ORIGINAL RESEARCH

D-dimer/Fibrinogen ratio and recurrent exacerbations might have a potential impact to predict 90-day mortality in patients with COPD exacerbation

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Abstract

Background

According to the World Health Organisation reports (WHO), COPD is the third leading cause of overall in the World by 2020.

Aim

We aimed to determine the prognostic predictors of 90-day mortality after an initial exacerbation in patients with acute exacerbation of COPD (AECOPD).

Results

Increased Charlson Comorbidity Score(CCS) (HR:1.47; p<0.05), readmission after initial exacerbation (HR:1.47; p<0.05) were predictive risk factors for 30-day mortality in multivariable regression model. The 90-day mortality rate was %11.8. Hypertension, increased median age, nutrition risk score (NRS), CCS, CAT score, and mMRC 4th level were possible risk factors for 90-day mortality. There was a significant difference in the mortality of patients with D-dimer/Fibrinogen ratios>0.11 and ≤0.11 (HR:2.47; p<0.05). Recurrent exacerbations after discharge were predictive risk factors for 90-day mortality in the multivariable regression model (HR:2.25; p<0.001) with the increased mortality risk 4.73 times (HR:4.73; p=0.002). Furthermore, a 1-unit increment of acute exacerbation increased the mortality risk 3.39 times (HR:3.39; p<0.001).

Conclusion

Our study showed that D-dimer/Fibrinogen ratio but not D-dimer and recurrent exacerbations after discharge might have a critical impact on 90-day mortality.

Keywords: COPD, D-dimer, exacerbation, mortality, prognosis

Introduction

According to the World Health Organisation reports (WHO), COPD is the third leading cause of overall in the World by 2020[1]. Acute exacerbation of COPD (AECOPD has a great impact on prognosis while associated with the severity and frequency[2-4]. Exacerbations have an increased risk of recurrence after an initial exacerbation and further deteriorate patients' health status[5]. The European Respiratory Society (ERS) reported high 90-day readmission rates with AECOPD across Europe about %40[6]. The time after the initial exacerbation of COPD may be a potential high-risk period for all-cause mortality [7]. Thus it needs to analyze possible prognostic factors associated with the 90-day mortality which would be a vulnerable period after an initial exacerbation. It would be important to show poor prognostic features in patients with AECOPD to enhance the management of high-risk patients.

Hypercoagulability state may be induced by hypoxemia and carbon dioxide retention in AECOPD[8]. D-dimer is a fibrin degradation product (FDP) after a blood clot is degraded by fibrinolysis. It has been suggested as a prognostic marker in limited studies including patients with AECOPD which were not prospectively designed and/or without any precisely well-defined inclusion criteria[9-10]. In a prospectively designed study, D-dimer ≥985 ng/L has been shown as an independent risk factor for both in-hospital and 1-year mortality. But they were not regarded as 90-day mortality. We aimed to determine the prognostic predictors of 90-day mortality which would be a vulnerable period after an initial exacerbation in patients with AECOPD.

We aim to determine the prognostic predictors of 90-day mortality after an initial exacerbation in patients with AECOPD.

Materials and Methods

Subjects

We screened all patients with acute exacerbation of COPD, who were admitted and hospitalized in the pulmonology clinics of tertiary care hospital between 15 November 2019 and 15 November 2020. The diagnosis of COPD was decided by pulmonary physicians based on Global Initiative for Chronic Obstructive Lung Disease criterion (GOLD) 2020. The severity of disease was evaluated by the degree of decrease in FEV1: (a) FEV1 ≥80% predicted mild (GOLD-1); (b) 50% ≤ FEV1 < 80% predicted moderate (GOLD-2); 30% ≤ FEV1 < 50% predicted severe (GOLD-3), and FEV1 <30% predicted extremely severe (GOLD-4)[2]. Patients rejected to sign the informed consent, having life-threatening severe illness including renal, liver and other organ failure did not include in the study. In addition, the

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diagnosis of CTEPH and acute pulmonary embolism in the admission has been accepted as an exclusion criterion. The ethics of Istanbul Training and Research Hospital approved the research protocol (approval number 2043, date 08.11.2019).

Methods

Patients' demographics including age, sex, the number of hospitalizations or admission to the emergency department for AECOPD in the previous year, smoking habit, and comorbidities were asked and recorded by the investigator. All medical records and laboratory results have been extracted from the hospital-based data system. The results of mMRC, pulmonary function test (PFT) results and CAT score were evaluated in the stable period and, CCS, NRS, CURB-65, and DECAF were evaluated and recorded in exacerbation periods.CURB-65 is a score to evaluate the AECOPD for physicians and it contains the letters of the words in order "Confusion, BUN, Respiratory rate, Blood pressure" and the number for age 65.

DECAF is a score that is developed by some physicians and used in some studies to determine the prognosis of AECOPD. DECAF contains the letters of the words in order "Extended MRC Dyspnea Scale (eMRCD), Eosinopenia, Consolidation on chest X-ray, Acidemia and atrial Fibrillation".

Clinical data, vital signs, and arterial blood gases (pH, arterial carbon dioxide tension (PaCO2), arterial oxygen tension (PaO2), and arterial oxygen saturation) on admission were recorded. We collected the blood samples from each patient at the time of admission to the inpatient clinic of pulmonology for D-dimer and laboratory measurements (creatinine, blood urea nitrogen (BUN), platelets, hemoglobin, hematocrit, fibrinogen, and C-reactive protein (CRP). Patients were followed up with telephone interviews for 90-days by the study investigators. Patients with at least two COPD exacerbations or one hospitalization for AECOPD in the previous year were considered frequent exacerbators.

Statistical analysis

The primary outcomes were 30-day and 90-day mortality. The secondary outcome is COPD exacerbation after discharge. Categorical variables are presented as n (%), and normally distributed values are presented as mean ± standard deviation. Comparisons between groups were made using the chi-squared test (for categorical variables) or analysis of variance (for continuous variables). Receiver operator curve analysis was applied to define the minimal optimal D-dimer level and D-dimer/fibrinogen ratio that predicted death. Multivariate logistic regression analysis was applied to determine the independent factors of 30-day and 90-day mortality. Kaplan–Meier survival curves and log-rank tests were used to compare the time to death between those with elevated D-dimer levels and those without. The results are presented as hazard ratios (HRs) with a 95% confidence interval (CI). We analyzed the data using SPSS 13.0 for Windows 20(SPSS Inc., Chicago, IL, USA). The p-value <0.05 was considered significant.

Results

Three hundred and sixty AECOPD patients were screened and 231 patients were included in our study. The demographic data of the subjects were shown in Table 1.

Table 1.Demographic Data

Demographic parameters (N:231)			
Gender, n(%)		Smoking, n(%)	
Male	168(72.7)	Nonsmoker	36(15.6)
Female	63(27.3)	Current smoker	61(26.4)
Age (years)	66.7±8.8	Exsmoker	134(58)
BMI, kg/m2	26.5±7.1	Smoking pack-years	50(0-240)
Comorbidities, n(%)			
Pneumoniae	125(54.1)	Hypertension	101(43.7)
Ischemic heart disease	53(22.9)	Diabetes Mellitus	51(22.1)
Myocardial infarction	6(2.6)	Congestive heart failure	48(20.8)
Atrial fibrilation	18(7.8)	Chronic renal failure	13(5.7)
Bronchiectasis	9(3.9)	Obstructive sleep apnea syndrome	3(1.3)
Peripheral vasculary disease	2(0.9)	Interstitial lung diseases	2(0.9)
Peptic ulcer	2(0.9)	Cerebrovascular disease	1(0.4)

Table 2. The relationship between demographic data and 90-day mortality

Demographic parameters	Survivors (N:201)	Non-survivors (N:27)	HR	%95 CI	p-value
Gender, n(%)					
Male	148(73.6)	18(66.7)	ref		
Female	53(26.4)	9(33.3)	1.35	0.61-3.01	0.462
Age,years	66.2±8.6	71.0±8.8	1.06	1.02-1.11	0.008*
BMI,kg/m2	26.5±7.0	25.4±7.3	0.98	0.92-1.04	0.513
FEV1 (%)	37.3±14	36±12.9	0.99	0.97-1.02	0.691
FEV1 (ml)	1±0.4	0.9±0.4	0.58	0.2-1.71	0.324
Smoking,n(%)					
Nonsmoker	30(14.9)	5(18.5)	ref		
Active smoker	56(27.9)	5(18.5)	0.56	0.16-1.95	0.564
Exsmoker	115(57.2)	17(63.0)	0.9	0.33-2.45	0.904
Smoking pack-years	50(0-180)	50(0-240)	1	1.00-1.01	0.397

Prognostic risk factors associated with 30-day mortality

The mortality rate of 30-day was 5.2 % (N:12). Congestive heart failure (CHF), hypertension (HT), chronic renal failure (CRF), peripheral vascular disease and obstructive sleep apnea syndrome (OSAS), and presence of pneumonia were related to mortality according to the univariate analysis. CCS was higher in patients who died. It was found 1-unit increment of CCS increases mortality 1.75 times. (HR: 1.75;

Table 3. The relationship the comorbidities and 90-day mortality

Comorbidities, n(%)	Survivors (N:201)	Non-survivors (N:27)	HR	%95 CI	p-value
CCS	2(1-6)	3(1-7)	1.31	1.01-1.68	0.451
Pneumoniae	104(51.7)	18(66.7)	1.83	0.82-4.08	0.137
Ischemic heart disease	45(22.4)	7(25.9)	1.21	0.51-2.86	0.662
Congestive Heart Failure	39(19.4)	8(29.6)	0.05	0.77-4.00	0.184
Atrial fibrilation	16(8.0)	2(7.4)	1.75	0.22-3.93	0.922
Hypertension	82(40.8)	17(63.0)	0.93	1.10-5.23	0.028*
Chronic renal failure	10(5.0)	3(11.1)	2.35	0.71-7.81	0.163
Peripheral vascular disease	1(0.5)	1(3.7)	7.01	0.95-51.83	0.076
Diabetes Mellitus	42(20.9)	9(33.3)	1.84	0.83-4.09	0.136
OSAS	2(1.0)	1(3.7)	3.76	0.51-27.75	0.194
Interstitial lung diseases	-	1(3.7)	-	-	-

Table 3. The relationship the comorbidities and 90-day mortality

Parameters	Univariable Cox Regression			Multivariable Cox Regression		
	HR	%95 CI	p-value	HR	%95 CI	p-value
Age	1.06	1.02-1.11	0.008*	-	-	-
Hypertension	2.40	1.10-5.23	0.028*	-	-	-
CCS	1.31	1.01-1.68	0.038*	-	-	-
mMRC						
0-2	Ref			-	-	-
4	5.87	1.27-27.17	0.026*	-	-	-
CAT	1.08	1.01-1.16	0.019*	-	-	-
HGB	0.80	0.68-0.94	0.007*	-	-	-
PLR	1.02	1.01-1.03	0.020*	-	-	-
DDFR						
≤0,11	Ref					
>0,11	2.47	1.02-5.98	0.045*	-	-	-
NA	0.91	0.84-0.98	0.008*	-	-	-
Albumin	0.90	0.83-0.98	0.013*	0.87	0.77-0.97	0.014*
pCO_2	1.03	1.01-1.05	0.043*	-	-	-
Oxygen saturation	0.97	0.94-0.99	0.020*	-	-	-
Number of readmission after initial exacerbation	3.39	2.31-4.97	<0.001*	2.25	1.43-3.54	<0.001*

p<0.001). None of the other clinical features have been related to mortality.

Decreased hemoglobin levels (HR:0.76; p<0.04), increased Platelet/Lymphocyte ratio (PLR) (HR:1.05; p=0.005), increased creatinine (HR:8.54; p<0.01) and uric acid levels (HR:1.43; p<0.04), decreased sodium levels (HR:0.87; p<0.001) were related to increased mortality. Fibrinogen and D-dimer levels, and D-dimer/Fibrinogen ratios were not related to 30-day mortality. Readmission to the hospital after initial exacerbation was associated with an increased risk of 30-day mortality (HR:2.70; p<0.001). Increased CCS (HR:1.47; p<0.05), readmission after an initial exacerbation (HR:1.47; p<0.05) were predictors for 30-day mortality in the multivariable regression model.

Prognostic factors associated with 90-day mortality

Two hundred and twenty-eight patients were followed up for 90-days and the mortality rate of 90-day was 11.8% (N:27). The relationship between demographic data and 90-day mortality has been shown in Table 2. Increased age, HT, mMRC score 4, increased CAT score were related to 90-day mortality. CCS in patients who died was significantly higher. (Table 3) Decreased RBC (HR: 0.56; p=0.014), hemoglobin (HR:0.80; p=0.007), sodium (HR:0.91; p<0.01) and albumin levels (HR:0.90; p=0.013), increased PLR (HR:1.02; p<0.03) and potassium levels (HR:2.04; p=0.040) associated with increased 90-day mortality.

D-dimer was not associated with mortality. The cut-off level of D-dimer was 1.16 mg/L, but the levels above 1.16 mg/L were not a risk factor for mortality (p>0.05). In the ROC curve analysis, the cut-off level of the D-dimer/fibrinogen ratio(DDFR) was 0.11. There was an increased risk for mortality in patients with D-dimer/fibrinogen ratios>0.11 and ≤0.11 (HR:2.47; p<0.05). (Figure 1) D-Dimer/fibrinogen ratio was mildly correlated with CCS (r=0,200; p<0.01) without any correlation with the other clinical or laboratory parameters. It was found that a 1-unit increment of pCO2 levels increased 1.03 times the mortality of the patient who mostly has hypercarbia arterial blood gas findings (HR:1.03; p<0.05). 1-unit decrement of oxygen saturation increased the mortality (1/0.97) 1.03 times (HR:0.97; p<0.03). Decreased albumin levels (HR: 0.87; p=0.0144), number of exacerbations after discharge (HR:2.25; p<0.001) were predictive risk factors for 90-day mortality in the multivariable regression model in which possible risk factors are included. Increased number of exacerbations after discharge was a predictive risk factor for 90-day mortality in the multivariable regression model (HR:2.25; p<0.001). (Table 4) Recurrent exacerbation after discharge increased the mortality risk 4.73

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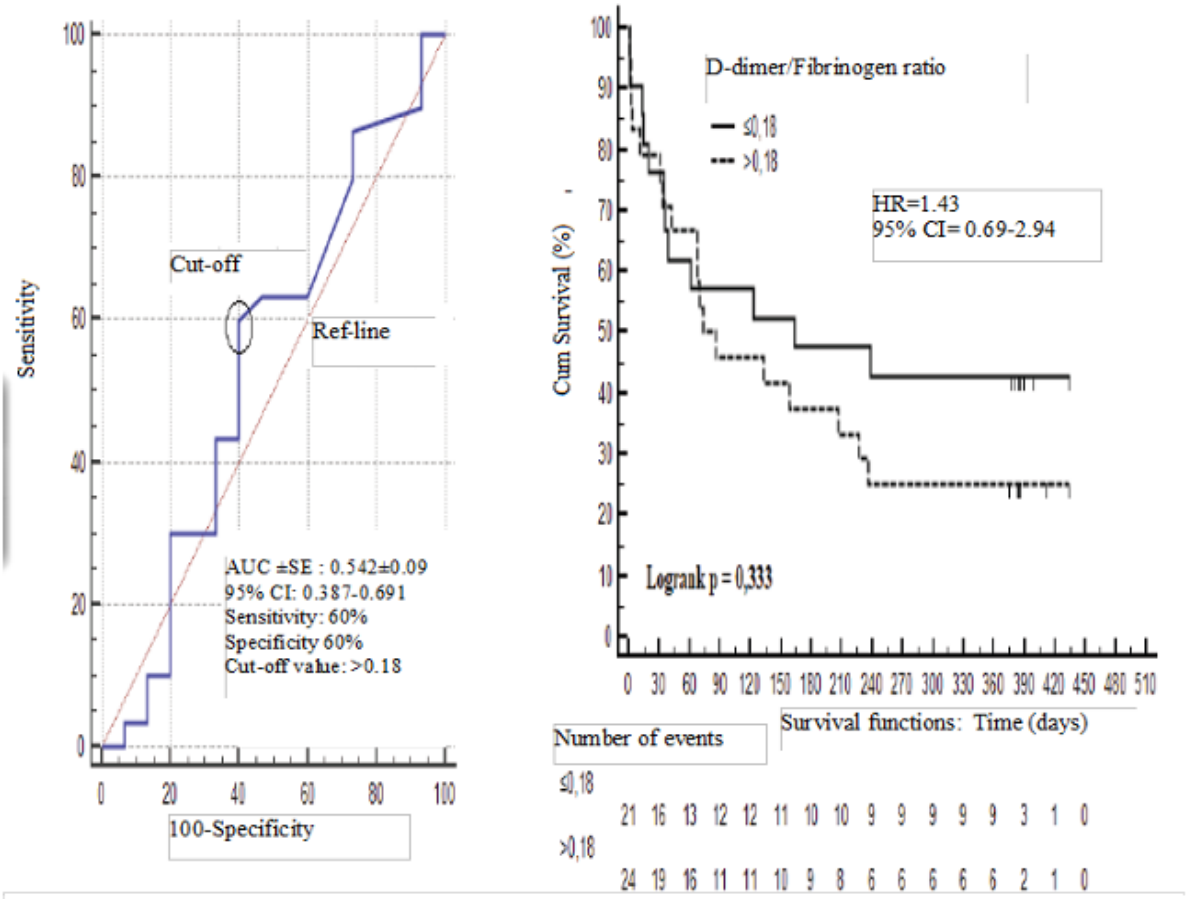

Figure 1: The predictive value of D-dimer / Fibrinogen ratio in predicting 1-year mortality and mortality risk

times (HR:4.73; p<0.01). 1-unit increment of exacerbation increased the mortality risk 3.39 times (HR:3.39; p<0.001).

Discussion

We showed that recurrent exacerbations after initial exacerbation were a predictor for poor prognosis of 30-day and 90-day mortality. It can be specifically concluded that recurrent exacerbation after discharge increased the mortality risk 4.73 times (HR: 4.73; p<0.01) in the 90-days periods of time. 1-unit increment of exacerbation increased the mortality risk 3.39 times (HR:3.39; p<0.001). We can conclude that the D-dimer/Fibrinogen ratio cut-off value of >0.11 would have a role to distinct patients as a poor and good prognosis. (HR:2.47; p<0.05). But D-dimer has no prognostic value in AECOPD.

In a prospectively designed study conducted by Hu and et al[10], D-dimer ≥985 ng/L has been shown as a predictor for both in-hospital and 1-year mortality. But they were not regarded as 90-day mortality. In our study, we showed that D-dimer by itself does not have a prognostic role in either 30-day or 90-day mortality. In 30-day short-term mortality can be influenced by several factors including the study design as well as patient selection criteria. Controversial results for about D-dimer as a prognostic role in AECOPD can be related with the cohorts' features that include heterogeneous patients with several confounding factors. Indeed, Hu et al did not exclude diseases that could affect mortality or conditions that could lead to an increase in D-dimer[10]. As a result of studies conducted without excluding major associated risks that may lead to mortality, it would not be realistic to think that the mortality associated with the increase in D-dimer alone reflects COPD-related mortality. In a study designed retrospectively with the excluded confounders such as pulmonary embolism, D-dimer > 1.52 mg/L cut-off value has been conducted with 1-year mortality in a relatively small population including 61 AECOPD patients[9]. But 30-day or 90-day mortality results were not reported. To determine prognostic factors associated with COPD, we excluded other important risk factors and conditions that lead to increasing D-dimer. In our study, we concluded that not D-dimer but D-dimer/Fibrinogen ratio with the cut-off value of >0.11 will be distinctive for the poor prognosis. D-dimer/Fibrinogen ratio might be a potential predictor in AECOPD while none of the studies at least in our knowledge to show the exact role of this marker in COPD. Our results may encourage researchers to specifically evaluate its role in COPD as a potential prognostic marker.

We clearly showed that recurrent exacerbations after initial hospitalization would be the only independent predictor both for 30-day short-term and 90-day mortality. There are several studies which were shown that the severity and also frequency of exacerbation would be related to an increased risk of mortality[11-14]. Exacerbations have an increased risk of recurrence after an initial exacerbation and further deteriorate patients' health status[15]. We can conclude that patients hospitalized with AECOPD should be followed up closely for recurrent exacerbations who have increased risk for mortality. In such patients with recurrent exacerbations in followed 90 days should refer as "high-risk AECOPD patients" for mortality.

Recently, exacerbation history in the previous 1-year has been approved to manage treatment in COPD[2]. However, the results about the association between mortality risk and previous history of AECOPD were controversial[10,13]. Due

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to this group of patients does not include in most of the clinical trials, it is difficult to evaluate the exact contribution to the COPD burden. Moreover, its' devastating effect on COPD outcomes is probably underestimated due to the lack of comprehensive analysis. It might be important to confirm if frequent exacerbators exacerbator was not a risk factor for mortality in COPD[10]. We confirmed that frequent exacerbators do not have a higher risk of mortality in both 30-day and 90-day mortality. However, we clearly showed that recurrent exacerbations after initial exacerbation were a predictor of increased mortality.

Limitations of the study

COPD is a heterogeneous disease including several comorbidities in natural history. Although several confounders accompany COPD patients in the real-life, we excluded severe diseases that could be a majör effect on mortality. We specifically excluded patients diagnosed with acute pulmonary embolism because it is a risk factor for death and may lead to an extreme increase in D-dimer levels due to aimed to show the value of D-dimer. Thus our cohort included patients without severe diseases and acute pulmonary embolism at the time of admission to the hospital.

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