–hypopnea index [AHI] ≥15 events/h), central sleep apnea with Cheyne–Stokes respiration (CSA-CSR), obesity hypoventilation syndrome (OHS), as well as isolated sleep-related hypoxemia (ISRH) (nocturnal oxyhemoglobin saturation [SpO_2] <88% for ≥5 minutes).[1] In the current report, we particularly emphasize OSA management, drug treatment for OSA, continuous positive airway pressure (CPAP) and cardiovascular outcomes, other effects of PAP in pregnancy and neurocognitive function, as well as the effects of surgical treatment and oral appliances. We also highlight future directions in OSA management, telemonitoring, and drug-induced sleep endoscopy (DISE) in managing the SRBD.

EFFECT OF TOTAL SLEEP OR RAPID EYE MOVEMENT SLEEP DEPRIVATION AND OBSTRUCTIVE SLEEP APNEA ON MALE REPRODUCTIVE FUNCTION

In a randomized trial by Alvarenga et al (NCT01884454),[2] the effects of sleep deprivation and OSA on male reproductive function have been evaluated in a 3-arm parallel study. A predefined OSA group as well as a group of healthy volunteers was randomized to total or rapid eye movement (REM) sleep deprivation. Circulating levels of total and free testosterone and high-density lipoproteins, as well as proportions of healthy sperm cells and sperm concentrations, were lower in participants with OSA compared to those in volunteers. Circulating levels of thyroid-stimulating hormone and insulin were higher, and homeostatic model assessment of insulin resistance levels was increased in healthy volunteers with total or REM sleep deprivation. Although spermiograms did not present any alterations, a reduction in total testosterone after total sleep deprivation was observed. Thus, OSA and sleep deprivation may be important factors that should be taken into consideration in the assessment of adults with impaired reproductive functions.

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EFFECT OF CONTINUOUS POSITIVE AIRWAY PRESSURE ON OVERACTIVE BLADDER IN WOMEN

Ertas et al[3] (NCT05250245) have examined the impact of CPAP therapy in 60 female OSA patients with overactive bladder (OAB) with and without tolterodine treatment for 3 months. Despite significant favorable improvements in both arms, a more pronounced improvement was observed in the combined treatment group in regard to mean incontinence questionnaire-urinary incontinence short form scores and mean OAB awareness-8-item tool scores compared to the CPAP-only group.

COGNITIVE BEHAVIORAL THERAPY AND CONTINUOUS POSITIVE AIRWAY PRESSURE FOR COMORBID INSOMNIA AND SLEEP APNEA

Tu et al[4] (NCT01785303) have investigated the effect of cognitive behavioral therapy for insomnia (CBT-I) and CPAP for comorbid insomnia and sleep apnea (COMISA) on sleep as well as daytime functioning. In the study examining 118 patients with COMISA, one group of patients received CBT-I followed by CPAP, and another group was allocated to self-monitoring followed by CBT-I in addition to CPAP, another group was randomized to self-monitoring followed by CPAP alone. Cognitive behavioral therapy for insomnia was better than CPAP and self-monitoring regarding the reduction in diary-measured sleep onset latency and wake after sleep onset and improving sleep efficiency, in addition to refining the scores of the Functional Outcome of Sleep Questionnaire and Flinders Fatigue Scale compared to results with self-monitoring. Thus, CBT-I concurrent with CPAP seems to be an efficient treatment modality for patients with COMISA.

AUTO-CONTINUOUS POSITIVE AIRWAY PRESSURE TREATMENT IN PREGNANCY

Kalkhoff et al[5] conducted a randomized control trial (RCT) (NCT02755831) of a targeted auto-CPAP for pregnant women at risk of OSA. Patients were randomized to a sleep study screening group receiving auto-CPAP (n = 100) or a control group (n = 93) followed with standard care. In addition to 2 sleep studies performed during pregnancy in the first group, all participants underwent a sleep study 3 months after the delivery. Auto-CPAP treatment was initiated in appropriate patients (n = 6) in the first group with AHI ≥5 events per hour detected in the sleep tests during pregnancy (n = 24). The study has revealed similar outcomes in both groups regarding adverse pregnancy outcomes (46% of the screened group vs. 43% of the control group; $P = .77$) including hypertension, preterm birth, stillbirth, low birth weight, diabetes mellitus, as well as average hospital expenses. The secondary outcomes were the severity of OSA and hospital expenses. The AHI has increased during the pregnancy and reached the highest levels at 3 months following delivery ($P < .001$). Positive airway pressure compliance was poor (2%-43%). Even if no meaningful differences are detected between the groups regarding the outcomes of the study, probably due to the small sample size and low power, this special patient population with increasing occurrence and AHI throughout the pregnancy and postpartum period requires special consideration.

Continuous Positive Airway Pressure and Cardiovascular Outcomes

Recent RCTs, the Randomized Intervention with CPAP in coronary artery disease and obstructive sleep apnea (RICCADSA) trial (NCT 00519597),[6] the Sleep Apnea Cardiovascular Endpoints (SAVE) study (NCT 00738179),[7] and the Impact of Sleep Apnea Syndrome in the Evolution of Acute Coronary Syndrome (ISAACC) study (NCT 01335087),[8] failed to show any reduction in major cardiovascular and cerebrovascular events (MACCEs) in intention-to-treat analyses. Several arguments have been suggested for the neutral results, comprising low adherence to CPAP therapy in those studies and those individuals with excessive daytime sleepiness were not included.[9] Other explanations of these null findings have also been attributed to the failure to consider OSA as a heterogeneous disorder that consists of multiple phenotypes.[10] In one of the post hoc investigations of the RICCADSA trial, Azarbarzin and colleagues reported that patients with higher elevated heart rate response (ΔHR) to respiratory events show greater cardiovascular benefits from CPAP treatment (NCT 00519597 for the main RCT).[11] The CPAP-related reduction in risk increased progressively with increasing pretreatment ΔHR. In another secondary investigation of the RICCADSA study, Eulenburg and colleagues compared the cardiovascular outcomes in sleepy vs. nonsleepy coronary artery disease (CAD) patients with OSA (NCT 00519597).[12] The researchers reported that adverse cardiovascular outcomes did not differ by the severity of excessive daytime sleepiness (EDS) for patients with CAD and OSA who were untreated or nonadherent to treatment. However, CPAP use for at least 4 hours per night was associated with less adverse outcomes in patients without EDS.[12]

Obstructive sleep apnea is associated with atrial fibrillation (AF). Catheter ablation with pulmonary vein isolation (PVI) has been used more and more to reduce symptoms of AF as well as the need for antiarrhythmic medication. In a recent RCT, Hunt and colleagues evaluated the impact of CPAP on the recurrence and burden of AF after PVI in adults with OSA (NCT 02727192).[13] A home sleep apnea test (HSAT) was conducted in all participants. Patients with paroxysmal AF and OSA were randomized to CPAP (n = 37) or no-CPAP (n = 46). There was no meaningful reduction in the risk of AF recurrence after PVI; the rate of AF recurrence was 57% in both groups.[13]

Postoperative atrial fibrillation (POAF) occurs in up to 50% of patients with CAD after coronary artery bypass grafting (CABG). In another post hoc investigation of the RICCADSA trial, 147 patients with CABG at baseline who underwent HSAT in 73 days after the surgical treatment were included (NCT 2000519597).[14] POAF was observed among 33% of the cases, and there was a significant risk increase for POAF across the AHI categories with the highest odds ratio (OR) for severe OSA (OR 6.8, 95% CI, 1.3-35.5; $P = .023$) compared to no-OSA, independent of age, sex, and body mass index (BMI). On the other hand, all patients with the POAF history at baseline were free from reoccurrence of AF at the long-term follow-up.

In another RCT by Lao and colleagues, the interaction among OSA, CPAP, and cardiovascular (CV) and cerebrovascular

(CeV) medications and the impact of medications on MACCEs as well as on survival in patients with comorbid OSA and CV/CeV were examined (NCT 00738179).[15] In this post hoc analysis of the SAVE trial, 131 patients were analyzed (63 in the CPAP arm vs. 68 in the no-CPAP arm), and 65% of the patients on CPAP had good adherence. During a median follow-up of 43.0 months, the independent factors for declining survival in patients with comorbid OSA and CV/CeV were angiotensin converting enzyme (ACE) inhibitors and nitrates. ACE inhibitors predicted increased death and secondary endpoints among patients allocated to CPAP but not in those with good CPAP compliance.[15]

Another RCT in adults with OSA and CVD was conducted by Zhao et al[16] (NCT 01261390). In all, 169 participants without severe sleepiness were randomized to CPAP or no-CPAP, addressing the impact of therapy on 24-hour systolic blood pressure (SBP) over 6-12 months. The 24-hour SBP was similar between the groups, whereas a significant effect was observed on the nighttime SBP (treatment effect −5.9 mm Hg [95% CI, −9.9 to −1.9]; *P* = .004).[16]

A recent post hoc analysis of the RICCADSA trial (NCT 2000519597)[17] study addressed the relationship between TNF-α polymorphism and TNF-α levels at 12 months among 239 CAD patients with OSA and showed that there was a significant change in circulating TNF-α levels from baseline across the genotypes from GA to GA and GA to AA, and that the relationship was more pronounced among the patients who were using the device for ≥4 hours per night. The patients carrying the TNF-α A allele responded less to CPAP therapy regarding the decline in circulating TNF-α levels despite good CPAP adherence. These findings may partly explain the cardiovascular heterogeneity in adults with OSA.

Continuous Positive Airway Pressure and Metabolic Outcomes

Dyslipidemia is a recognized risk issue for CAD. Obstructive sleep apnea and dyslipidemia are independently related to increased mortality, cardiovascular disease, and stroke. In another secondary investigation of the RICCADSA trial, Celik and colleagues included 196 patients with CAD and nonsleepy OSA (NCT 2000519597).[18] The participants were randomized to CPAP or no-CPAP, and they were all on lipid-lowering medication. CPAP did not have an additional lipid-lowering effect in the cohort.[18]

Similarly, Giampá et al[19] studied the impact of CPAP on metabolic syndrome in adults with OSA (NCT 02295202). They found that most patients using CPAP retained metabolic syndrome diagnosis after 6 months, although 18% of the patients allocated to CPAP were reversed compared to 4% in the group who were randomized to nasal dilator strips (placebo) (OR, 5.27; 95% CI, 1.27-35.86; *P* = .04).[19]

CONTINUOUS POSITIVE AIRWAY PRESSURE VS. BILEVEL POSITIVE AIRWAY PRESSURE TREATMENT IN OBESITY HYPOVENTILATION SYNDROME

Obesity, being an important risk factor in sleep-related disorders, also has an important role in PAP treatment choices. In a pilot RCT by Zheng et al[20] (ACTRN12605000096651) the effect of CPAP vs. bilevel PAP (BPAP) spontaneous mode on hypoventilation in adults with obesity and obstructive airway disease has been examined. Among 32 participants receiving treatment for 3 months, a greater improvement in $PaCO_2$ has been detected in the BPAP group compared to CPAP group (intergroup difference 9.4 mm Hg, 95% CI, 4.3-15 mm Hg). Patients in the BPAP group had greater changes in lung function and quality of life in comparison to patients who received CPAP.

Drug Therapy

To date, there is no effective pharmacological treatment for OSA. Recent advances regarding the pathophysiological features that lead to OSA point to the collapsibility of the upper airways, pharyngeal dilator muscle dysfunction, and ventilation instability. Specifically, sleep-related hypotonia of the pharyngeal muscles is thought to be due to impairment of noradrenergic activity in non-REM (NREM) sleep[21] and to muscarinic activity dysfunction in REM sleep.[22] Preliminary studies have shown a meaningful decrease in AHI using norepinephrine reuptake inhibitors (atomoxetine and reboxetine) in combination with antimuscarinics (oxybutynin or hyoscine butyl bromide).[23,24]

In a recent phase 2 RCT, Schweitzer et al[25] compared AD036 (fixed-dose combination of atomoxetine 80 mg and oxybutynin 5 mg), atomoxetine 80 mg alone, and placebo during 3 HSAT studies in OSA patients (NCT04445688). They found that AD036 significantly improved the OSA severity (AHI was reduced by 54% in median value) compared to the placebo. The time spent with SpO_2 < 90% as well as hypoxic burden was also significantly reduced in the AD036 group.

The efficacy of 4 mg reboxetine in addition to 5 mg oxybutynin (Reb-Oxy), another combination of antimuscarinic and noradrenergic drugs, was evaluated in adults with OSA by Perger et al[26] (NCT04449133). Reb-Oxy reduced AHI, hypoxic burden as well as oxygen desaturation index (ODI) compared with the values at baseline. Reboxetine–oxybutynin improved even muscle compensation and decreased the arousal threshold. Several surrogates of milder collapsibility were found to be related with greater responses to Reb-Oxy. The authors concluded that these findings confirm the idea that pharmacologic treatment for OSA may be most effective in adults with less severe pharyngeal compromise.[26]

In an RCT by Messineo et al[27], the effects of a histamin-3 -autoreceptor antagonist, betahistine (Beta), combined with an antimuscarinic, oxybutynin (Oxy), on OSA severity, OSA endotypes, and polysomnographic parameters were addressed. In a crossover, randomized, double-blind design, they included 13 adults with OSA who received the combination Beta-Oxy (96-5 mg) or placebo. Beta-oxybutynin increased the loop gain (respiratory control sensitivity) without any significant changes in OSA severity in terms of AHI, sleep efficiency, arousal index, or markers of hypoxemia.

In a recent RCT,[28] 68 adults with OSA who did not accept or tolerate PAP therapy allocated to placebo, sulthiame (STM) 200 mg or STM 400 mg for 4 weeks to explore safety and

tolerability of STM (registered at www.clinicaltrialsregister.eu). Sulthiame showed an acceptable safety profile, with significant improvement regarding OSA severity. More than 50% reduction in AHI was achieved in 40% of patients who were allocated 400 mg of STM, 25% of patients receiving 200 mg, and 5% of patients receiving placebo. Intermittent paresthesia was a commonly reported adverse event (79%, 67%, and 18% of participants receiving 400 mg STM, 200 mg STM, and placebo, respectively.

Liraglutide is a glucagon-like peptide-1 receptor agonist (GLP-1RA), which is used as a glucose-lowering drug for patients with type 2 diabetes mellitus (T2DM) as well as for weight loss in obese patients. In a recent RCT, Jiang et al[29] addressed the impact and safety of liraglutide concerning OSA metrics, weight control, cardiac function, and glycolipid metabolism in adults with T2DM and severe OSA. In all, 90 participants with OSA who were on CPAP treatment were randomly allocated liraglutide or placebo for 3 months. BMI, AHI, and average systolic blood pressure decreased in the liraglutide group compared to baseline, whereas no significant changes were observed in the placebo group. Improvements in the OSA metrics were attributed to weight loss in the liraglutide group, reducing the upper airway adipose tissue compression or preventing the upper airway muscle collapse.

Persistent excessive daytime sleepiness (EDS) is reported by up to 41% of patients treated with PAP.[30] Solriamfetol is a dopamine and norepinephrine reuptake inhibitor that is used for the treatment of EDS in adults with OSA or narcolepsy. In previous studies, the TONES (Treatment of OSA and Narcolepsy Excessive Sleepiness) RCTs were conducted to address the efficacy and safety of solriamfetol for the treatment of impaired wakefulness in patients with narcolepsy type 1 or type 2 (TONES 2, NCT02348593),[31] OSA, and EDS (TONES 3, NCT02348606).[32] In a post hoc analysis of the TONES 2 and 3 studies, the researchers compared the impact of solriamfetol treatment on EDS in participants who had depression vs. no depression.[33] The occurrence of a depression history was 28.1% (in those with narcolepsy) and 23.5% (in those with OSA), respectively. The results suggested that solriamfetol was effective in treating EDS regardless of the occurrence of depression.

In other post hoc analyses, changes in weight were addressed at baseline and at end of study in participants with OSA or narcolepsy.[34] After up to 1 year of solriamfetol treatment, one-fourth of the participants achieved a weight loss of ≥5% relative to baseline, and there was a dose-response relationship (4.5% of participants receiving 75 mg achieved the targeted weight loss, and the corresponding values were 17.3% among the patients receiving 150 mg and 32.4% in the group receiving 300 mg solriamfetol).

Rosenberg et al[35] addressed the incidence and overall duration of common early-onset, treatment-emergent adverse events (TEAEs) weekly during solriamfetol treatment in the same cohort. They found that common early-onset TEAEs during week 1 were similar during the follow-up period, and they included headache, nausea, and decreased appetite (occurring from 2.5% to 8.5%).

Surgical Treatment of Obstructive Sleep Apnea

Postoperative hypoxemia commonly occurs after general anesthesia in obese individuals. Rosén et al[36] addressed whether early application of high-flow nasal oxygen (HFNO) would improve postoperative oxygenation compared with standard oxygen therapy following general anesthesia for laparoscopic bariatric surgery in obese adults. The results were neutral. Thus, HFNO treatment does not provide additional benefit compared to nasal oxygen in obese patients.

There are some challenges associated with the use of CPAP therapy in the postoperative period of untreated OSA patients. Sakaguchi et al[37] addressed whether the combination of high-flow nasal cannula and upper-body elevation would improve postoperative OSA management. High-flow nasal cannula was randomly applied with or without 30° head-of-bed elevation on the first and second postoperative nights to 23 patients with OSA. They concluded that the combination of high-flow nasal cannula and upper-body elevation was beneficial in reducing the AHI and nocturnal hypoxemia.

Uvulopalatopharyngoplasty (UPPP) has been one of the most common surgical treatment modalities for OSA. Tonsillectomy (TE) alone is a less extensive alternative. Sundman et al[38] investigated whether modified UPPP (mUPPP) is better than TE alone in treating adult patients with tonsillar hypertrophy and OSA. In all, 45 patients underwent mUPPP and 45 TE alone. After 6 months, the results did not differ significantly; mean AHI decreased by 43% in the mUPPP group and 56% in the TE group. Thus, mUPPP was not more effective than TE alone in patients with tonsillar hypertrophy and concomitant OSA (Table 1).[2-5,11,12,14-20,25-29,33-49]

Oral Appliance Therapy

In many past studies, oral appliances (OA) are effective, especially in mild to moderate OSA patients, and have better treatment adherence than PAP treatment. In recent years, importance has been given to the development of OA. Fransson and colleagues treated OSA patients with an OA aimed to determine the effect of sleeping positions.[39] In their study, 314 patients with OSA were included for addressing the effect of OA on positional OSA (POSA). The response to the treatment was defined as AHI below 10 and/or an at least 50% reduction in total AHI. The ratios were 56% for the non-POSA group and 69% for the POSA group, respectively (not significant).

Obstructive Sleep Apnea Management

Lajoie et al[40] (NCT03455920) investigated the noninferiority of diagnosis and management of uncomplicated sleep apnea by a clinical nurse in an RCT including 200 patients. The difference in mean change in ESS between groups 3 and 6 months were −0.71 and −0.21, respectively, indicating a noninferiority of the nurse-communicated management in 6 months. The noninferiority of the nurse-communicated management has also been reported in regard to Quebec Sleep Questionnaire results as well as PAP adherence. Thus, the assessment of uncomplicated OSA patients by a trained clinical nurse can be evaluated in sleep centers with busy schedules.

Along with increasing public awareness as well as technological developments, sleep health education and use of

Table 1. Clinical Trials in Sleep-Related Breathing Disorders Published Through January 2022 to August 2023

Authors	Year	Journal	Participants	Clinical Registration Number
Alvarenga et al[2]	2023	*Front Neurol.*	46	NCT01884454
Ertaş et al[3]	2022	*Int Urogynecol J*	60	NCT05250245
Tu et al[4]	2022	*J Clin Sleep Med.*	118	NCT01785303
Kalkhoff et al[5]	2022	*Am J Obstet Gynecol MFM.*	193	NCT02755831
Azarbarzin et al[11]	2022	*Am J Respir Crit Care Med*	226	NCT00519597
Eulenburg et al[12]	2023	*Ann Am Thorac Soc*	399	NCT00519597
Peker et al[14]	2022	*J Clin Med.*	147	NCT00519597
Lao et al[15]	2022	*BMC Pulm Med*	131	NCT00738179
Zhao et al[16]	2022	*J Clin Sleep Med*	169	NCT01261390
Celik et al[17]	2023	*J Clin Med.*	239	NCT00519597
Celik et al[18]	2022	*J Clin Med*	196	NCT00519597
Giampá et al[19]	2022	*Chest*	100	NCT02295202
Zheng et al[20]	2022	*J Clin Sleep Med*	32	ACTRN12605000096651
Schweitzer et al[25]	2023	*Sleep Breath.*	62	NCT04445688
Perger et al[26]	2022	*Chest*	16	NCT04449133
Messineo et al[27]	2022	*Nat Sci Sleep.*	13	ACTRN12621000158864
Hedner et al[28]	2022	*Am J Respir Crit Care Med.*	68	EU Clinical Trials Register 2017-004767-13
Jiang et al[29]	2022	*Sleep Breath.*	90	Shenzhen Yantian District 20180329
Krystal et al[33]	2022	*J Psychiatr Res*	710	NCT02348593, NCT02348606
Malhotra et al[34]	2022	*Sleep Med.*	1229	NCT02348632
Rosenberg et al[35]	2022	*J Clin Sleep Med*	710	NCT02348593, NCT02348606
Rosén et al[36]	2022	*Health Sci Rep.*	34	ISRCTN37375068
Sakaguchi et al[37]	2022	*Anesthesiology*	23	UMIN000037265
Sundman et al[38]	2022	*JAMA Otolaryngol Head Neck Surg.*	93	NCT02523248
Fransson et al[39]	2022	*Am J Orthod Dentofacial Orthop*	205	NCT02148510
Lajoie et al[40]	2022	*J Clin Sleep Med*	200	NCT03455920
Robbins et al[41]	2022	*BMJ Open*	1355	NCT04224285
Murphy et al[42]	2023	*Thorax*	82	NCT02342899, ISRCTN51420481
Horne et al[44]	2022	*J Clin Sleep Med*	100	missing
Boulos et al[45]	2022	*Stroke*	250	NCT02454023
Fridriksson et al[46]	2023	*Ann Am Thorac Soc.*	409	NCT03446560
Murase et al[47]	2022	*Chest*	168	UMIN000033607
Kazemeini et al[48]	2022	*Sleep Breath.*	10	NCT03716648
Wang et al[49]	2022	*Front Neurol.*	24	NCT03523013

sleep-related applications for smartphones remain important factors for investigators. In an open-label, randomized, parallel-group controlled trial by Robbins et al[41] (NCT04224285), the effect of a sleep health education combined with a personalized smartphone application on sleep, productivity, and health-care utilization has been examined among employees at a large health-care organization. An online Sleep Health and Wellness (SHAW) program was paired with a personalized sleep training program deployed via a smartphone application (Dayzz app). Having received 9 months of SHAW educational program and access to Dayzz app, the intervention group (n = 794) reported an increased sleep duration (in average, 21 minutes on work nights and 22 minutes on work-free nights) compared to the control group (n = 561) having received the intervention at month 10.

Telemonitoring

Home-based sleep studies are widely used in most sleep laboratories across the world for appropriate patient populations. Telemedicine facilitates the close follow-up of patients prescribed PAP therapies. These approaches also aim to prevent excessive health-care costs and work overload in sleep laboratories. Additionally, current guidelines have recommendations regarding the initiation of home NIV in subjects with clinically stable OHS in outpatient settings. Other investigators (NCT02342899)[42] have conducted a multicenter

open-labelled clinical trial to examine the cost-effectiveness of titration of 82 OHS patients in inpatient vs. outpatient settings in 3 months. Safety and efficacy analysis have demonstrated similar differences in inpatient and outpatient cases regarding $PaCO_2$ levels and equivalent per-patient costs (£2962 ± £580 vs. £3169 ± £525) with comparable clinical improvements, including health-related quality of life. The authors suggested that home NIV can be considered for managing stable OHS patients, depending on the preferences of the patient and the physician.

In-Person vs. Video Hookup Instructions: A Comparison of Home Sleep Apnea Testing Quality

Home sleep apnea tests (HSATs) (types 2-4 sleep studies) have been an alternative way of OSA,[43] in a possibly more comfortable, more accessible, and quicker manner compared to standard in-lab testing. Although there have been studies about improving different telemonitoring aspects of HSATs, there is yet not enough evidence to make the hookup procedure more telemedicine compatible. In a double-blind study by Horne et al,[44] 100 patients (of 127 screened patients) with supposed OSA were randomly assigned to receive either in-person or video hookup instructions for the Nox T3 device (Nox Medical, Reykjavik, Iceland) to compare the quality of the sleep study. The instructional video in the intervention arm explained the contents of the HSAT kit, attachment, and recording procedures using animations. The overall and sensor [any of the 4 sensors (pulse oximeter, nasal cannula, thorax, and abdomen respiratory inductance plethysmography belts)] signal quality of HSAT recordings were similar (on average of high quality for both groups, with over 90% of the recording durations being artifact-free (mean quality >90%) in the group randomized to in-person and video hookup instructions. The authors listed insecurity of the patients for the procedure by using video instructions, language barriers, and technological limitations (i.e., unavailable internet access) as possible barriers to be managed based on the reasons for refusal to participate in the study. In eligible patients, providing video recordings of hookup instructions for HSATs is a viable alternative to providing them in-person, allowing patients in remote and rural areas more effortless access to sleep studies and saving health-care personnel time.

SLEAP SMART (Sleep Apnea Screening Using Mobile Ambulatory Recorders after TIA/Stroke)

In an RCT by Boulos et al[45] (NCT02454023), 250 consecutively recruited patients with a history of stroke or TIA were randomized to ambulatory (performed in their hospital bed or at home) or in-laboratory sleep testing, and the rates of OSA diagnosis were 49% vs. 35% (P = .04), respectively. The functional outcomes, daytime sleepiness assessed at 6 months, were significantly improved in the prior arm compared to later in a cost-effective manner. Thus, screening for OSA with HSATs should be strongly considered to improve nonvascular outcomes for patients with stroke.

Effects of Early Intervention Telemedicine-Based Follow-Up in Sleep Apnea

Cloud-based telemonitoring of PAP therapy as a method of transmission of therapeutic data has been investigated lately for its effect on improving adherence rates. In a multicenter, randomized controlled superior trial by Fridriksson et al[46] (VGFOUREG663941) evaluated clinical utility and patient satisfaction of PAP follow-up with an early intervention telemedical protocol in 9 adults with OSA. Patients were allocated to either standard PAP follow-up or early intervention telemedical follow-up (with close telemonitorization regarding compliance, treatment efficiency, and mask leakage, and management of patients with related problems by teleconsultation or outpatient visit (if required) for the first month) for 3 months. Adherence to PAP treatment was higher in the intervention group, but the difference was comparatively small. The intervention group experienced less problematic mask leakage, but the proportion of switching mask types was still similar.

Multimodal Telemonitoring for Weight Reduction in Patients with Sleep Apnea

Murase et al[47] conducted a multicenter RCT including 168 obese (average BMI of 31.7 ± 4.9 kg/m^2) patients with OSA using CPAP (>1 month) (UMIN000033607). In the usual PAP telemonitorization group, PAP data was followed remotely, and monthly feedback calls were provided to increase PAP adherence. In the intervention group, on top of PAP telemonitoring, electronic scales, blood pressure monitors, and pedometers were implemented to transmit data from devices wirelessly for 6 months. Monthly feedback calls were provided by attending physicians to encourage patients to PAP adherence and body weight reduction. Multimodal telemonitoring was found to enhance weight loss more effectively compared to usual PAP telemonitoring, independent of the body weight at baseline.

Drug-Induced Sleep Endoscopy

The rapid developments in technological innovations have a great influence on the management of sleep disorders. The DISE has been an important topic for researchers and has been compared and combined with other modalities. In a pilot cross-over study by Kazemeini et al[48] (NCT03716648) compared the clinical effectiveness of subjective titration vs. objectively guided titration during polysomnography and drug-induced sleep endoscopy in mandibular advancement device (MAD) treatment for patients with OSA. In the study, which included 10 OSA patients and performed 3 different titration methods, targeted optimal protrusion and maximal comfortable protrusion were similar in both groups. Similar and nonsignificant differences have been reported in the reduction in AHI as well. Notwithstanding, a higher predictive accuracy has been observed (83.3% sensitivity and 100% specificity) in the DISE group.

The comparison of DISE-guided CPAP titration and conventional sleep center CPAP titration was also examined by Wang et al[49] in a randomized controlled crossover trial including 24 patients with moderate-to-severe OSA patients (NCT03523013). At the end of 2 months, the patients received both treatments. Similar outcomes regarding the upper limit of the pressure levels and equivalent residual AHI, as well as compliance, have been reported in both groups following 4 weeks of CPAP treatment. A significant association between epiglottis and tongue base collapse and 95% CPAP pressure has been reported. Multivariate regression analyses have

defined the epiglottis as an independent determining variable for 95% CPAP level. Although a high incidence rate of bradycardia (58%) was observed in the DISE group, all patients recovered following treatment. Thus, DISE-guided CPAP titration can be an option for uncomplicated OSA patients.

CONCLUSIONS

Important progress in the field of SRBD has occurred since January 2022. They cover important insights into the heterogeneity of cardiometabolic disorders among adults, OSA management, drug therapy for OSA, PAP therapy and cardiovascular outcomes, PAP in pregnancy, as well as the effects of surgical treatment and oral appliances. We also underline future directions in OSA management, telemonitoring, and DISE in the management of the SRBDs, especially OSA. We ascertain concurrently that more studies are needed in the fields of CSA, OHS, and ISRH.

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Erratum

In the original article authored by Ceyhan et al, titled "An Analysis of Coronavirus Disease 2019 Infection-Related Characteristics of Chronic Obstructive Pulmonary Disease Patients with and without Inhaler Training: A Case–Control Study" (Thorac Res Pract. 2023;24(4):186-193. DOI: 10.5152/ThoracResPract.2023.22114) published in the July 2023 issue of Thoracic Research and Practice, the declaration regarding the funding of the article was written incorrectly by an oversight. Subsequently, the correct funding declaration added and the online version of the original article has been updated accordingly. You can access the revised version of this original article via the following link: https://thoracrespract.org/en/an-analysis-of-coronavirus-disease-2019-infection-related-characteristics-of-chronic-obstructive-pulmonary-disease-patients-with-and-without-inhaler-training-a-case-control-study-132236

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