What Are the Factors Affecting on the Mortality of COPD Patients in the ICU?

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ABSTRACT

Background: Morbidity and mortality rates of Chronic obstructive pulmonary disease (COPD) are continuously increasing throughout the world. It is a major cause of death, imposes a great socioeconomic burden and constitutes a significant part of ICU patients.

Aim: To determine factors associated with in-hospital-mortality of all causes following critical care admissions of patients with COPD.

Material and methods: COPD patients that admitted to ICU were included retrospectively. Patients were divided into two groups: Survived and non-survived patients. Features during admission to the ICU of patients were studied dividing into three: First, demographic and clinical features including GCS ve APACHE II scores. Second, laboratory analyses including Uric acid, Leukocyte, Red cell Distribution Width (RDW), Mean Platelet Volume (MPV), Gamma-Glutamyl Transferase (GGT), lymphocyte, neutrophil, urea, creatinine, arterial blood gases. Third, comorbid diseases accompanying COPD. Parameters that were significant between two groups were analyzed using logistic regression with enter method.

Results: A total of 178 patients were included: 120 (67.42%) of them belonged to mortal COPD patients and 58 (32.58%) were in the alive group. For demographic and clinical features, logistic regression analysis showed that initial intubation in ED (OR: 0.33 (95% CI: 0.13–0.83), p = 0.018), duration of Mechanical Ventilation (MV) (OR: 0.873, 95% CI: 0.802–0.949, p = 0.002) and Ejection Fraction (EF) % (OR: 1.072, 95% CI: 1.013–1.135, p = 0.016) were independent variables to define mortality. Second logistic regression analysis demonstrated that creatinine was the only independent laboratory parameter to define mortal patients (OR: 0.596 (95% CI: 0.397–0.897, p = 0.013). Among comorbidities, Congestive Heart Failure (CHF) (OR: 2.783 (95% CI: 1.225–6.323, p = 0.014), initial Atrial Fibrillation (AF) (OR: 0.45, 95% CI: 0.203–0.998, p = 0.049), Post-op care (OR: 0.07, 95% CI: 0.012–0.417, p = 0.004) were found to be independent parameters to define mortality.

Conclusion: Our results show that patients pre-ICU intubation situation, CHF and AF were major parameters for mortality. The only independent diagnostic laboratory feature was patients' creatinine levels. Longer duration of MV was independently associated with mortality.

Keywords: Co-morbidity, COPD, Creatinine, ICU, mortality

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INTRODUCTION

COPD has been defined as the presence of airway obstruction attributable to chronic bronchitis or emphysema (1).

Morbidity and mortality rates of Chronic obstructive pulmonary disease (COPD) are continuously increasing throughout the world; it is a major cause of death and imposes as a great socioeconomic burden (2, 3). COPD exacerbation is the main cause of ICU admissions and 4th main reason of death (4). The course of COPD is characterized with recurrent exacerbations and progressive deterioration of pulmonary functions. In addition to quality of life of patients being affected negatively, as the disease progresses need for ICU hospitalization increases and prognosis for this group of patients is believed to be poor (5). Studies report hospital mortality varies between 20% and 82% due to heterogeneous patient population and difference in severity of the disease (5–8). COPD patients who were admitted to ICU for acute hypercapnic respiratory failure have poor results, especially if intubation is needed, because they have had depleted body's reserve supplies. Type of ICU, co-morbid diseases, patient characteristics, age and severity of the disease determine high mortality rates of these patients (1, 9–13).

Defining predictive factors for morbidity and mortality in COPD patients has always been appealing for ICU specialists. Because determining high risk patient is essential for adjusting monitorization, approach and management of the disease and guidance for family members. Several factors for predicting mortality of COPD patients have been determined; these include need for mechanical ventilation, severity of underlying condition, renal failure, sepsis, presence of malignity, age, certain biochemical and physiological parameters, cardiac failure, arrhythmias, body mass index and APACHE II (Acute Physiological and Chronic Health Evaluation) score (1, 8, 9, 13).

In this study we aimed to examine effects of uric acid, Gamma-Glutamyl Transferase (GGT), Mean Platelet Volume (MPV) and Red cell Distribution Width (RDW) levels upon admission in addition to co-morbid diseases on mortality of COPD patients who were admitted to ICU.

MATERIAL AND METHOD

Setting

This study was conducted in Anesthesiology and Reanimation ICU department of a research and training hospital. Our hospital has 550 beds and includes all departments except obstetrics and gynecology. Semi-closed, 18 bed ICU is managed by anesthesiologists 24/7. Anesthesiologists decide admittance and discharge of patients in ICU. All data in this study (physical examination findings, APACHE II, GCS and laboratory tests) are routinely done by the anesthesiologists during patient's admission to ICU. Nurse to patient ratio is 1/2 during the day shift and 1/3 during the night shift. There are no emergency, pulmonary and neurology ICU departments in our hospital.

After obtaining local Ethical Committee approval (Date 03.11.2015; Decree no: 37732058-6429) files of the COPD patients who were admitted to Anesthesiology and Reanimation ICU between January 2014 and December 2015 were examined retrospectively. Among these 178 patients with COPD, 26 (%14.6) were admitted primarily to ICU because of COPD and acute exacerbation.

Patients

GCS (Glasgow Coma Scale), APACHE II score, presence of intubation, systolic-diastolic blood pressures (SBP-DBP), pulse rates, uric acid, GGT, blood glucose, CRP (C-Reactive Protein), urea, K (potassium), Na (sodium), total cholesterol, triglyceride, WBC, lymphocyte

(%), neutrophile (%), MPV, RDW, PLT, ABG (Arterial blood gases); pH, $PaCO_2$, PaO_2, lactate, HCO3 and base excess upon admission for all of these 178 patients were recorded.

In addition history of DM (Diabetes Mellitus), HT (hypertension), CHF (congestive heart failure), ARF (acute renal failure), CRF (chronic renal failure), CVA (cerebrovascular accident), CAD (coronary artery disease) and sepsis were recorded. Echocardiography (ECHO) was performed and EF (ejection fraction, %) presence or absence of PHT (pulmonary hypertension), AF (atrial fibrillation) and pulmonary embolism were recorded. Drug use that can affect uric acid levels such as insulin, statins, diuretics, ACE inhibitors and need for inotropic support upon admission were recorded.

Inclusion criteria: COPD patients who were hospitalized in ICU for at least one day and patients whose files were accessible were included in this study.

Exclusion criteria: Patients who were hospitalized for less than 24 hours and could not be diagnosed, patients whose laboratory results, ABG, GCS, APACHE II scores, medical histories and ECHO results could not be accessed were excluded from this study.

Biochemical tests

Blood Gases have been analyzed within ICU with ABL800 flexdevice. All samples were delivered to the laboratory within 30 minutes. Blood count was made by Abbott, Ruby-celldyn, and CRP analysis made by Siemens BN II device and nephelometry. All biochemical parameters in the study were analyzed by Abbott Architect-C 16000 device and spectrophotometric method.

Statistics

Continuous variables are presented as mean±SD; discontinuous variables are presented as n (%). Evaluation of significance of two averages was made by t-test or Mann Whitney U test. Significance of two percentages was analyzed with chi-square test. Results are presented with 3 different tables: 1) demographic and vital parameters, clinical scores and some of the

clinical characteristics, 2) laboratory values and 3) co-morbid diseases. Significant variables in these 3 tables were analyzed with 3 different logistic regression analyses. In all 3 analyses Hosmer and Lemeshow tests $p < 0.05$.

RESULTS

A total of 178 patients were included in the study: 120 (67.42%) of them were in deceased COPD patients group and 58 (32.58%) were in the survived COPD patients group. Overall demographic variables are presented in Tables 1-6.

Comparison of demographic data, vital parameters, clinical scores and some of the clinical characteristics:

There was no significant difference between deceased and surviving patients in terms of age and gender. Being intubated during admission was statistically more significant in deceased patients than surviving patients ($p < 0.0001$). Among deceased patients, the ratio of hospitalization due to acute COPD exacerbation was more than that of the ratio seen in the alive group (%18.3 *vs* %6.9; $p = 0.045$). Deceased patients had lower GCS and higher APACHE II scores than surviving patients ($p < 0.0001$ and $p = 0.001$ respectively). Durations of ICU hospitalization and mechanical ventilation were longer in deceased patients than surviving patients ($p = 0.029$ and $p < 0.0001$ respectively). SBP, DBP and MBP were significantly lower during admission in deceased patients than surviving patients ($p=0.014$, $p<0.0001$ and $p=0.007$ respectively). There was no statistically significant difference between groups in terms of pulse rate during admission (Table 1).

Among the significant parameters in table 1, Intubation in ED, Acute COPD exacerbation, APACHE II, duration of MV (day), MBP and EF% were taken into logistic regression analysis using entermethod. It showed that initial intubation in ED (wald: 5.6, OR:

0.33 (95% CI: 0.13-0.83), P=0.018), duration of MV (wald: 10.03, OR: 0.873 (95% CI: 0.802-0.949), P=0.002) and EF% (wald: 5.83, OR: 1.072 (95% CI: 1.013-1.135), P=0.016) were independent variables to define mortality (Table 2).

Comparison of initial laboratory parameters

There was no significant difference between groups in terms of initial uric acid, GGT, WBC, RDW, CRP, glucose, triglyceride, total cholesterol, Na, K, urea, pH, PaO2, PaCO2 and HCO3 levels; whereas initial MPV, PLT, neutrophil, lymphocyte, creatinine and base excess levels were significantly different between deceased and surviving patients (Table 3).

Among the significant parameters in table 3, PLT count, MPV, RDW, NLR, creatinine and BE were taken into logistic regression analysis using enter method which demonstrated that creatinine was the only independent laboratory parameterto define mortal patients (wald: 6.17, OR: 0.596 (95% CI: 0.397–0.897), $p = 0.013$) (Table 4).

Comparison of co-morbid diseases and drug use between two groups

There was significant difference between deceased and surviving patients in terms of CHF (p=0.004), post-CPR (0.010), pulmonary embolism (p=0.004), AF (p=0.041), initial inotropic support (p=0.050) and postoperative care (p=0.009); whereas other conditions did not have significant difference (Table 5).

Multivariate logistic regression analysis was done including CHF, inotropic support in ICU, AF, Post-cpr and Post op. care using enter method. CHF (wald: 5.98, OR: 2.783 (95% CI: 1.225-6.323), P=0.014), initial AF (wald: 3.86, OR: 0.45 (95% CI: 0.203-0.998), P=0.049), Post-op care (wald: 8.51, OR: 0.070 (95% CI: 0.012-0.417), P=0.004) were found to be independent parameters to define mortality among COPD patients in ICU (Table 6).

DISCUSSION

The present study aimed to determine whether RDW, MPV, uric acid and co-morbid diseases were associated with mortality of all causes following ICU admission of patients with COPD. We could not find any association with laboratory parameters independently except that of creatinine levels. But comorbidities, namely CHF and AF were strongly and independently correlated with mortality.

International COPD organization called GOLD (Global Initiative for Obstructive Lung Disease) defined COPD in 2006 as "a preventable and treatable disease with abnormal inflammatory response in lungs to harmful gases and particles, generally non-reversible, characterized by progressive air flow limitation and with some significant extra pulmonary effects that may contribute to the severity in individual patients (www.goldcopd.com). Some factors such as genetic factors (especially alpha-1-antitrpsin deficiency), smoking, environmental and occupational factors, factors effecting lung development, bronchial hyper reactivity and asthma are thought to have a role in development of COPD (18). Sings of the disease are irreversible air flow limitation and chronic inflammation. Progressive inflammatory and fibrotic changes cause small airway obstruction. Additional elastic tissue damage and apoptosis also have roles (19). In the advancing years nearly 10% of the COPD patients require nursing. Significant portion of the remainder of the COPD patients have to continue their lives with important activity limitations and poor quality of life compared to their peers (20). Whatever reason causes COPD, it is an important cause of mortality throughout the world and its incidence is increasing. It is a known reality that COPD patients who need to be hospitalized in ICU are in advanced state, have acute pulmonary failure and co-morbid diseases and thus have increased rate of mortality. Connor et al reported that COPD patients with acute exacerbations have 11% in hospital mortality and 43% one-year mortality rates (21). COPD patients with acute exacerbations who needed invasive

mechanical ventilation have 37-54% one-year survival rates and patients who needed noninvasive mechanical ventilation have 62-87% one-year survival rates. There are studies that report noninvasive mechanical ventilation in addition to standard treatment significantly reduces hospital mortality (22, 23). Ucgun et al reported that mortality rate in 151 COPD exacerbation patients who were admitted to ICU and needed mechanical ventilation was 52.9% (1).

Mortality rate in our study was 67.4%. This high rate may have some logical reasons; first our patients mainly consist of the elders, second 63.7% of our patients were already intubated during admission, third high frequency of co-morbid diseases, fourth %27 of our patients had accompanying pneumonia.

A study showed association between age and hospital mortality of COPD patients is affected by severity of the acute condition and other co-morbid diseases; and advanced age was a prognostic factor for hospital mortality (5). There are other parameters besides age that determine prognosis of COPD patients who are admitted to ICU. It is shown in studies that in addition to prolonged oral corticosteroid use and high PaCO2 values (13); intubation and need for mechanical ventilation, inadequate compensation for respiratory acidosis, presence of mechanical ventilation complications, low GCS and high APACHE II score also are risk factors for mortality in COPD patients who were admitted to ICU (1, 8, 9, 11). Ucgun et al defined inadequate compensation for respiratory acidosis, low hemoglobin levels, low GCS and low DBP as independent risk factors for COPD patients who were admitted to ICU (1). There are some other studies that define mechanical ventilation requirement for longer than 3 days, cardiac arrhythmias, low hemoglobin levels, coma, sepsis, iatrogenic complications, renal failure and accompanying pulmonary infections as important predictive factors for mortality of COPD and acute pulmonary failure patients who were admitted to ICU (1, 9, 11, 24-26). Our results were similar to these reports. There was no significant difference between

deceased and surviving patients in terms of age, gender, pH, PaCO2, PaO2, lactate and HCO3; whereas there was a statistically significant difference between groups in terms of APACHE II scores (29.07 in deceased patients, 25.05 in surviving patients), GCS scores (9.08 in deceased patients, 12.23 in surviving patients), duration of ICU hospitalization (11.39 days in deceased patients, 7.57 days in surviving patients), duration of mechanical ventilation (9.38 days in deceased patients, 2.52 days in surviving patients), DBP and SPB (Table 1).

Besides abovementioned risk factors, studies report other biochemical risk factors. Some of these are uric acid, low platelet count, RDW, GGT, MPV, CRP, urea, creatinine (14, 15, 17, 27-30). Konstantinos et al reported that uric acid is associated with increased risk and 30 day mortality in COPD patients; and this low-cost biomarker can be useful for defining high risk in COPD patients and managing ICU (15). However Naksya et al emphasized that there was no association between high levels of uric acid in first day of ICU hospitalization and mortality (17). In a retrospective study that Seyhan et al conducted on 270 stable COPD patients, it was reported that elevated RDW levels were associated with increased mortality (31). Another study showed an independent association between high RDW levels and unfavorable results in ICU and emphasized it can be relatively predictive of clinical outcome (16). On the other hand Bazick et al suggested that RDW was a strong predictive factor in critical patients (27). Also there are studies about association between thrombocytopenia (28, 32), MPV (33, 34) and mortality of ICU patients. In our study there were no significant differences regarding uric acid, triglyceride, total cholesterol, RDW, WBC, CRP and urea; whereas MPV, lymphocyte, neutrophile, NLR (neutrophile/lymphocyte ratio), PLT and creatinine levels were significantly different between deceased and surviving COPD patients (Table 2).

Present study has a number of limitations. First of all this study was conducted by examining only theadmission data. Mortality rates were not analyzed according to secondary

or tertiary infections, ventilator-associated pneumonia, complications of mechanical ventilation or other iatrogenic complications. Moreover we did not include laboratory tests that may also affect mortality; such as hemoglobin and albumin levels.

CONCLUSION

As a result; co-morbid diseases such as CHF, AF and postoperative care affect mortality the most in COPD patients who are hospitalized in ICU. Laboratory tests like creatinine and clinical features like being intubated upon admission, duration of mechanical ventilation and EF are other independent variables that affect mortality.

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Table 1: Comparison of demographic, vital parameters, clinical scores and some of the clinical characteristics of deceased and surviving COPD patients

	Deceased (n=120) Mean±SD	**Surviving (n=58) Mean±SD**	**P**	**Total Mean±SD**
Age (Years)	74.33±9.98	73.47±10.63	0.599	74.04±10.2
Gender (Female) %	54.2	51.7	0.759	46.6
Intubation in ED	50.8(61)	12.9(9)	<0.0001	63.7 (70)
Acute COPD exacerbation	18.3 (22)	6.9 (4)	0.045	14.6 (26)
GCS	9.08±4.06	12.23±3.26	<0.0001	10.10±4.08
APACHE II score	29.07±7.77	25.05±7.61	0.001	27.76±7.92
Duration of ICU hospitalization (Days)	11.39±11.86	7.57±8.44	0.029	10.15±10.99
Duration of MV (Days)	9.38±11.54	2.52±6.42	<0.0001	7.15±10.64
EF (%)	50.6±8.4	54.8±6.1	<0.0001	51.95±7.98
DBP (mmHg)	66.17±21.01	75.14±20.25	0.008	69.09±21.13
SBP (mmHg)	112.88±32.75	125.74±32.16	0.014	117.07±33.03
MBP (mmHg)	81.7±24	92±23.2	0.007	85.1±24.2
Pulse rate/min	104.75±23.28	99.47±22.03	0.151	103.03±22.95

Table 2: Logistic regression analysis of demographic, vital parameters, clinical scores and some of the clinical characteristics to define deceased among COPD patients

Parameters	**Wald**	**P**	**OR**	**95%CI**
Intubation in ED	5.6	0.018	0.33	0.132-0.825
Acute COPD exacerbation	2.69	0.101	2.81	0.817-9.693
APACHE II	0.76	0.383	0.977	0.928-1.029
MV (day)	10.03	0.002	0.873	0.802-0.949
MBP (mmHg)	3.45	0.063	1.016	0.999-1.034
EF%	5.83	0.016	1.072	1.013-1.135

CORD: Chronic Obstructive Pulmonary Disease, GCS: Glasgow Coma Scale, APACHE II: Acute Physiological and Chronic Health Evaluation, MV: Mechanical Ventilation, EF: Ejection Fraction, DBP: Diastolic Blood Pressure, SBP: Systolic Blood Pressure, MBP: Mean Blood Pressure

Table 3: Comparison of initial laboratory parameters of deceased and surviving COPD patients

Laboratory parameters	Deceased (n=120) Mean±SD	Surviving (n=58) Mean±SD	P	Total Mean±SD
Uric acid (mg/dL)	9.03±4.32	8.98±3.89	0.945	9.02±4.17
GGT (U/L)	79.00±71.60	66.09±67.94	0.253	74.79±70.50
Leukocyte ($x10^3$/uL)	15.52±7.85	17.15±30.26	0.580	16.05±18.35
Platelet ($x10^3$/uL)	198.93±95.28	241.63±148.27	0.022	212.84±116.56
MPV (fL)	8.51±1.92	7.76±1.84	0.015	8.26±1.92
RDW (%)	16.32±3.71	15.23±3.35	0.062	15.96±3.63
Neutrophile (%)	85.73±13.76	80.25±19.97	0.034	83.95±16.20
Lymphocyte (%)	7.66±8.60	10.69±10.74	0.044	8.64±9.43
NLR ratio	29.5±49.8	17.1±21.4	0.027	25.5±43
CRP (mg/dl)	10.40±10.64	8.15±8.18	0.157	9.67±9.94
Glucose (mg/dl)	166.16±76.36	174.93±117.21	0.550	169.02±91.44
Triglyceride (mg/dl)	141.58±102.40	154.65±128.69	0.516	154.88±111.42
Total cholesterol (mg/dl)	130.96±55.34	132.58±49.49	0.874	131.45±53.42
Creatinine (mg/dl)	1.69±1.26	1.27±0.82	0.024	1.55±1.15
Urea (mg/dl)	61.10±36.08	51.39±32.07	0.083	57.94±35.03
Sodium (mmol/L)	139.73±6.30	141.02±9.75	0.289	140.15±7.60
Potassium (mmol/L)	4.59±1.06	4.59±1.14	0.991	4.59±1.08
Ph	7.29±0.14	7.28±0.12	0.584	7.28±0.14
PaO2 (mmHg)	71.49±44.00	73.60±48.04	0.776	72.23±45.32
PaCO2 (mmHg)	52.94±22.23	47.94±17.99	0.142	51.19±20.93
Lactate	2.64±2.42	2.69±2.19	0.894	2.65±2.33
Bicarbonate	22.01±7.10	20.26±6.43	0.121	21.40±6.90
Base excess	-1.66±9.06	-4.48±8.60	0.055	-2.63±8.98

Table 4: Logistic regression analysis of laboratory characteristics to define deceased among COPD patients

Parameters	Wald	P	OR	95%CI
Platelet ($x10^3$/uL)	1.86	0.172	1.002	0.999-1.005
MPV (fL)	0.81	0.368	0.91	0.741-1.117
RDW (%)	1.53	0.216	0.94	0.852-1.037
NLR ratio	3.08	0.079	0.981	0.961-1.002
Creatinine (mg/dl)	6.17	0.013	0.596	0.397-0.897
Base excess	3.408	0.65	0.958	0.916-1.003

GGT: Gamma-Glutamyl Transferase, MPV: Mean Platelet Volume, RDW: Red cell distribution width
NLR: Neutrophile/Lymphocyte ratio, CRP: C-Reactive Protein

Table 5: Comparison of co-morbid diseases and drug use between two groups

	Deceased % (n=120)	Surviving % (n=58)	P	Total %
Diabetes Mellitus	19.2	17.2	0.757	18.5
Acute ischemic CVA	4.2	5.2	0.761	4.5
Hypertension	29.2	22.4	0.341	27.0
CHF	40.8	19.0	0.004	33.7
Acute Renal Failure	34.2	46.6	0.111	38.2
Chronic Renal Failure	7.5	1.7	0.117	5.6
Sepsis	19.2	10.3	0.135	16.3
Inotropic support	22.5	10.3	0.050	18.5
Insulin use	11.7	5.2	0.167	9.6
ACE inhibitor use	20.0	19.0	0.871	19.7
Diuretic use	51.7	63.8	0.127	55.6
Beta-blocker use	7.5	5.2	0.562	6.7
Total CVA	10.8	12.1	0.807	11.2
CAD	19.2	13.8	0.376	17.4
PHT	76.2	86.2	0.332	79.8
Malignancy	5.0	1.7	0.292	3.9
Pulmonary embolism	5.8	5.2	0.004	5.6
Atrial fibrillation	17.5	31.0	0.041	21.9
Post-CPR	14.2	1.7	0.010	10.1
Statin use	10.8	13.8	0.566	11.8
Post-op care	2.5	12.1	0.009	5.6
Pneumonia	30.0	20.7	0.162	27.0
GI bleeding	5.8	3.4	0.496	5.1

Table 6: Logistic regression analysis of co-morbid diseases to define deceased among COPD patients

Parameters	Wald	P	OR	95%CI
CHF	5.98	0.014	2.783	1.225-6.323
Inotropic support	2.41	0.120	2.468	0.789-7.717
AF	3.86	0.049	0.45	0.203-0.998
Post-cpr	3.46	0.063	8.895	0.889-88.983
Post op. care	8.51	0.004	0.070	0.012-0.417

PHT: Pulmonary Hypertension, CAD: Coronary Artery Disease, Post- CPR: Post- cardiopulmonary resuscitation, Post-op care: Postoperative care, CVA: Cerebrovascular accident, AF:Atrial Fibrillation, CHF:Congestive Heart Failure, GI bleeding: Gastrointestinal bleeding