

Outcome of short-term systemic steroid therapy in chronic obstructive pulmonary disease patients with acute exacerbation

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Background There are insufficient data on the optimum duration of systemic steroid therapy during acute exacerbation of chronic obstructive pulmonary disease (COPD).

Aim To evaluate the outcome of short-term systemic steroid therapy in patients hospitalized with acute exacerbation of COPD and to identify factors associated with treatment failure.

Patients and methods Fifty severe and very severe COPD patients with acute exacerbation were consecutively included in this study. Patients were assessed by a clinical symptom score, peak expiratory flow rate (PEFR), arterial blood gases and laboratory investigations [blood count indices, high sensitive C-reactive protein, erythrocyte sedimentation rate (ESR) and fibrinogen level]. Short-term systemic steroids were initiated and the outcome was assessed at day 5 of therapy and the patients were classified into treatment success group or failure group.

Results Treatment failure was observed in 27 (54%) of patients. Patients with treatment failure had significantly higher cough and chest tightness scores, higher partial pressure of CO₂ in arterial blood (PaCO₂), lower partial pressure of O₂ in arterial blood (PaO₂), lower PEFR, higher red distribution width (RDW), and higher ESR compared with the success group. By binary logistic regression, higher

PaCO₂, lower PaO₂, and higher ESR were independent risk factors associated with treatment failure. The optimum cutoff level of PaCO₂, PaO₂, and PEFR associated with treatment failure was more than or equal to 59.5 mmHg, up to 43.5 mmHg, and up to 225 l/min, respectively. ESR first hour of at least 35 and RDW of at least 15.5% were also associated with treatment failure.

Conclusion Most severe and very severe COPD during acute exacerbations need prolonged course of systemic steroids (>5 days). Clinical evaluation, gasometric parameters, PEFR, RDW, and ESR could be good predictors of treatment failure on short-term systemic steroid.

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Introduction

Chronic obstructive pulmonary disease (COPD) is a common preventable and treatable disease, characterized by airflow limitation and persistent respiratory symptoms that is usually progressive and is associated with an enhanced chronic inflammatory response in the airways to noxious particles or gases [1]. During the course of the disease, periods of exacerbations or flares up may occur [2]. During exacerbations, inflammatory markers such as tumor necrosis factor- α [3,4] and inflammatory cells such as neutrophils [5], eosinophils [6], and cluster of differentiation 4 (CD4) cells [7] are collected in the respiratory system causing local inflammation. The markers of systemic inflammation also increase. The fibrinogen level is increased when purulent sputum is observed during exacerbations [8]. The C-reactive protein (CRP) levels are also increased in bacterial acute exacerbation of chronic obstructive pulmonary disease (AECOPD) [9].

There were strong evidence that systemic corticosteroids in COPD exacerbations improve FEV₁, arterial hypoxemia, decrease hospital stay, and

decrease the incidence of treatment failure. Oral prednisolone at a dose of 30–40 mg (or equivalent) is preferred as daily therapy during exacerbations [1]. However, there are insufficient data concerning the optimum duration of systemic steroid therapy during COPD flare-up.

Aim

To evaluate the outcome of short-term systemic steroid therapy (≤ 5 days) in COPD patients hospitalized with acute exacerbation and to identify factors associated with treatment failure.

Patients and methods

This prospective study was carried out in the Department of Chest Diseases, Faculty of Medicine, Assiut University

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Hospital during the period from October 2015 to October 2016. COPD patients hospitalized with acute exacerbation were consecutively enrolled in this study. The study was approved by the Faculty of Medicine Ethics Committee, Assiut University.

Study design

Fifty COPD patients [diagnosed by spirometry ($FEV_1/FVC < 70\%$ within 6 months)] [1] hospitalized with acute exacerbation were consecutively enrolled in this study. Anthonisen's Winnipeg criteria [10] were used to define COPD exacerbation into either type I, type II, or type III. All patients received short-term steroid (40 mg *prednisolone* or equivalents for 5 days) [11], controlled oxygen therapy, inhaled B2 agonist, ipratropium bromide, and systemic antibiotics [12].

Exclusion criteria

- (1) COPD overlapped with either bronchial asthma, interstitial lung diseases, and obstructive sleep apnea syndrome.
- (2) COPD associated with pneumonia.
- (3) COPD patients in whom systemic corticosteroids were contraindicated.
- (4) COPD patients who used home systemic steroids in the last 4 weeks before admission.

Assessment of the study group

COPD patients underwent clinical, gasometric, functional, bacteriological, and laboratory assessment.

Clinical assessment

Data on demographic variables (age of the patient, sex, smoking history) and the presence of cor-pulmonale or comorbidities such as diabetes mellitus and hypertension were recorded on admission to hospital.

Clinical assessment score was used to assess COPD exacerbation severity [13]. It includes four symptom scores: shortness of breath score, cough score, chest tightness score, and the nighttime awaking score. Each of which takes a score according to the severity grading from 0 to 4. The total score was calculated as the sum of all scores and equals 16. With a score of 16 being the worst and a score of 0 being the best. Each symptom score and the total score were recorded at day 1 and 5 after initiation of treatment [13].

Gasometric assessment

ABGs were obtained at room air using heparinized blood sample and were analyzed using blood gas analyzers (Rapid lab850; CHIRON/Diagnostics; critical care systems, Medfield, MA, USA).

Functional assessment

PEFR (Using Clement Clarke International the Mini-Wright Peak Flow Meter) was applied for monitoring of patients' pulmonary function at day 1 and 5 of the study period.

Bacteriological assessment

Sputum samples were collected early in the morning in sterile containers and sent to the laboratory. Samples were then cultured using blood agar to show the characteristic colonies. Then identification was made by various serological or biochemical tests. According to sputum culture, the patients were classified into: class A; class B, and class C [14].

Laboratory assessment

For evaluation and monitoring of systemic inflammation during exacerbation, laboratory investigations including blood count indices, high sensitive CRP, erythrocyte sedimentation rate (ESR), and fibrinogen level were collected at day 1 and day 5 of the study period. All venous samples were processed from 1 to 6 h. For the evaluation of blood indices, 2 ml of venous blood was placed in standard tubes containing K3 EDTA. The samples were processed within 1 h to minimize bias variation due to possible sample aging. ESR were measured using the Westergren method where the rate of sedimentation of RBCs in a column of blood was recorded at the first hour and second hour. Using the CardioPhase high sensitivity CRP device, 3 ml of venous blood was put in a serum separator tube containing polystyrene particles coated with monoclonal antibodies specific to human CRP. These particles when mixed with the samples aggregated and emitted a beam of light in proportion to the concentration of the CRP in the sample. Serum fibrinogen levels were also detected using the electromagnetic mechanical clot detection/radial immunodiffusion method.

Outcome assessment

At day 5 of treatment of AECOPD, treatment failure was defined by the presence of anyone of the following: persistence or deterioration of symptoms, appearance of new symptoms, need for noninvasive ventilation, ICU admission, or occurrence of death [15].

Statistical analysis

Statistical package for the social sciences (SPSS) program, version 20 for Windows was used for statistical analysis of the results in this study. Data were analyzed by nonparametric tests. The predictors of short-term systemic steroid therapy failure in AECOPD was done using binary logistic regression.

Results will be considered significant with a *P* value of less than 0.05. Receiver operating characteristic curve was applied to determine the optimum cutoff level of gasometric, functional, and laboratory parameters associated with treatment failure.

Results

This study included 50 severe and very severe COPD patients hospitalized with acute exacerbation. Sixty-four percent of the included patients were men, with a mean age of 60.96 ± 9.08 and 14% of them were current smokers. According to response to systemic steroids, 27 (54%) of the patients were classified as the treatment

failure group and 23 (46%) as the treatment success group. Demographic and clinical data of the two groups are presented in Table 1. There was no significant difference between treatment failure and success groups as regards age, sex, GOLD stage, sputum culture, and type of exacerbation.

On univariate analysis between the two groups, patients with treatment failure were significantly presented with higher cough and chest tightness scores compared with the treatment success group (3.1 ± 0.7 vs. 2.6 ± 0.7 , $P=0.012$; 2.9 ± 0.6 vs. 2.5 ± 0.2 , $P=0.003$, respectively). They had a significantly higher partial pressure of CO_2 in the arterial blood

Table 1 Demographic and clinical data of treatment failure and treatment success groups among chronic obstructive pulmonary disease patients

	Treatment failure group (<i>n</i> =27) [<i>n</i> (%)]	Treatment success group (<i>n</i> =23) [<i>n</i> (%)]	<i>P</i> -value
Age (mean \pm SD) (years)	62 \pm 8.2	59 \pm 9.8	0.771
Sex			
Female	9 (33)	9 (39)	0.440
Male	18 (66)	14 (60)	0.448
Gold stage			
III	10 (37)	8 (34)	0.670
IV	17 (62)	18 (78)	0.771
Sputum culture			
Class A	9 (33)	14 (60)	0.356
Class B	12 (44)	8 (34)	0.304
Class C	6 (22)	1 (4)	0.312
Winnipeg score			
Level I	10 (37)	8 (34)	0.584
Level II	14 (51)	10 (43)	0.583
Level III	3 (11)	5 (21)	0.521
Comorbidities			
DM	22 (81)	14 (60)	0.126
HTN	10 (37)	7 (30)	0.767
Cor-pulmonale	21 (77)	12 (52)	0.076
IHD	4 (14)	1 (4)	0.357

DM, diabetes mellitus; HTN, hypertension; IHD, ischemic heart disease.

Table 2 Baseline clinical, gasometric, and functional parameters of treatment failure and treatment success groups among chronic obstructive pulmonary disease patients

	Treatment failure group (<i>n</i> =27) (mean \pm SD)	Treatment success group (<i>n</i> =23) (mean \pm SD)	<i>P</i> -value
Clinical symptom score			
Shortness of breath score	3.3 \pm 0.6	3.4 \pm 0.5	0.452
Cough score	3.1 \pm 0.7	2.6 \pm 0.7	0.012*
Chest tightness score	2.9 \pm 0.6	2.5 \pm 0.2	0.003*
Nighttime awaking score	2.9 \pm 0.6	2.5 \pm 0.8	0.099
Total score	11.9 \pm 2.1	11.5 \pm 1.9	0.430
Gasometric parameters			
pH	7.35 \pm 0.05	7.38 \pm 0.08	0.038*
PaCO ₂ (mmHg)	67 \pm 11.3	52 \pm 15	0.002*
PaO ₂ (mmHg)	39 \pm 5.2	49 \pm 12	0.001*
SaO ₂ (%)	72 \pm 7.1	80 \pm 12.4	0.005*
Functional parameters (PEFR) (l/min)	228 \pm 69	269 \pm 69	0.028*

PaCO₂, partial pressure of CO₂ in arterial blood; PaO₂, partial pressure of O₂ in arterial blood; PEFR, peak expiratory flow rate; SaO₂, oxygen saturation in the arterial blood; *Significant.

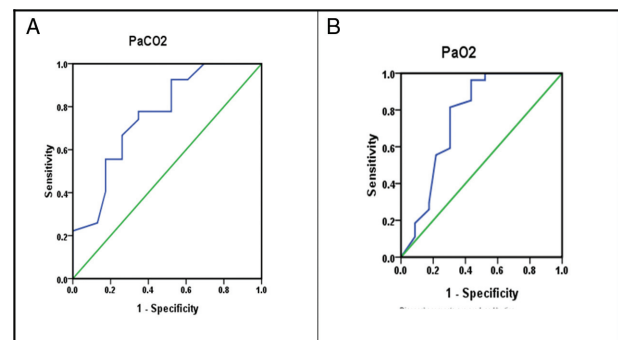
(PaCO₂), but lower partial pressure of O₂ in the arterial blood (PaO₂) compared with the success group (67±11.3 vs. 52±15, $P=0.002$; 39±5.2 vs. 49±12, $P=0.001$, respectively). Functionally, the treatment failure group had significantly lower PEFR compared with the success group (228±69 vs. 269±69, $P=0.028$) (Table 2). Regarding laboratory parameters, red distribution width (RDW), ESR first, and ESR second hours were significantly higher in the treatment failure group compared with the success group (17.8±4.1 vs. 15±4, $P=0.021$; 40.6±20 vs. 28.6±15.6, $P=0.036$; 55.7±21.9 vs. 41.9±19.1, $P=0.016$) (Table 3). Also baseline CRP and fibrinogen levels were higher in the treatment failure than the treatment success group, but the result does not reach significance difference.

However by binary logistic regression, higher PaCO₂, lower PaO₂, and higher ESR were independent risk factors associated with treatment failure with short-term steroid therapy in AECOPD (Table 4).

Receiver operating characteristic curve was done to evaluate the optimum cutoff level of gasometric, functional, and laboratory parameters associated with treatment failure. The optimum cutoff level of

PaCO₂ associated with treatment failure was at least 59.5 mmHg with a sensitivity of 77.8% and specificity of 66.2% as shown in Fig. 1a. A PaO₂ of up to 43.5 mmHg was associated with treatment failure with a sensitivity of 81.5% and specificity of 69.6% (Fig. 1b). A PEFR of up to 225 l/min was associated with treatment failure with a sensitivity of 74.1% and specificity of 69.6% (Fig. 2). ESR first hour of at least 35 was associated with treatment failure with a sensitivity of 55.6% and specificity of 74.9% (Fig. 3a). An

Figure 1



ROC curve of optimal cut-off level of PaCO₂ (≥ 59.5) associated with treatment failure with sensitivity of 77.8% and specificity of 66.2% (figure A). ROC curve of optimal cut-off level of PaO₂ (≤ 43.5) associated with treatment failure with sensitivity of 81.5 % and specificity of 69.6% (figure B).

Table 3 Baseline laboratory parameters of treatment failure and treatment success group among chronic obstructive pulmonary disease patients

	Treatment failure $n=27$ (mean±SD)	Treatment success $n=23$ (mean±SD)	P -value
WBCs ($\times 10^3/\mu\text{l}$)	13±5.7	12.1±4	0.533
Eosinophil ($\times 10^3/\mu\text{l}$)	0.59±0.4	0.33±0.46	0.143
Platelet ($\times 10^3/\mu\text{l}$)	272±121	247.8±85	0.704
MPV (fI)	9±2.3	9.5±2.5	0.544
RDW (%)	17.8±4.1	15±4	0.021*
Basophils ($\times 10^3/\mu\text{l}$)	0.13±0.12	0.16±0.15	0.422
ESR first hour (mm/h)	40.6±20	28.6±15.6	0.036*
ESR second hour (mm/h)	55.7±21.9	41.9±19.1	0.016*
CRP (mg/l)	54.1±50.4	48.6±44.2	0.777
Fibrinogen level (g/l)	15.5±7.5	14.2±8.9	0.530

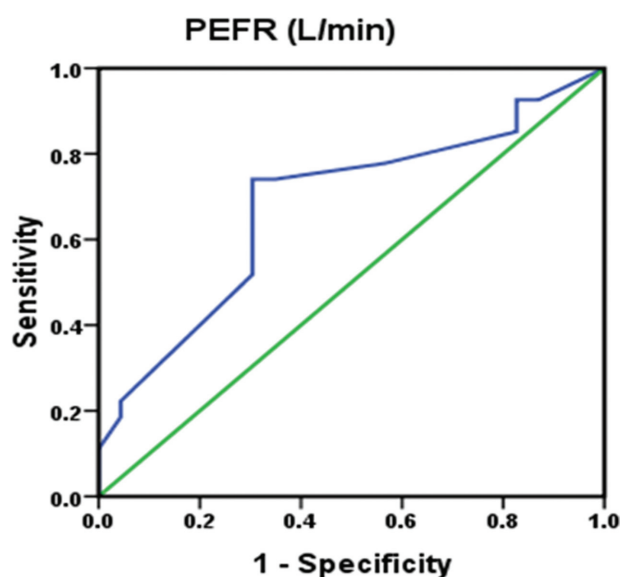
CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; MPV, mean platelet volume; RBCs, red blood cell count; RDW, red blood cells distribution width; WBCs, white blood cell count. *Significant.

Table 4 Predictors of treatment failure among chronic obstructive pulmonary disease patients

	P -value	OR	95% CI	
			Lower	Upper
PaCO ₂ (mmHg)	0.017*	0.818	0.694	0.965
PaO ₂ (mmHg)	0.018*	3.702	1.253	10.939
ESR first hour (mm)	0.040*	1.488	1.012	2.188
RDW%	0.307	0.883	0.697	1.120
PEFR (l/min)	0.098	1.024	0.996	1.053

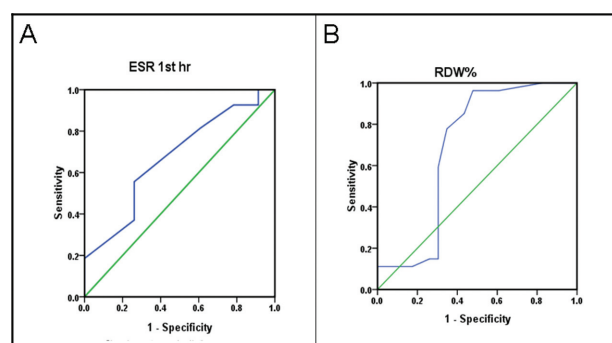
CI, confidence interval; ESR, erythrocyte sedimentation rate; OR, odds ratio; PaCO₂, partial pressure of CO₂ in arterial blood; PaO₂, partial pressure of O₂ in arterial blood; PEFR, peak expiratory flow rate; RDW, red distribution width; SaO₂, oxygen saturation in the arterial blood; *Significant.

Figure 2



ROC curve of optimal cut-off level of PEFR ≤ 225 L/min associated with treatment failure with sensitivity of 74.1 % and specificity of 69.6%.

Figure 3



ROC curve of optimal cut-off level of ESR 1st hour (≥ 35) associated with treatment failure with sensitivity of 55.6% and specificity of 74.9% (figure A). ROC curve of optimal cut-off level of RDW $\geq 15.5\%$ associated with treatment failure with sensitivity of 77.8% and specificity of 65.2% (figure B).

RDW of at least 15.5% was associated with the treatment failure with a sensitivity of 77.8% and specificity of 65.2% (Fig. 3b).

Discussion

COPD is a worldwide prevalent disease [16]. Hospitalized patients with COPD exacerbations are at increased risk of morbidity [17] and expenses related to disease management [18]. There are strong data indicating that systemic corticosteroids are highly indicated in COPD exacerbations. However, there are insufficient data about the optimal duration of corticosteroid therapy during AECOPD. Furthermore, the factors predicting treatment failure during hospitalization have not yet been described. That study

was carried out to evaluate the outcome of short-term systemic steroid therapy (≤ 5 days) in COPD patients hospitalized with acute exacerbation and to identify the factors associated with treatment failure.

In this study, patients of COPD exacerbations using short-term steroid therapy were evaluated. Patients were assessed clinically, functionally, and by gasometric and laboratory markers at day 1 and 5 after initiation of 40 mg systemic steroids. At day 5, the outcome of treatment was assessed. Treatment failure was found in 27 (54%) of the patients with AECOPD. This rate of treatment failure was higher than previously observed in studies. Some studies reported treatment failure by 14.5% [19,20] and others reported [21] a higher rate of failure (about 39%) in the treated group. That variability in outcome could be related to different grades of COPD stages or their exacerbations and the timing of each study identified the treatment failure.

Clinically, patients were evaluated using a clinical symptom score. Patients with treatment failure were significantly presented with higher cough and chest tightness scores compared with the treatment success group. Paradoxically, Crisafulli and colleagues found that the COPD patients with failed short-term steroid therapy had low prevalence of cough at admission. As cough has an essential role in enhancing mucus clearance, it surely has a beneficial impact on the treatment [22]. It is suggested that not absence of cough, but insufficient cough could account for retention of secretions with vicious circle of secondary infection and more deterioration of the condition [23].

On functional assessment of COPD patients, PEFR was used as a method of monitoring during the follow-up study period. Emerman *et al.* [24] have studied the use of peak expiratory flow rate in the emergency department for evaluation of AECOPD and found a good correlation between FEV1 and PEFR. However, Orio *et al.* [25] have found that there was no statistical difference in the response to ED treatment of AECOPD by measuring PEF between patients successfully treated as outpatients and those who were admitted or failed outpatient treatment. But the later study evaluated PEFR in the assessment of outcome of outpatient treatment in ED and not during the whole exacerbation period. So, we could suggest that PEFR could be used as an option for the evaluation of airway obstruction during an exacerbation period. Owing to being a cheap, easy-to-use, and rapid test, PEF can be applied for the monitoring of COPD patients [26].

Regarding laboratory parameters, this study observed that RDW was significantly higher in the treatment failure group compared with the success group. RDW was also shown to be significantly increased in patients with acute exacerbation compared with stable COPD subjects [27]. Deformation of red cell membranes is a known entity in inflammation. Due to the presence of systemic inflammation in COPD patients, inflammatory molecules may interact with erythropoiesis in the bone marrow and stimulate the production of red cells in variable sizes [28].

CRP is also produced by the liver in response to systemic inflammation in COPD exacerbation [29]. Elevated CRP levels are also possibly associated with treatment failure [30] and are independent predictor of prognosis [31] in COPD patients. However, in the present study, no significant differences were observed between the treatment failure group and success group regarding the baseline CRP level. As elevated serum CRP levels are seen with bacterial exacerbation [9], both our groups were presented with bacterial exacerbation, so it could be expected that the two groups were not different. However CRP can be used in monitoring during COPD exacerbation as it is usually elevated at exacerbation and decreased with treatment [32].

The most hopeful blood biomarker in COPD was fibrinogen. Plasma fibrinogen had been variably associated with the risk of COPD progression [33]. The level of plasma fibrinogen was also increased during exacerbations in comparison to stable COPD cases [34]. At day 1 of our study, although the level of fibrinogen is less in the success group than in the failure group, it did not reach significant difference. Its levels needed at least 30 days to return to previous pre-exacerbation levels [35,36].

Conclusion

Most patients with severe and very severe COPD presented with acute exacerbations need prolonged course of systemic steroids (>5 days). Clinical parameters, laboratory parameters such as RDW and ESR, PEFR and gasometric parameters could be good predictors of treatment failure on short-term systemic steroids during AECOPD and on the need for a more prolonged course of steroid therapy. Further studies are recommended to assess short-term systemic steroid in mild and moderate COPD patients with acute exacerbation.

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Conflicts of interest

There are no conflicts of interest.

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