Clinical phenotype as a predictor of outcome in mechanically ventilated chronic obstructive pulmonary disease patients

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Background The outcome in patients with chronic obstructive pulmonary disease (COPD) who need mechanical ventilation (MV) is altered by several factors such as severity of the disease, severity of acute exacerbation, advanced age, the cause of exacerbation, and development of complications.

Aim This study aimed to assess the outcome of clinical phenotypes of MV COPD patients who were admitted to the respiratory ICU in 2014 and the influencing factors.

Patients and methods This prospective study included 106 MV COPD patients. All patients underwent a thorough medical history, routine and specific investigations including: chest radiography, high-resolution computed tomography, serum immunoglobulin E, total and differential leukocytic count, serial arterial blood gases immediately before intubation, during MV and just before weaning.

Results There were many predictors of bad outcome with statistical significance such as: older age (62.94±12.5 vs. 57.81±12.6 years), higher temperature on admission (37.48 ±0.67 vs. 37.20±0.42°C), higher serum of HCO_3 on admission (42.5±4.5 vs. 38.9±7.8 mEq/l), longer duration of MV (12.05±4.4 vs. 4.8±1.84 days), higher last year number of exacerbations (1.94±0.9 vs. 1.47±0.6 times), with shorter duration from last exacerbation (40.4±1.2 vs. 50.5±2.04 days), dyspnea as the main presenting symptom, past history of MV, occurrence of complications during MV, emphysema phenotype (52.7 vs. 22.8%).

Conclusion Past history of MV, emphysema phenotype, duration of MV, higher last year number of exacerbations, and shorter duration since the last exacerbation are reliable predictors of poor outcome and mortality in MV COPD patients with acute on top of chronic respiratory failure.

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Introduction

The outcome of these patients with chronic obstructive pulmonary disease (COPD) who need invasive mechanical ventilation (MV) is altered by several factors such as the severity of the underlying lung disease, severity of acute illness, advanced age, and development of ventilator-related complications [1,2].

It was reported that the development of ventilator-associated pneumonia (VAP) was not only one of the determinants of prolonged MV but also was responsible for increased mortality. The need for MV beyond 72 h and the occurrence of extubation failure also portends a worse prognosis [1,3].

The estimated mortality rate of COPD patients who need invasive MV ranged from 6 to 24% [4]. It is known that reintubation worsens the outcome and considered a marker of severity of the disease [5]. We hypothesized that clinical phenotype may be a predictor of outcome in MV COPD patients.

The aim of the current study was to assess the factors influencing the outcome of MV COPD patients admitted to respiratory ICU (RICU), Zagazig University Hospitals in 2014.

Patients and methods

This prospective observational study included 106 MV COPD patients admitted to RICU at Zagazig University Hospitals during the period from November 2013 until January 2015. The study protocol was approved by the Institutional Review Board of Zagazig University; all patients or their relatives had signed an informed consent.

For all patients the following were done: thorough medical history, history of atopic manifestations (dermatitis, allergic rhinitis), frequency of exacerbation in the last year, past history of MV, medications used for COPD, patient compliance for medications and the presence of comorbidities.

Radiological evaluation: chest radiography (postero-anterior and lateral views), high-resolution computed tomography (HRCT) was done for those with

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manifestation of hyperinflation in chest radiography (emphysematous pattern).

Laboratory investigations: complete blood count, erythrocyte sedimentation rate, C-reactive protein, serum albumin, phosphorus, magnesium, serum total immunoglobulin (Ig)E, peripheral blood total, and differential leukocytic count for eosinophil count for (please revise) those with a history suggestive of allergic rhinitis or atopic dermatitis, sputum (tracheal aspirate) culture and sensitivity, and eosinophilic count, serial arterial blood gases (ABGs) immediately before intubation, during the period of MV and at the onset of weaning from MV.

Recent echocardiography or old one if done within the period between the current and previous exacerbation

Spirometric pulmonary function tests, post recovery if not available.

Determination of COPD phenotype was done according to Celli *et al.* [6], Lancelot *et al.* [7], and Mair *et al.* [8].

An assessment of complications of MV, the length of ICU stay, duration of MV, different trials of weaning from MV, and the outcome were made.

Successful weaning and extubation were reported as good outcome, while reventilation, reintubation, or deaths were reported as bad outcomes.

Statistical analysis

(1) Data were entered, checked, and analyzed using Epi-Info version 6 and SPSS for Windows, version 11.0 (SPSS Inc., Chicago, IL, USA). Data were summarized using the arithmetic mean and the SD.
(2) Analysis of variance (ANOVA of *F* test): for comparison of means of more than two groups, the significance level (*P* value) of '*F*' was obtained from '*F*' tables. If the value is significant, the least significant difference is calculated at different probability values as follows:
(3) χ^2-Test, used to find the association between raw and column variables:
    (a) Kruskal–Walis test is equivalent to χ^2: it is used when the Bartelet test of variance shows that it is not homogeneous and when it is so different the nonparameteric result was considered.
    (b) Student's *t*-test: compare difference between two groups.
    (c) Regression analysis, multiple logistic regression analysis, along with backward stepwise analysis was performed to examine the correlation between patient characteristics and outcome.
    (d) A *P* value more than 0.05 indicates nonsignificant results; a *P* value of less than 0.05 indicates significant results.

Results

The present study included 106 COPD patients with acute on top of chronic respiratory failure; all were candidates for invasive MV according to GOLD 2014 criteria, they were 34 women and 72 men. Twenty were nonsmokers and 86 were smokers.

Patients were classified into the clinical phenotypes according to the collected clinical, radiological, and laboratory data based on the classification of Celli *et al.* [6], Lancelot *et al.* [7], and Mair *et al.* [8]. Thirty-five patients were found to have emphysematous phenotype, 32 patients had exacerbator phenotype, 14 patients showed chronic bronchitic phenotype, and the remaining 25 patients were found to have mixed asthma COPD overlap phenotype.

Patients were further assigned according to the outcome of MV into two groups; group1 (good outcome) included 70 patients who were successfully weaned and group 2 (bad outcome) that included 36 patients with failed weaning after the initial spontaneous breathing trial (SBT); 33 of them died while on MV and three were weaned thereafter.

A comparison between bad and good outcome groups showed that bad outcome group patients were significantly of older age (62.94±12.5 vs. 57.81±12.6 years, $P<0.05$), with higher temperature (37.48±0.67 vs. 37.2±0.42°C, $P<0.05$), higher level of HCO_3 (42.5±4.5 vs. 38.9±7.8 mEq/l, $P<0.05$) on admission than those of good outcome group patients, and had a positive history of MV, and history of complications on MV (Table 1).

The bad outcome group patients spent longer days on MV (12.05±4.4 vs. 4.8±1.84, $P<0.05$), with shorter duration from last exacerbation (40.4±1.2 vs. 50.5± 2.04, $P<0.05$) and higher last year number of exacerbations (1.94±0.9 vs. 1.47±0.06, $P<0.05$) (Table 2).

Table 1 Demographic, clinical, laboratory, pulmonary function test, arterial blood gases (before intubation) in the studied groups

	Bad outcome (*N*=36) [*n* (%)]	Good outcome (*N*=70) [*n* (%)]	χ^2	*P*
Sex				
Female	8 (22.2)	26 (37.1)	2.4	>0.05
Male	28 (77.8)	44 (62.9)		
Age	62.94±12.5	57.81±12.6	–2.19[a]	<0.05*
Smoking				
Nonsmoker	4 (11.1)	16 (22.9)	2.1	>0.05
Smoker	32 (88.9)	54 (77.1)		
Peripheral blood eosinophils				
High	0 (0.0)	25 (35.7)	16.8	<0.05**
Normal	36 (100.0)	45 (64.3)		
History of allergic rhinitis				
Absent	36 (100.0)	45 (64.3)	16.8	<0.05**
Present	0 (0.0)	25 (35.7)		
History of atopic dermatitis				
Absent	36 (100.0)	45 (64.3)	16.8	<0.05**
Present	0 (0.0)	25 (35.7)		
IgE				
High	0 (0.0)	25 (35.7)	16.8	<0.05**
Normal	36 (100.0)	45 (64.3)		
Sputum eosinophils				
High	0 (0.0)	25 (35.7)	16.8	<0.05**
Normal	36 (100.0)	45 (64.3)		
Last year number of exacerbations				
I	17 (47.2)	41 (58.6)	20.2	<0.05**
II	5 (13.9)	25 (35.7)		
III	13 (36.1)	4 (5.7)		
IV	1 (2.8)	0 (0.0)		
Past history of MV				
Absent	11 (30.6)	67 (95.7)	51.92	<0.05**
Present	25 (69.4)	3 (4.3)		
Complications				
Not complicated	20 (55.6)	59 (84.1)	10.33	<0.05**
Complicated	16 (44.4)	11 (15.7)		
Respiratory rate (beats/min)	27.55±3.1	28.08±2.4	–0.955[a]	>0.05
Heart rate (beats/min)	98.2±13.2	96.2±13.5	0.711[a]	>0.05
Temp (deg.)	37.48±0.67	37.2±0.42	2.003[a]	<0.05*
White blood cell (cell/mm^3)	14.58±4.2	13.08±4.1	1.741[a]	>0.05
Hb (g/dl)	13.63±2.3	12.8±1.9	1.796[a]	>0.05
Platelet	233.69±46.8	231.5±48.2	0.222[a]	>0.05
FEV1/FVC	49.3±9.3	50.58±6.9	–0.792[a]	>0.05
FEV1	59.3±11.6	62.6±11.2	–1.442[a]	>0.05
pH	7.26±0.04	7.2±0.04	0.761[a]	>0.05
$PaCO_2$	92.36±9.4	93.3±8.2	–0.770[a]	>0.05
PaO_2	51.3±6.9	51.2±8.7	0.080[a]	>0.05
HCO_3	42.5±4.5	38.9±7.8	2.507[a]	<0.05*
SaO_2	68.6±11.2	70.5±12.3	–0.756[a]	>0.05
K	3.4±0.4	3.3±0.4	0.261[a]	>0.05

FEV1, forced expiratory volume in the first second; FVC, forced vital capacity; Hb, hemoglobin; IgE, immunoglobulin E; MV, mechanical ventilation; PLT, platelet; [a]*t*-Test. *,**, significant values.

Table 2 Mechanical ventilation and exacerbation history in both studied groups

	Bad outcome (*N*=36)	Good outcome (*N*=70)	*t*	*P*
Duration of MV (days)	12.05±4.4	4.8±1.84	11.551	<0.05**
Duration from last exacerbation (days)	40.4±1.2	50.5±2.04	3.443	<0.05**
Last year number of exacerbations	1.94±0.9	1.47±0.06	3.053	<0.05*

MV, mechanical ventilation. *,**, significant values.

Regarding the clinical phenotypes, emphysema phenotype was more prevalent among the bad outcome group patients than in the good outcome group (52.7 vs. 22.8%, $P<0.05$), while the other clinical phenotypes were more prevalent in the good outcome group (20 exacerbator phenotype patients vs. 12 in the bad outcome group, nine chronic bronchitic phenotype patients vs. five in the bad outcome group, 25 mixed asthma COPD overlap patients vs. zero patients in the bad outcome group) ($P<0.05$) (Tables 3 and 4 and Fig. 1).

Discussion

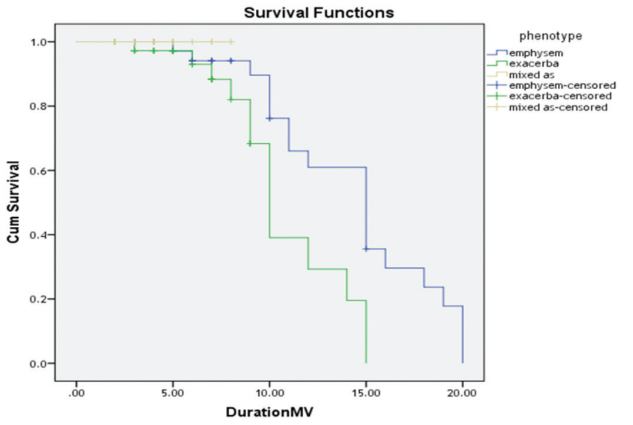
The outcome of patients in acute exacerbation of chronic obstructive pulmonary disease (AECOPD) who need MV was usually altered by several factors such as the degree of the underlying airway disease, severity of acute illness, advanced age and development of VAP during ICU stay [1].

This prospective observational study included 106 MV COPD patients admitted to RICU at Zagazig University Hospitals. Patients were assigned according to the outcome of MV into two groups: group 1 (good outcome) included 70 patients who were successfully weaned and group 2 (bad outcome) that included 36 patients with failed weaning after the initial SBT; 33 of them died while on MV and three were weaned thereafter.

Several studies had evaluated the predictors of outcome in ventilated COPD patients such as clinical, demographic, laboratory data of the studied patients, and complications developed in the ICU.

The study was designed specifically to study the clinical phenotypes of COPD patients in acute on top of chronic respiratory failure requiring ICU admission to assess the impact of the clinical phenotype on the outcome. To our best knowledge, no studies had been done to assess the outcome of ventilated COPD

Figure 1



The cumulative survival function curve demonstrated that survival was better with shorter duration of mechanical ventilation (MV) which was the best in mixed asthma chronic obstructive pulmonary disease patients and worst in emphysema phenotype patients even when centered for these parameters (i.e. after normalization of other factors affecting the outcome).

Table 3 Distribution of clinical phenotypes among the studied groups

Phenotypes	Bad outcome (*N*=36)		Good outcome (*N*=70)		χ^2	*P*
Emphysema phenotype	19	52.7	16	22.8	19.96	<0.05**
Exacerbator phenotype	12	33.3	20	28.5		
Chronic bronchitis phenotype	5	13.8	9	12.8		
Asthma COPD overlap phenotype	0	0	25	35.7		

COPD, chronic obstructive pulmonary disease. **, significant values.

Table 4 Multivariate logistic regression analysis of independent predictors of outcome

	B	SE	Wald	Significance	Exp (*B*)	95% CI for Exp (*B*)	
						Lower	Upper
Age	0.112	0.121	0.862	0.353	1.119	0.883	1.418
Sex	−2.300	2.576	0.797	0.372	0.100	0.001	15.614
Chest wheeze	4.477	2.687	1.776	0.096	0.983	0.454	174.928
Serum eosinophil	−14.149	6273.551	0.000	0.998	0.000	0.000	–
Phenotype (emphysema)	1.299	0.984	5.000	0.032*	6.139	1.35	3.254
Last year number of exacerbation	−1.353	3.849	0.124	0.725	0.258	0.000	7.980
Compliance to treatment	−3.977	2.608	2.325	0.127	0.019	0.25	3.110
History of MV	1.654	0.98	4.025	0.042*	5.547	1.021	25.014
Duration of MV (>7 days)	1.791	0.878	4.160	0.041*	5.994	1.072	33.507

CI, confidence interval; MV, mechanical ventilation. *, significant values.

patients in relation to the clinical phenotype of COPD patients.

Although more than one phenotype can exist in the same patient, in the present study, we tried as much as possible to classify patients using the available clinical, radiological, and laboratory data into the most predominant phenotype. Previous studies focused on the outcome of ventilated AECOPD patients regarding the severity of the acute illness, presence of comorbidities, and even the presence of metabolic abnormalities which could directly affect the outcome of ventilated AECOPD patients, rather than the natural history of such progressive disease.

In the present study; there was a statistically nonsignificant difference between bad and good outcome groups regarding sex ($P>0.05$) with an overall male predominance among both groups (44 vs. 26 in good outcome and 28 vs. 8 in bad outcome). This finding could be due to the higher prevalence of smoking, outdoor exposure to risk factors, and consequently development of COPD among men.

On the other hand, there was a statistically significant difference between both groups regarding age where the bad outcome group patients were older ($P<0.05$). This finding may be the result of the nature of COPD as a chronic and progressive disease where the rate of decline of lung functions especially the forced expiratory volume in the first second (FEV1) will be more in older patients and more severe disease, more exacerbations, more respiratory muscle fatigue, and less respiratory reserve, thus the patients have less ability to tolerate spontaneous breathing and hence difficult weaning from MV. The findings were consistent with El-Qusy *et al.* [9] who reported that several predictors can affect the outcome of COPD patients on MV, including age, failure of several trials of weaning, presence of VAP, presence of tracheotomy and prolonged MV duration. In contrast, Richard *et al.* [10] have found that those who were successfully weaned were older than those who failed to wean. This finding may be due to the fact that most of those who were successfully weaned, although older, were with less comorbidities than the other group who failed to be weaned.

Regarding clinical and laboratory parameters, there were statistically nonsignificant difference between both groups regarding heart rate, respiratory rate, white blood cells, and platelet counts ($P>0.05$). On the other hand, temperature was higher in the bad outcome group of patients than the good outcome group ($P<0.05$); the higher temperature on admission may reflect the severity of infection as a cause of exacerbation or could be the first sign of systemic inflammatory response syndrome which may explain the worse prognosis in such group.

Regarding the pulmonary function tests and ABGs in both studied groups, the present study showed statistically nonsignificant differences regarding pulmonary functions and ABG parameters ($P>0.05$) except for HCO_3 which was higher in the bad outcome group than in the good outcome group of patients ($P<0.05$). The high HCO_3 in the bad outcome group is a reflection of the chronicity of CO_2 retention in such group of patients, long history of hypoventilation, and poor respiratory muscle reservoir, which could be responsible for their inability to tolerate SBT and therefore their need for longer time of MV and difficult weaning. El-Qusy *et al.* [9] have reported that among all ABG parameters, only $PaCO_2$ before intubation differed significantly between survivors and nonsurvivors (92.6±14.9 vs. 81.0±18.2, respectively, $P=0.025$). In this study HCO_3 was higher in the bad outcome group, since the high level of HCO_3 is a reflection of the kidneys' compensation for elevated $PaCO_2$, which is variable from patient to patient regarding the time of occurrence and the kidney performance of each patient.

In contrast to the present study, Hill *et al.* [11] have reported that HCO_3 was higher in those who survived than those who did not survive (27 vs. 23 mmol, respectively), this finding could be attributed to the poor kidney function in the nonsurvivor group of patients since most of the comorbidities recorded in these groups were renal impairment.

Regarding the duration of MV and last year number of exacerbations;the present study showed statistically significant differences between both groups as they were higher in the bad outcome group than in the good outcome group. Also interval from last exacerbation was significantly shorter in bad outcome group than in good outcome group. These findings indicated the severity of the disease in the bad outcome group. Another fact is the last year number of exacerbations which was higher in the bad outcome group reflects not only the poor pulmonary reserve and resistance to infection but also the poor compliance to treatment. Also the interval passed since last exacerbation was shorter in the bad outcome group as a sequence of the higher number of exacerbation/year in this group and it is known that FEV1 needs

more than 8–12 weeks to return to the pre-exacerbation level, and the short time since the last exacerbation does not allow enough time for respiratory muscles to get rest between the burden and the load of exacerbation during which the work of breathing is much more increased. The finding of the present study was in agreement with that of Michael *et al.* [3] who reported that the mean duration of MV in COPD exacerbation survivors was 3.5 days versus a mean of 21 days for nonsurvivors.

Regarding the collected clinical and laboratory parameters in both studied groups; there were statistically nonsignificant differences in both groups regarding smoking habit and its degree ($P>0.05$), but there were statistically significant differences in both groups regarding:

(1) Cough and chest wheeze which were present more in the good outcome group ($P<0.05$).
(2) Dyspnea, which was present more in the bad outcome group ($P<0.05$).
(3) History of allergic rhinitis andatopic dermatitis were more frequent in the good outcome group ($P<0.05$).
(4) Last year number of exacerbations was more frequent in the bad outcome group ($P<0.05$).
(5) Past history of MV was more common in the bad outcome group ($P<0.05$).
(6) Compliance to treatment was less common in the bad outcome group ($P<0.05$).
(7) Complications of MV were more frequent in the bad outcome group ($P<0.05$).
(8) Peripheral blood and sputum eosinophils and serum IgE were higher in the good outcome group ($P<0.05$).

The predominance of cough and chest wheeze in the good outcome group could be attributed to higher prevalence of mixed asthma COPD phenotype (25 patients), the chronic bronchitis phenotype (nine patients), and some of the exacerbator phenotype among this group, which are characterized by the presence of chest wheezes and cough during their natural history and during their exacerbation phase. On the other hand, dyspnea was the dominant symptom at the bad outcome group, which included most of the emphysema patients (19 out of 30 patients) as dyspnea is the main complaint of the emphysema phenotype patients during their natural history, which worsens during the exacerbation phase.

Among the collected data to determine the predominant clinical phenotype, the present study showed high predominance of allergic rhinitis, atopic dermatitis, peripheral blood and sputum eosinophilia and elevated serum IgE among the good outcome group in whom the mixed asthma COPD phenotype constitutes the majority of patients.

Regarding the prevalence of clinical phenotypes among both groups the present study showed that mixed asthma COPD phenotype was the predominant phenotype among the good outcome group [25 (35.7%) patients in the good outcome vs. 0 patients among the bad outcome group, followed by exacerbator phenotype 20 (28.5%) patients in the good outcome group vs. 12 (33.3%) patients in the bad outcome and chronic bronchitic phenotype nine (12.8%) patients in the good outcome group vs. five (13.8%) patients in the bad outcome group]. On the other side, emphysema phenotype showed the worst outcome [19 (52.7%) patients in the bad outcome group vs. 16 (22.8%) patients in the good outcome group]. There was statistically significant difference between both groups regarding the clinical phenotype prevalence ($P<0.05$).

In this study, multivariate analysis logistic regression for the detection of independent predictors of outcome showed that among all clinical and laboratory parameters, clinical phenotype (Wald=0.5, $P=0.032$), history of MV (Wald=4.025, $P=0.042$) and longer duration of MV (Wald=4.16, $P=0.041$) were the most significant independent predictors of bad outcome (upper and lower confidence interval were 3.25–1.35 for emphysema phenotype, 25.014–1.021 for history of MV, and 33.507–1.072 for the duration of MV >7 days).

The cumulative survival function curve confirmed the same finding and showed that the survival of patients increases with shorter duration of MV and the best prognosis and survival was in mixed asthma COPD patients as they have the least duration of MV, while the worst was emphysematous patients with the longest duration on MV.

The better outcome of the asthma COPD mixed phenotype patients in the present study was attributed to more than one factor: first, these groups of patients were younger with greater reversibility in their airway obstruction. Second, they were with less number of exacerbation per year which means less airway remodeling and less residual airway inflammation post each exacerbation and lastly, they were more compliant to treatment, a factor that keeps those patients at lower risk of frequent exacerbation

and less need to systemic steroid and less frequent systemic manifestations of steroid therapy which keep their respiratory muscle in a good status enabling them to be weaned faster with shorter duration and fewer complications of MV.

Emphysema phenotype patients showed the worst outcome because of their poor pulmonary reserve, poor compliance to treatment, frequent exacerbations, and week body built and poor muscle power. All these factors made these patients in need for prolonged ventilatory support during their exacerbation and more prone for complications of MV and consequently poor outcome and even at greater risk of mortality.

Regarding the mortality rate in this study, among the 36 patients constituting the bad outcome group, three patients were able to be weaned after failure of the first SBT and 33 patients died while on MV, comparison between survivors (70 patients with good outcome after the first SBT + three patients passed the second and third SBT) and those patients who died (33 patients, after exclusion of three patients from the 36 in the bad outcome group) showed no additional findings rather than the previous finding that was reported when comparing the good with the bad outcome groups except that the nonsurvivors were of older age (data not shown).

This present study recorded a mortality rate of 31%, which was comparable to the findings of Mair *et al.* [6] and El-Qusy *et al.* [9]. While Milo *et al.* [12] reported a mortality rate of 36% and Chua *et al.* [13] reported a mortality rate of 40% among MV COPD patients, these slightly higher rates could be attributed to the mean ages of patients included in their studies (71±12.4 and 74±9.4 years, respectively, which were older than the patients included in the present study (63.33±12.9 years).

Conclusion

The present study reported that past history of MV, emphysema clinical phenotype, duration of MV, higher number of exacerbation in the last year, and shorter duration since the last exacerbation are reliable predictors of poor outcome and mortality in MV COPD patients with acute on top of chronic respiratory failure.

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Conflicts of interest

There are no conflicts of interest.

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