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ORIGINAL RESEARCH

Can the ADO Index Be Used as a Predictor of Mortality from COVID-19 in Patients with COPD?

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Background: Several studies have shown that the risk of mortality due to COVID-19 is high in patients with COPD. However, evidence on factors predicting mortality is limited.

Research Question: Are there any useful markers to predict mortality in COVID-19 patients with COPD?.

Study Design and Methods: A total of 689 patients were included in this study from the COPET study, a national multicenter observational study investigating COPD phenotypes consisting of patients who were followed up with a spirometry-confirmed COPD diagnosis. Patients were also retrospectively examined in terms of COVID-19 and their outcomes.

Results: Among the study patients, 105 were diagnosed with PCR-positive COVID-19, and 19 of them died. Body mass index ($p= 0.01$) and ADO (age, dyspnoea, airflow obstruction) index ($p= 0.01$) were higher, whereas predicted FEV_1 ($p< 0.001$) and eosinophil count ($p= 0.003$) were lower in patients who died of COVID-19. Each 0.755 unit increase in the ADO index increased the risk of death by 2.12 times, and each 0.007 unit increase in the eosinophil count decreased the risk of death by 1.007 times. The optimum cut-off ADO score of 3.5 was diagnostic with 94% sensitivity and 40% specificity in predicting mortality.

Interpretation: Our study suggested that the ADO index recorded in the stable period in patients with COPD makes a modest contribution to the prediction of mortality due to COVID-19. Further studies are needed to validate the use of the ADO index in estimating mortality in both COVID-19 and other viral respiratory infections in patients with COPD.

Keywords: body mass index, COVID-19, eosinophils, FEV_1, mortality, pneumonia, pulmonary disease, chronic obstructive

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that caused the coronavirus disease 2019 (COVID-19) pandemic has immensely affected the world since the beginning of 2020.[1] During the pandemic, identifying who is more prone to COVID-19, who will have a more severe infection or who will be more likely to die is of great interest. Many studies have shown that patients with chronic obstructive pulmonary disease (COPD) are more vulnerable to respiratory viral infections and have a more severe infection than the healthy population.[2,3] However, initial data showed that the COVID-19 rates in patients with COPD are not as high as expected.[4–6]

In terms of infection severity, COPD has been associated with severe COVID-19 and increased mortality risk in several studies and meta-analyses as predicted.[7–9] Several studies have shown that the mortality risk due to COVID-19 is higher in COPD compared to both the healthy population and various chronic diseases.[7,10]

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However, clinical and functional features associated with increased mortality risk among patients with COPD have been addressed in a few studies, and these studies have several limitations such as poor methodological design, data based on hospital records, insufficient evaluation of confounding factors, lack of data on pulmonary function tests, exacerbation history, and drug usage.[11–13]

In this study, we included the COPET cohort of patients with COPD whose demographic and clinical characteristics were recorded face-to-face and in detail during their stable period.[14] We aimed to investigate the COVID-19 transmission status of the COPET cohort and their clinical, functional, prognostic and phenotypic features that may be associated with infection-related mortality during the pre-vaccination period.

Materials and Methods

The COPET Study was published as a national multicenter study investigating COPD phenotypes, conducted between December 2018 and January 2020, including 12 centres in Turkey.[14] A total of 1141 stable patients included in the COPET cohort were diagnosed with COPD by spirometry for at least one year. Demographic and disease characteristics (symptom scores; exacerbation history; radiological features; pulmonary function tests; ADO (age, dyspnoea, airflow obstruction) index; phenotypic features; and drug usage) were recorded as cross-sectionally. In the COPET Study, we calculated the ADO index which combines age, the mMRC score and the FEV_1 in each patient. The total score of the ADO index ranges from zero to 10 points, and a higher score indicates worse prognosis in patients with COPD.[15] Ten centres from the COPET study agreed to participate in this study. The ethical committee approval was obtained from the Health Sciences University, Yedikule Chest Diseases, and Thoracic Surgery Training and Research Hospital (ethics committee date and protocol number: 29.07.2021; 2021–137). A written informed consent which included a review of their medical records was obtained from each patient and the study was conducted in accordance with the Helsinki Declaration. Patients included in this study were retrospectively screened during the pre-vaccination period; thus, the effect of the vaccine as a confounding factor was eliminated. Patients from non-participating centers within the COPET study, those who have lost follow-up, those who died prior to the pandemic, and those with probable COVID-19 but negative polymerase chain reaction (PCR) results were excluded from the study.

Patients with COVID-19 with PCR positive (group 1) and who did not have COVID-19 (group 2) were included in the study. The study flowchart is displayed in Figure 1. The COVID-19 status, infection severity, and outcomes of patients were

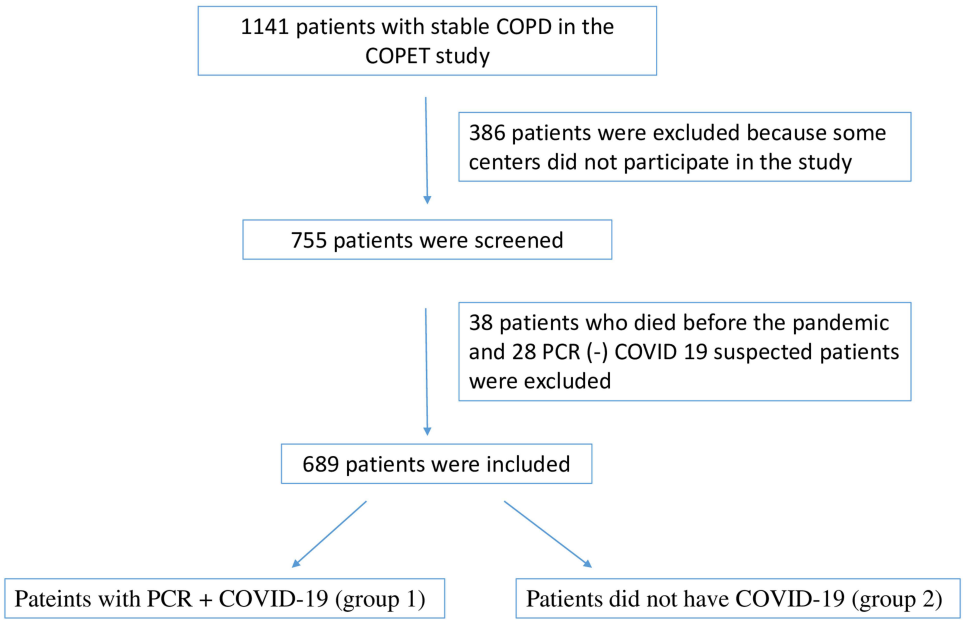

Figure 1 The study flowchart.

obtained from the hospital's electronic database. Telephone visits were performed as necessary. Radiological imaging during the infection was retrospectively re-evaluated, and all data were added to the data file of the COPET study.

Statistical Analysis

The SPSS 22 programme was used for data analysis. Normally distributed data were expressed in means and standard deviations, whereas non-normally distributed data were expressed as medians and interquartile ranges. The Shapiro–Wilk test was used as the normality test. For normally distributed data, *t*-tests were used, whereas, for non-normally distributed data, Mann–Whitney *U*-tests were used. The Chi-square test was used for categorical data analysis. In addition, binary logistic regression analysis and receiver operating characteristics (ROC) analysis were used in multivariate analyses. A *p*-value of <0.05 was considered statistically significant.

Results

The study cohort included 689 patients with COPD with a mean age of 66.3 (range, 40–90) years. Among them, 105 patients were diagnosed with PCR-positive COVID-19 (group 1), whereas 584 patients did not have COVID-19 (group 2). Group 1 had significantly lower forced vital capacity (FVC) values than group 2. No difference was found between the two groups in other characteristics. The comparison of group 1 and group 2 in terms of demographic and clinical characteristics is given in Table 1.

Table 1 The Comparison of Group 1 and Group 2 in Terms of Demographic and Clinical Characteristics

Variables	Group 1 n=105	Group 2 n=584	p value
Male/Female,n (%)	92(87.6)/13(12.4)	505(86.5)/79(13.5)	0.87
	Mean ± SD	Mean ± SD	
Age (years)	64.9 ± 10.2	66.4±8.8	0.11
BMI	26.5 ± 5.2	25.6±4.7	0.08
	Median (IQR)	Median (IQR)	
Smoking (package-year)	40 (22.5)	40 (25)	0.30
Biomass exposure (year)	40 (40)	35 (37)	0.42
COPD duration (year)	5.0 (7)	5.0 (5)	0.27
FEV_1% predicted	49 (40.5)	51 (30.1)	0.18
FVC % predicted	64 (42,8)	70 (24,0)	0.03
FEV_1/FVC	59.0 (16,8)	58.0 (17,3)	0.86
CAT score	14 (20,3)	14 (13,3)	0.21
mMRC score	2 (2)	2 (1)	0.12
The number of exacerbations in previous year	1.0 (3)	1.0 (2)	0.13
BEC (10^3/uL)	0.14 (0,23)	0.18 (0,19)	0.21
Percentage of BEC	2,1 (2,4)	2.1 (2,5)	0.52
ADO index	4.0 (3,8)	4.0 (2)	0.56

Note: Patients with PCR + COVID-19 (group 1); patients did not have COVID-19 (group 2).
Abbreviations: SD, Standard deviation; IQR, Interquartile range; BMI, Body mass index; COPD, Chronic obstructive pulmonary disease; FEV_1, Forced expiratory volume in 1 second; FVC, Forced vital capacity; CAT, COPD assessment test; mMRC, modified medical research council; BEC, blood eosinophil count; ADO index, age, dyspnoea, airflow obstruction.

The body mass index (BMI) (p=0.01) and ADO index (p=0.01) were statistically higher in contrast forced expiratory volume in 1 s (FEV_1) % predicted (p<0.0001), FEV_1/FVC ratio (p=0.046), blood eosinophil count (BEC) (p=0.003), and percentage (p=0.018) were statistically lower in the group of patients who COVID-19 nonsurvivors compared to those who COVID-19 survivors. The comparison of COVID-19 survivors and nonsurvivors in terms of demographic and clinical characteristics is shown in Table 2. Pneumonia rates, hospitalisation rates, intensive care unit (ICU) admission, and intubation rates were significantly higher in patients who died from COVID-19 (p < 0.001). No difference between mortality rates was observed among COPD phenotypes (p = 0.88) or Global Initiative for Chronic Obstructive Lung Disease (GOLD) spirometry staging (p = 0.36). Inhaled corticosteroid (ICS) use rate in patients who died from COVID-19 (78.9%) was similar to that in survivors (76.7%).

The binary logistic regression analysis for predicting mortality in patients with COPD and COVID-19 was found to be important (omnibus test p = 0.004). The independent variables of the model were $FEV_{1\%}$ predicted, FEV_1/FVC, CAT score, mMRC score, ADO index, BEC, and smoking pack-years, whereas the dependent variable of the model was death. Independent variables in the model explain 30.8% of the change in the dependent variable. The accuracy rate of the model was 83.2%. The ADO index and BEC significantly contributed to the model, each 0.755 unit increase in the ADO index increased the risk of death by 2.12 times, and each 0.007 unit increase in the BEC decreased the risk of death by 1.007 times. The estimation of mortality in patients with COPD and COVID-19 was given in Table 3.

Table 2 The Comparison of COVID-19 Survivors and Nonsurvivors in Terms of Demographic and Clinical Characteristics

Variables	Survivors n=86	Nonsurvivors n= 19	p value
Male/Female n, (%)	76(88.4)/10(11.6)	16(84.2) / 3(15.8)	0.700
	Mean ± SD	Mean ± SD	
Age (years)	66.9 ± 9.1	63.6±11	0.137
BMI (kg/m2)	26.4±4.8	26.8±6.4	0.010
FEV_1% predicted	51.9±20.1	34.8±18	<0.001
FVC % predicted	66 ±29	59 ± 28	0.122
FEV_1/FVC	54.7±9.1	49.3±10.9	0.046
ADO index	4.4±2.1	5.6±1.8	0.010
	Median (IQR)	Median (IQR)	
Smoking (package-year)	40 (22.5)	45 (27,5)	0.629
Biomass exposure (year)	36.7±19.3	50.2±21.7	0.126
COPD duration (year)	5 (7)	5 (10)	0.536
FEV_1 (liter)	1.4 (1)	1.1 (0.9)	0.014
FVC (liter)	2.4 (1.2)	2.1 (1)	0.032
CAT score	14 (14)	18 (16)	0.201
mMRC score	2 (2)	2 (1.3)	0.199
The number of exacerbations in previous year	1 (2)	1 (5)	0.668
BEC (10^3/uL)	0.15 (0.22)	0.08 (0.05)	0.003
Percentage of BEC (%)	2.1 (2.5)	1.2 (2)	0.018

Abbreviations: SD, Standard deviation; IQR, Interquartile range; BMI, Body mass index; COPD, Chronic obstructive pulmonary disease; FEV_1, Forced expiratory volume in 1 second; FVC, Forced vital capacity; CAT, COPD assessment test; mMRC, modified medical research council; BEC, blood eosinophil count; ADO index, age, dyspnoea, airflow obstruction.

Table 3 Multivariable Regression Model for Mortality in COPD Patients with COVID-19

	B	p	OR	95% CI
				Lower - Upper
FEV_1 (%)	−0.032	0.191	0.969	0.923–1.016
FEV_1 / FVC	0.006	0.882	1.006	0.931–1.086
CAT score	−0.001	0.975	0.999	0.912–1.093
mMRC score	−0.981	0.117	0.375	0.110–1.280
ADO index	0.755	0.025	2.127	1.097–4.123
BEC	−0.007	0.021	0.993	0.986–0.999
Smoking pack/yr	−0.002	0.910	0.998	0.970–1.027

Abbreviations: FEV_1, Forced expiratory volume in 1 second; FVC, Forced vital capacity; CAT, COPD assessment test; mMRC, modified medical research council; ADO index, age, dyspnoea, airflow obstruction; OR, Odds ratio; 95% CI, 95% Confidence interval; BEC, blood eosinophil count; pack/yr, package-year.

The ADO index had a diagnostic value, and the area under the curve (AUC) was important in distinguishing the development of mortality in patients with COVID-19 (AUC = 0.681). The optimal cut-off value for the ADO index was estimated as 3.5 with a sensitivity of 94% and specificity of 40%. The mortality was 18% in patients with PCR-positive COVID-19. The positive predictive value (PPV) was 26% and the negative predictive value (NPV) was 97%. The ROC curve of the ADO index is presented in Figure 2.

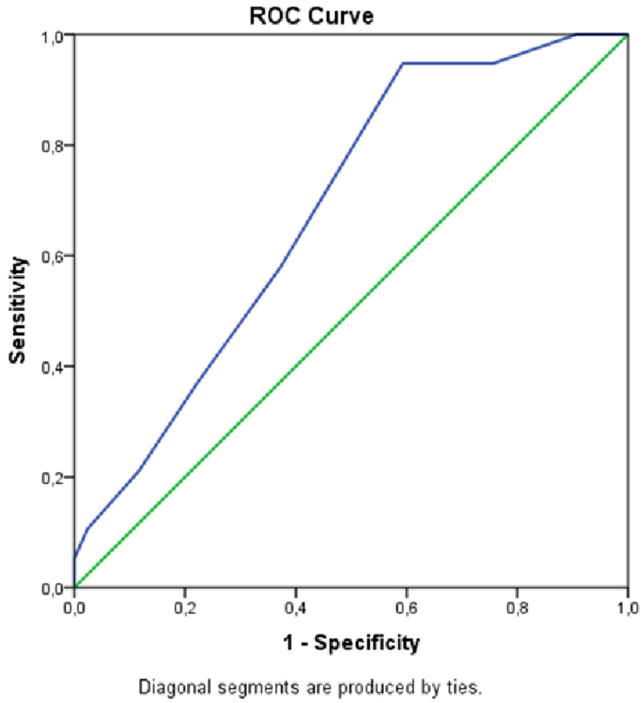

Figure 2 Receiver operating characteristics (ROC) curve for the ability of ADO index to predict mortality.

Discussion

Our study showed that the BMI and ADO index were significantly higher, whereas FEV_1% predicted and BEC were lower in patients who died compared to those who survived COVID-19 in patients with COPD. In the model created to predict COVID-19-related mortality in patients with COPD, each 0.755 unit increase in the ADO index was found to increase the risk of death by 2.12 times, and each 0.007 unit increase in the BEC reduced the risk of death by 1.007 times. In addition, increasing values in the ADO index could be used to estimate mortality, and the optimum cut-off value for 3.5 was diagnostic with 94% sensitivity and 40% specificity. The mortality was 18% in patients with PCR-positive COVID-19, the PPV was 26% and the NPV was 97%. According to our results the ADO index may help identify patients who are unlikely to die from COVID-19.

During the pandemic, the COVID-19 rates in patients with COPD were not as high as expected. However, studies involving large patient series have shown that COVID-19 is more severe and more fatal in patients with COPD. The mortality rate was found to be higher than that in the control group, with 5.5 times in the asthma-COPD-overlap (ACO) group and 4.8 times in the COPD group.[13] No difference in COVID-19 related mortality was observed in patients with COPD based on phenotypes, such as emphysema, chronic bronchitis, and ACO in our study.

A population cohort study conducted in England reported that COPD is an independent risk factor for hospitalisation and death due to COVID-19 after adjusting for age, sex, and comorbidities. The risk was found to be higher in younger patients with COPD in this study.[16] Conversely, a study in Sweden based on hospital records reported older age was associated with severe COVID-19 in patients with COPD.[11] In our study, there was no age-related mortality difference in patients with COPD who had COVID-19 whereas the ADO index, which also takes into account age, was significantly higher in nonsurvivors than in survivors.

A recent study evaluated risk factors associated with severe COVID-19 among 68,902 patients with COPD according to the Swedish National Airway Register (SNAR). They found that 991 patients had severe COVID-19, of whom 308 resulted in death. Clinical data from SNAR showed that male sex, older age, educational status, obesity, underweight, diabetes, cardiovascular disease, depression, FEV_1<50% pred, and a CAT score of ≥18 were all associated with severe COVID-19. Interestingly, the current smoking status was found to be inversely related to severe COVID-19.[11] Conversely, a systematic review indicated that the current smoking status was identified as a strong predictor of worse outcomes, including mortality.[17] In our study, no difference was observed between patients who died and survived after COVID-19 regarding their smoking history (pack-years). The Swedish cohort had a large patient population and had significant implications for clinically relevant characteristics, however, this study also had some limitations as it was a registered study.[11] The most important strength of our study is that data from patients with COPD were recorded in a stable period, face-to-face, and in detail, and all patients were diagnosed with the pulmonary function test.[14] The patients were screened for COVID-19 in the pre-immunisation period; thus, vaccination bias was eliminated in our study.

At the beginning of the pandemic, some concerns regarding the use of inhalers, especially ICSs, were identified in obstructive pulmonary diseases. The GOLD 2020 report suggested insufficient evidence to support these concerns and maintenance therapy should not be changed for patients who need ICS.[18] To date, results in the literature regarding this context are conflicting. A multicenter study including 130 critically ill patients with COVID-19 reported that patients who received ICS had lower 30-day mortality than those who did not. However, the in-hospital mortality, intensive care unit length of stay, and ventilator-free days were not statistically significant between the two groups.[19] Conversely, the OpenSAFELY UK primary care cohort study analysing mortality outcomes in 148,557 patients with COPD indicated that COVID-19-associated mortality was increased in ICS users versus nonusers. However, this was a retrospective study including electronic health records, and this result may be due to the typically more frequent use of ICS in those with more severe COPD.[20] In our study, no difference was observed between patients with and without COVID-19, and no difference was observed between patients who died and survived after COVID-19 regarding ICS use. Furthermore, in the first year of the pandemic to reduce hospital admissions in our country, inhaler drugs were similarly available from pharmacies without a prescription, thus increasing the reliability of the inhaled drug use records.

The effects of eosinophil count on respiratory infections have become an important research topic in both healthy people and patients with COPD. In a meta-analysis of 10,861 patients with COPD for whom eosinophil data were available, patients were divided into two groups based on the percentage of eosinophils. Patients with COPD with a BEC of <2% were associated

with an increased risk of developing pneumonia independent of ICS use.[21] A meta-analysis showed a significant decrease in eosinophil count in the severe COVID-19 group compared with the non-severe COVID-19 group.[22] Another meta-analysis found that eosinophil counts were significant indicators of severity in patients with COVID-19.[23] Our study is the first in the literature that investigates the relationship between the BEC in the stable period and mortality due to COVID-19 in COPD. The BEC was higher in survivors of COVID-19 than in nonsurvivors according to our results. Additionally, we found that in COPD patients with COVID-19, each 0.007 unit increase in eosinophil count reduces the risk of death by 1.007-fold.

The ADO index is a useful multidimensional assessment that is a good predictor for mortality in COPD.[15] In a recent study, 646 patients with COPD (GOLD stage I–IV) were enrolled by general practitioners and followed for 2 years. They showed the ADO index was an excellent predictor of 2-year mortality in an out-of-population validation in patients with COPD from primary care settings.[24] Similarly, 1892 patients of COPD were recruited from 71 general practices in the UK between 2012 and 2014 as part of the Birmingham COPD cohort study. The results suggested the ADO score is a promising predictor of 3-year mortality in patients with COPD in the primary care population.[25] Our study is the first in the literature investigating the relationship between the ADO score recording in the stable period of patients with COPD and mortality due to COVID-19. We found that the optimal cut-off value for the ADO score was estimated as 3.5 points with a sensitivity of 94% and specificity of 40%. The ADO index makes a modest contribution to the prediction of mortality due to COVID-19 in patients with COPD. According to our results the mortality was 18% in the patients with PCR-positive COVID-19. The PPV was 26% and the NPV was 97%. We can conclude that the ADO index helps to detect patients who are unlikely to die from COVID-19.

This study has some limitations. First, since we screened patients during the first year of the pandemic and most of them during the quarantine period, the number of patients who had COVID-19 was relatively low; thus, the number of patients who died due to COVID-19 was also low. On the other hand the patients were unvaccinated during the COVID-19 screening period also eliminated the vaccination bias in our study. Another limitation was that we retrospectively screened patients for morbidity and mortality from COVID-19. However, patients were followed from the participating centres, and their contact numbers were available. Telephone interviews were made with patients when necessary, so we had very little missing data.

In conclusion, although many studies have demonstrated that COPD is an independent risk factor for mortality due to COVID-19, evidence on factors predicting mortality is limited. Even while we found that the ADO index contributed modestly to predicting COVID-19 mortality in COPD patients, it might be useful in identifying patients who are unlikely to die from the virus. More widespread use of the ADO index, which can be easily calculated in clinical practice, may guide the approach to patients with COPD with viral respiratory infections. We believe that further studies are needed to validate the use of the ADO index in estimating mortality in both COVID-19 and other viral respiratory infections in patients with COPD.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work. All authors agreed on the journal to which the article should be submitted. All authors have responsibility for the content of the article.

Disclosure

The authors declare that they have no conflicts of interest in relation to this article.

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