STUDY ON PROGNOSTIC VALUES FOR MORTALITY OF CLINICAL AND SUBCLINICAL FACTORS IN ACUTE EXACERBATION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Nguyen Hai Cong[1], Ta Ba Thang[2]
Nguyen Huy Luc[2], Vu Tung Son[3]

Summary

***Objectives**: To determine the clinical, subclinical characteristics and their prognostic value of mortality in patients with acute exacerbations of chronic obstructive pulmonary disease (AECOPD) to built a CDAPP scale.*

***Subjects and method:** A prospective, cross-sectional observational study on 97 patients with AECOPD were admitted to the Military Hospital 103 from October 2015 to August 2017.*

***Results**: Among a total of 97 patients enrolled in the study, there were 30 deaths (31%). Severe dyspnea (mMRC > 3), confusion, pneumonia, increased serum PCT concentration and an arterial blood gas test with acidosis were significantly independent prognostic factors for death in AECOPD (p < 0.05). We have built a CDAPP score for prognosis of mortality in AECOPD with the combination of these clinical and subclinical factors. CDAPP score > 2 points has the ability to predict the risk of death with a sensitivity of 83.3%, a specificity of 94% and a positive predictive value of 86.2%, a negative predictive value of 92.6%.*

***Conclusion**: Severe dyspnea (mMRC > 3), confusion, pneumonia, increased serum PCT concentration and an arterial blood gas test with acidosis were independent prognostic factors of mortality in AECOPD. CDAPP score had a higher prognostic value for mortality in AECOPD.*

**Keywords: Chronic obstructive pulmonary disease; Acute exacerbation; Prognostic values; Mortality*

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a global burden, with roughly 340 million people worldwide suffering from the disease [1]. Vietnam is one of the countries with the highest prevalence of COPD in the Asia-Pacific region and COPD is the third leading cause of death 4.9%) [2].

Acute exacerbation is a serious event of COPD. Firstly, due to the high mortality rate, it is estimated to range from 2.5 to 30% depending on the sample population. In addition, it also seriously affects the quality of life and lung function decline. A research to improvise a tool that can help with an early, fast, simple prognosis with

[1]*Department of Tuberculosis and Lung Diseases, Military Hospital 175*
[2]*Military Hospital 103,* ***Vietnam Military Medical University***
[3]*Department of Military Epidemiology,* ***Vietnam Military Medical University***
****Corresponding author: Nguyen Hai Cong (nguyen_med@ymail.com)***
Date received: 31/12/2020
Date accepted: 25/2/2021

routine clinical and paraclinical standards is essential in practice [3, 4, 5]. Thus, our study aimed: *To determine the clinical, subclinical characteristics and their prognostic value of mortality in patients with AECOPD.*

SUBJECTS AND METHODS

1. Subjects

97 patients were diagnosed with COPD and hospitalized for AECOPD, treated at the Respiratory Center, Military Hospital 103, Military Medical University, from 10/2015 - 8/2017. Patients were divided to discharge group (Patients have been clinically stable after treatment and discharge from hospital) and death group (In-hospital mortality or discharge by death). Patients with severe heart failure, renal failure, cirrhosis, HIV, pulmonary tuberculosis, extrapulmonary infections were excluded from the study.

2. Methods

***** *Study design:* Prospective, cross-sectional observational sudy.

***** *Data collection:*

Using a convenient sampling method.

Information of patients was collected using a medical form, including: clinical and subclinical characteristics at the admission and discharge.

For death group, in-hospital mortality or request for discharge by death at any point during the hospitalization served as primary end points.

COPD and AECOPD were diagnosed following GOLD guideline (2015) [6].

The tests were conducted at Military Hospital 103 and Military Medical University.

** Ethical issue:* Study has been approved by the Council, all written consent forms were collected.

3. Data analysis

Using SPSS 20.0 statistical software. The qualitative variables were compared by χ^2 test, quantitative variables by Student's t test and ANOVA test. Univariate and multivariate linear regression analysis were applied to determine the prognostic factors of mortality.

RESULTS AND DISCUSSIONS

During 22 months, there were 250 patients hospitalized due to AECOPD. However, 97 patients were enrolled in the study. Males took up the majority in the study (96.9%). The age group of 70 years and over accounted for 57.7%; only 8.2% of patients were under 60 years old. The average age was 72.3 ± 8.1, with the lowest and the highest being 52 and 87 years.

1. Clinical characteristics ~~of clinical~~ in AECOPD

Table 1: Characteristics of clinical symptoms in AECOPD (n = 97).

Symptoms		n	%
Dyspnea	Mild	01	0.01
	Moderate	11	11.3
	Severe	48	49.5
	Very severe	37	38.1
	mMRC	3.2±0.7	
Cyanosis		29	29.9
Edema		23	23.7
Fever		26	26.8
Confusion		23	23.7
Wheeze		85	87.6
Crackles		55	56.7
Emphysema		67	69.1

Severe dyspnea was present in 49.5% and very-severe dyspnea in 38.1%; average mMRC score was 3.2 ± 0.7. Wheeze was 87.6%, crackles: 56.7% and emphysema was 69.1%. Severe symptoms found with high rates in AECOPD was cyanosis and edema.

Table 2: Distribution of treatment outcomes according to severity of the AECOPD.

Outcomes (n = 97)	Severity of AECOPD				Total (n, %)	p
	Non - life threatening		Life-threatening			
	n	%	n	%		
Discharge	52	94.5	15	35.7	67 (69.1)	< 0.01
Death	03	5.5	27	64.3	30 (30.9)	

The death rate in the life-threatening group accounted for 64.3%, and this rate was 5.5% in the non-life-threatening group. The discharge rate in the non-life threatening group was 94.5% and was only 35.7% in the life-threatening group (p < 0.01).

2. Subclinical characteristics in acute exacerbation.

- Complete blood count: Leukocytosis was 54.6% and thrombocytopenia was 10.3%, which are indicators of infection in acute exacerbation.

- Blood biochemical tests: Blood glucose disorders and renal function were encountered at a relatively high rate. Increased serum PCT concentration accounted for 54.6% and serum CRP concentration increased by 68%, which are indicators of inflammation and infection in acute exacerbation.

- Reduced blood oxidation expressed in the reduction of PaO2 (34%) and SaO2 (41.2%) were common. Increased PaCO2 was observed in 47.4%, reflecting chronic respiratory failure in patients with severe COPD. Respiratory acidosis was up to 33%, reflecting a decompensated acid-base balance.

3. Mortality prognostic values of clinical and subclinical factors in acute exacerbation

First, a univariate regression analysis was performed to select factors that significantly affect the risk of death in acute exacerbation. These factors were then included in multivariate analysis to identify valid factors that are independent prognostic risk of mortality.

Table 3: Results of multivariate regression analysis of mortality prognostic values of clinical factors in acute exacerbation.

Factors	OR	p	95%CI	
			Lower	Upper
Duration of disease > 5 years	0.778	0.78	0.13	4.48
Number of acute exacerbation per 12 months	1.13	0.76	0.5	2.6
MRC > 3	0.09	0.03	0.01	0.79
Pulse > 100 beats/minute	1.55	0.62	0.27	8.76
Confusion	0.1	0.024	0.01	0.74
Pneumonia	0.045	0.004	0.006	0.36
Congestive heart failure	0.49	0.42	0.087	2.79

Results of multivariate analysis showed severe dyspnea (mMRC > 3), confusion and pneumonia were the clinical factors that have independent prognostic values for mortality risk in acute exacerbation (p < 0.05).

Severe dyspnea was not only the prognostic factors of death in AECOPD, but it also helps give a prognosis and propose plan of care and support patients after discharge because the majority of patients need assistance requiring oxygen or non-invasive ventilation [4].

Roche N et al. (2008) had three clinical criteria with strong prognosis of the risk of severe morbidity and mortality that can be widely used in practice, including: age over 70 years, severe clinical signs and dyspnea. Among them, confusion and use of accessory respiratory muscles were factors that have independent prognostic values of death in acute exacerbation [3].

The TORCH (2006) study found that fluticasone/salmeterol reduced AE but increased the risk of pneumonia, which led to the perception that acute exacerbation without pneumonia and the one with pneumonia were the other two entities. Since then, pneumonia/COPD has received more attention [7].

Table 4: Results of multivariate regression analysis of mortality prognostic values of subclinical factors in acute exacerbation.

Factors		OR	p	95%CI	
				Lower	Upper
Complete blood count	Leukocytosis	0.818	0.802	0.171	3.927
Blood biochemical tests	Increased creatinine	0.309	0.268	0.039	2.470
	Uremia	0.267	0.106	0.054	1.321
	Increased CRP	2.843	0.372	0.286	28.228
	Increased PCT	0.011	0.001	0.001	0.159
	Increased AST	0.744	0.774	0.099	5.583
	Increased ALT	0.461	0.463	0.059	3.633
	Hyperkalemia	0.511	0.795	0.003	80.868
Artery blood gas	Hypercapnia	0.623	0.578	0.118	3.301
	Acidosis	0.157	0.035	0.028	0.879

Increased serum PCT levels and acidosis were two factors that had independent prognostic values for mortality risk in acute exacerbation ($p < 0.05$).

The increase in serum PCT concentration reflects the severity of the systemic infection. This factor was related to the evolution and negative prognosis in acute exacerbation. Lacoma A et al (2011) found that an increase in serum PCT and CRP concentrations were associated with a poor prognosis in acute exacerbation [8].

Acute respiratory failure and respiratory acidosis are very severe in acute exacerbation, which are the result of severe air exchange disturbance and are manifested by rapid deterioration of respiratory and systemic symptoms. Supportive ventilation for these cases is essential to avoid "fatigue" of the respiratory muscles, increased ventilation and saturation of blood oxygen. Non-invasive auxiliary ventilation is often considered the first choice over intrusive ventilation, helping to avoid the risk of ventilator associated pneumonia [9].

4. Develop a prognostic scale for mortality by combining clinical, subclinical factors

Combining 5 clinical and subclinical factors with independent prognostic values of death in AE into the combined CDAPP scale: Confusion, severe dyspnea (mMRC > 3), acidosis, procalcitonin and pneumonia. The presence of each factor was calculated 1 point respectively and the total score was 5 points.

The mortality rate increased gradually according to CDAPP score, the 3-point group had 58.3% of death and 100% of the CDAPP 4 and 5-point group died. In contrast, there was no mortality in the group of 0 and 1 point. (p < 0.001).

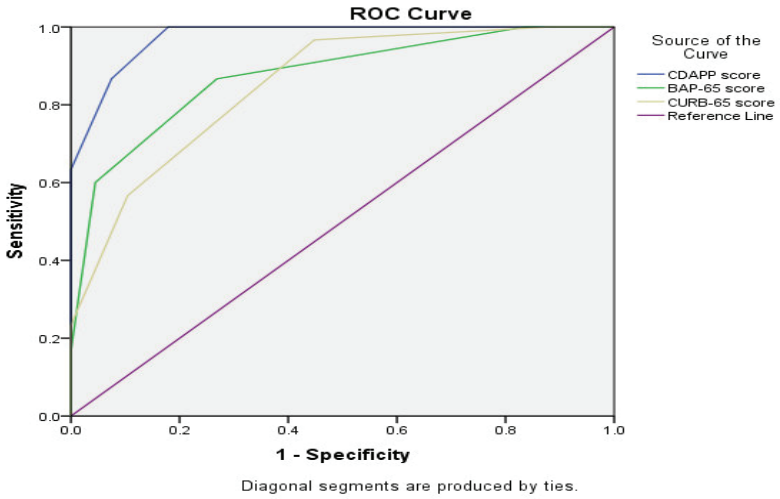

Chart 1: ROC curve comparing mortality prediction ability of the CDAPP and BAP-65, CURB-65 scales.

The area under the curve of the CDAPP scale was 0.974, the BAP-65 was 0.875, and the CURB-65 was 0.85. It showed good prognostic values for these three scales in acute exaberation, especially CDAPP. The cutoff points with the best prognostic value were CDAPP > 2 points, BAP-65 ≥ 3 and CURB-65 ≥ 2 points.

Table 5: Prognostic values for mortality of CDAPP, BAP-65, CURB-65 scales.

Scales		Death	Discharge	Ss (%)	Sp (%)	PPV	NPV
CDAPP	> 2	25	04	83.3	94	86.2	92.6
	≤ 2	05	63				
BAP-65	≥ 3	26	18	86.7	73.1	59	92.4
	< 3	04	49				
CURB-65	≥ 2	29	30	96.7	55.2	49.1	97.4
	< 2	01	37				

CDAPP > 2 points had a predictive value of mortality in AE with a sensitivity of 83.3%, a specificity of 94% and a PPV of 86.2%, a NPV of 92.6%. The BAP-65 ≥ 3 score had a mortality prognostic value with a sensitivity of 86.7%, a specificity of 73.1% and a PPV of 59%, a NPV of 92.4%. CURB-65 score ≥ 2 had a mortality prognostic value with a sensitivity of 96.7%, a specificity of 55.2% and a PPV of 49.1%, a NPV of 97.4%. Thus, the CDAPP scale has a prognostic value for mortality with a higher specificity than the BAP-65 and CURB-65 scales.

We combined 5 factors with independent prognostic value in acute exaberation to build a prognosis scale, abbreviated as CDAPP. The area under the ROC curve of the CDAPP scale was 0.954, indicating a good ability to predict mortality. The cutoff point with the best prognostic value was CDAPP > 2 points. CDAPP scores also had a higher specificity than the BAP-65 and CURB-65 scales in prognosis of mortality.

Although Roche's “2008” scale has shown accuracy in the prognosis of death in acute exaberation, the assessment has many subjective factors and requires analysis of many factors representing the degree of mortality, severity of the disease into a separate variable [5]. CDAPP scale appears to be more suitable for clinical practice, with highly objective and generalized factors.

CURB-65 scale was developed and proposed by Lim et al (2003) as a predictive tool for mortality risk in patients with community pneumonia [10]. We conducted a survey on the mortality prognostic value of the CURB-65 scale because in fact most causes of acute exaberation in Vietnam are due to lower respiratory tract infections. By comparison, CURB-65 has a high sensitivity, but its specificity is low (55.2%) compared with a sensitivity of 83.3% and a specificity up to 94% of CDAPP scale.

The BAP-65 scale was developed by Shorr et al. A retrospective study and diagnostic criteria for COPD and acute exaberation were based on information about encrypted hospital discharge. Therefore, the selection criteria are not strict, objective and may be confused with other diseases such as bronchial asthma, bronchiectasis [11]. The comparison also shows that the CDAPP scale had a higher prognostic value than the BAP-65 scale.

CONCLUSIONS

Severe dyspnea (mMRC > 3), confusion and pneumonia were clinically significant factors with independent prognosis of mortality in acute exaberation. Increased serum PCT concentration and an arterial blood gas test with acidosis were two factors that have independent prognosis of mortality in AECOPD ($p < 0.05$).

We have built a CDAPP scale for prognosis of mortality in AE with the combination of 5 clinical and subclinical factors. The comparison showed that the CDAPP scale had a higher prognostic value for the risk of death in acute exaberation than the BAP-65 and CURB-65 scores. CDAPP score > 2 points had the ability to predict the risk of death with a sensitivity of 83.3%, a specificity of 94% and a positive predictive value of 86.2%, a negative predictive value of 92.6%.

However, the CDAPP scale has limitations. Firstly, the sampling was only performed at a central hospital, so the representative of the population was low. Secondly, we have not been able to assess the survival rate of patients after discharge over time to determine the long-term prognosis of the CDAPP scale.

References

1. Global intiative for chronic obstructive lung disease. Global strategy for diagnosis, management and prevention of chronic obstructive pulmonary disease 2020.

2. WHO (2015). Global Health Estimates: Life expectancy and leading causes of death and disability. Viet Nam: WHO statistical profile.

3. Roche N, Zureik M, Soussan D, et al. Predictors of outcomes in COPD exacerbation cases presenting to the emergency department. Eur Respir J 2008; 32(4):953-961.

4. Steer J, Gibson J, and Bourke SC. The DECAF Score: predicting hospital mortality in exacerbations of chronic obstructive pulmonary disease. Thorax 2012; 967:970-976.

5. Roche N, Chavaillon JM, et al. A clinical in-hospital prognostic score for acute exacerbations of COPD. Respir Res 2014; 15(1):99.

6. Global intiative for chronic obstructive lung disease. Global strategy for diagnosis, management and prevention of chronic obstructive pulmonary disease. 2015.

7. Vestbo J. and et al. The TORCH (Towards a Revolution in COPD Health) survival study protocol. Eur Respir J 2004; 24(2):206-210.

8. Lacoma A, Prat C, Andreo F, et al. Value of procalcitonin, C-reactive protein, and neopterin in exacerbations of chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis 2011; 6:157-169.

9. Iqbal Z, Ullah Z, Basit A, et al. Changes in arterial blood gases and respiratory rate before and after noninvasive positive pressure ventilation in acute exacerbation of COPD. Pak J Chest Med 2008; 14 20.

10. Lim W, Van Der Eerden MM, Laing R, et al. Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. Thorax 2003; 58(5):377-382.

11. Shorr AF, Sun X, Johannes RS, et al. Validation of a novel risk score for severity of illness in acute exacerbations of COPD. Chest 2011; 140(5):1177-1183.