# بسم الله الرحمن الرحيم

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تم رفع هذه الرسالة بواسطة / حسام الدين محمد مغربي

بقسم التوثيق الإلكتروني بمركز الشبكات وتكنولوجيا المعلومات دون أدنى مسئولية عن محتوى هذه الرسالة.

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| ملاحظات : لا يوجد |

# Prognostic Value of C - Reactive Protein in Patients with Acute Exacerbation of Chronic Obstructive Pulmonary Disease Admitted to Intensive Care Unit

Thesis

Submitted for Partial Fulfillment of master degree in Master of Critical Care Medicine

By

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2022


سورة البقرة الآية: ٣٢

# Acknowledgment

*First and foremost, I feel always indebted to* ALLAH, *the Most Kind and Most Merciful.*

*I'd like to express my respectful thanks and profound gratitude to* Prof. Dr. Sherif Sayed Ali Sultan, *Professor of Anesthesiology, Faculty of Medicine, Ain Shams University for his keen guidance, kind supervision, valuable advice and continuous encouragement, which made possible the completion of this work.*

*I am also delighted to express my deepest gratitude and thanks to* Ass. Prof. Dr. Ahmed Ali Elshebiny, *Assistant Professor of Anesthesiology, Faculty of Medicine, Ain Shams University, for his kind care, continuous supervision, valuable instructions, constant help and great assistance throughout this work.*

*I am deeply thankful to* Dr. Ahmed Mohamed Khamis, *Lecturer of Anesthesiology, Faculty of Medicine, Ain Shams University, for his great help, active participation and guidance.*

*I wish to introduce my deep respect and thanks to* Dr. Ramy Wahba Mounir, *Lecturer of Anesthesiology, Faculty of Medicine, Ain Shams University, for his kindness, supervision and cooperation in this work.*

*I would like to express my hearty thanks to all my family for their support till this work was completed.*

*Last but not least my sincere thanks and appreciation to all patients participated in this study.*

Masoud Mostafa Masoud Ali Khedr

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# List of Abbreviations

| Abb. | Full term |
|---|---|
| *AECOPD* | *Acute Exacerbation of COPD* |
| *ALT* | *Alanine aminotransferase* |
| *ARF* | *Acute Respiratory Failure* |
| *AST* | *Aspartate aminotransferase* |
| *BAL* | *Bronchoalveolar lavage* |
| *CBC* | *Complete blood picture* |
| *CNS* | *Central nervous system* |
| *COPD* | *Chronic obstructive pulmonary disease* |
| *CRP* | *C-reactive protein* |
| *DALY* | *Disability Adjusted Life Year* |
| *ELISA* | *Enzyme linked immunosorbent assay* |
| *GSC* | *Glasgow Coma Score* |
| *IBD* | *Inflammatory bowel disease* |
| *ICU* | *Intensive care unit* |
| *IL-6* | *Interleukin-6* |
| *LTB4* | *Leukotriene B4* |
| *NHS* | *National Health Service* |
| *NIV* | *Non-invasive ventilation* |
| *TNF-α* | *Tumor necrosis factor-α* |

# Prognostic Value of C - Reactive Protein in Patients with Acute Exacerbation of Chronic Obstructive Pulmonary Disease Admitted to Intensive Care Unit

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## ABSTRACT

***Background:*** Chronic obstructive pulmonary disease (COPD) is a leading and increasing cause of worldwide morbidity and mortality. Recently, COPD has gained interest as a major public health concern and is currently the focus of intense research because of its persistently increasing prevalence, mortality, and disease burden. COPD is the third leading cause of death in the world, and further increases in its prevalence and mortality can be predicted in the coming decades.

***Aim of the Work:*** The aim of the present work was to detect the possible role of CRP levels in predicting the prognosis of ICU admitted patients with AECOPD.

***Patients and Methods:*** This prospective Cross sectional study was conducted on 66 adult patients of both sexes admitted to the ICUs of Al-Mabarra governmental hospital in Port Said and Ain Shams University Hospitals.

***Results:*** In our study, it was noticed that duration of NIMV (Days) ranged from 2 h - 11 days in low group and ranged from 1 day - 14 days in high group, While Duration of IMV (Days) ranged from 2 h – 7 days in low group and ranged from 3 day - 18 days in high group. In the present study, we found that 33patients were discharged after improvement (100%) from low group (it reflects the benefit of grouping our study cases), while 26patients were discharged after improvement (78.79%), and 7 patients (21.21%) unfortunately were dead from high group. In the current study, as regards the correlation between CRP with MV, ICU stay and hospital stay, it was noticed that the serum CRP level was significantly elevated in relation to increased period of IMV days ($r = 0.714$, $p = <0.001$), NIMV days ($r = 0.491$, $p = <0.001$), ICU stay ($r = 0.690$, $p = <0.001$) and hospital stay ($r = 0.686$, $p = <0.001$).

***Conclusion:*** The following conclusion was obtained from the current study: CRP as biological marker was noticed to be elevated in patients with AECOPD who needed ICU admission. CRP is good indicator of future increase of MV days, hospital stay and ICU stay. There was a significant relation between CRP level and mortality. 100% of our study cases of low group discharged on improvement it reflects the benefit of grouping our study cases. There was no significant relation between CRP level and development of acute heart failure regarding the inclusion criteria in the study.

***Keywords:*** C - Reactive Protein; Acute Exacerbation; Chronic Obstructive Pulmonary Disease; Intensive Care

## INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a leading and increasing cause of worldwide morbidity and mortality ***(Hart et al., 2012).*** Recently, COPD has gained interest as a major public health concern and is currently the focus of intense research because of its persistently increasing prevalence, mortality, and disease burden ***(Mannino et al., 2007)***. COPD is the third leading cause of death in the world, and further increases in its prevalence and mortality can be

predicted in the coming decades ***(Pauwels et al., 2012; Wouters et al., 2011; National Collaborating Centre for Chronic Conditions et al., 2004)***.

**Definition:** Chronic Obstructive Pulmonary Disease, a common preventable and treatable disease, is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases ***(Global Initiative for Chronic Obstructive Lung disease; Accessed on 25 May, 2021)***. Exacerbations and comorbidities contribute to the overall severity in individual patients ***(MacNee et al., 2013).***

COPD is the name for a group of lung conditions that cause breathing difficulties.

**It includes:**

**Emphysema**, or destruction of the gas-exchanging surfaces of the lung (alveoli), is a pathological term that is often, but incorrectly, used clinically and describes only one of several structural abnormalities present in patients with COPD.

**Chronic bronchitis**, or the presence of cough and sputum production for at least 3 months in each of two consecutive years, remains a clinically and epidemiologically useful term ***(Hart et al., 2012; National Health Service (NHS); Accessed on 25 May, 2021).***

Chronic bronchitis is an independent disease entity that may precede or follow the development of airflow limitation and may be associated with development and/ or acceleration of fixed airflow limitation. Chronic bronchitis also exists in patients with normal spirometry ***(Vestbo et al., 2013).***

While the new guidelines do not specifically include chronic bronchitis and emphysema in the definition of COPD, it is made clear that they are considered the predominant causes of COPD ***(Russell et al., 2011).***

**Acute COPD Exacerbation:** Acute Exacerbation of COPD (AECOPD) is defined as an event in the natural course of the disease characterized by a change in the patient's baseline dyspnea, cough, and/or sputum that is beyond normal day-to-day variations, is acute in onset, and may warrant a change in regular medication in a patient with underlying COPD ***(Global Initiative for Chronic Obstructive Lung disease; Accessed on 25 May, 2021; Vestbo et al., 2013).***

**Serum inflammatory biomarkers and its role in the diagnosis of AECOPD:** Patients with COPD have an ongoing systemic inflammation**.** In addition, it is believed that many of the systemic manifestations of COPD are mediated through increased systemic levels of inflammatory proteins such as and C-reactive protein (CRP) ***(Kolsum et al., 2009)***, interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α).

COPD is thought to be intimately linked to inflammation, documented locally and systemically. And as a consequence, attention has been centered on the level of inflammatory markers and their relation to clinical and physiological measurements ***(Pinto-Plata et al., 2012)***. How and why individuals with COPD develop systemic inflammation is uncertain and unknown. COPD is characterized by an intense inflammatory process in the airways, parenchyma, and pulmonary vasculature. It is possible in some cases that the inflammatory process may ''spill'' over into the systemic circulation, promoting a generalized inflammatory reaction ***(Barnes et al., 2009)***.

It is also possible that there are common genetic or constitutional factors that may predispose individuals with COPD to both systemic and pulmonary inflammation. Furthermore, while we believe that COPD is responsible for the systemic inflammation, there exists the possibility of reverse causation ***(Mannino et al., 2007)***.

The possibility that systemic inflammation causes injuries to the airways leading to COPD changes cannot be fully discounted. Whatever the mechanism, the presence of systemic

inflammation in COPD has been linked with a variety of complications including weight loss, cachexia, osteoporosis, and cardiovascular diseases ***(Sin et al., 2006)***.

Moreover, Individuals with increased systemic inflammatory markers such as fibrinogen experience an accelerated decline in lung function and are at increased risk of COPD hospitalizations in the future. The relationship between COPD, systemic inflammation, and cardiovascular diseases may be especially germane as over half of patients with COPD die from cardiovascular causes. Indeed, airflow limitation doubles the risk of cardiovascular mortality independent of smoking. Moreover, during periods of exacerbation, plasma levels of fibrinogen and serum levels of IL-6 increase significantly, this may further contribute to increased cardiovascular morbidity and mortality in patients with COPD ***(Higashimoto et al., 2009)***.

**CRP:** C-reactive protein is an acute phase protein, which has been shown to be a marker of inflammation in atherosclerosis and its levels correlate with the degree of pulmonary inflammation in stable COPD.CRP has been proposed to be useful marker for COPD early diagnosis and prognosis in COPD. However, the relationship between serum biomarkers and clinical expressions of COPD is still limited ***(Celli et al., 2010)***.

Besides an increase in airway inflammation, COPD exacerbations are associated with an increase in systemic inflammation. It has been established that stable COPD is associated with low-grade systemic inflammation as demonstrated by an increase in blood leukocytes, acute-phase proteins CRP and fibrinogen, and inflammatory cytokines ***(Barnes et al., 2009)***.

There is limited information relating the clinical and physiologic changes that define AECOPDs and the changes in the systemic expressions of plasma cytokine levels ***(Anzueto et al., 2007)***.

The majority of the studies of AECOPD have centered on the evaluation of the sputum, and rightly so because sputum is thought to represent the visible expression of the process causing the exacerbation. These studies have shown the role of viruses and bacteria as possible causative agents in the genesis of the episodes. They have also shown that there is an increase in sputum neutrophils, IL6, IL-8, and TNF-α and other proinflammatory markers, all of which seem to confirm the presence of increased airway inflammation. Several studies have extended the observations to the systemic compartment but with limited clinical information ***(Pinto-Plata et al., 2007; Agusti et al., 2008)***.

Even among non-current smokers there was evidence for low grade systemic inflammation in those with chronic airflow limitation. This suggests that, once COPD develops, cessation of smoking may not fully attenuate the inflammatory process associated with this condition ***(Barnes et al., 2009)***.

## AIM OF THE WORK

The aim of the present work was to detect the possible role of CRP levels in predicting the prognosis of ICU admitted patients with AECOPD.

## PATIENTS AND METHODS

This Cross sectional study (Diagnostic Accuracy Test) was conducted on 66 adult patients of both sexes admitted to the ICUs of Ain Shams University Hospitals and Al-Mabarra governmental hospital in Port-Said.

The study was approved from the ethical committee of the Faculty of Medicine–Ain Shams University (MS 141/2021) and Ministry of Health (No: 17-2021/18).

**All patients recruited in the study according to inclusion and exclusion criteria were subjected to the followings:** Informed consent was taken from all patients or their legal guardians.

**Inclusion Criteria:** Patients with acute exacerbation of COPD whom was defined as acute change in the patients' base line dyspnea, cough, and/or sputum production severe enough to be referred to hospital and admitted to ICU according to Global Initiative for Chronic Obstructive Lung Disease (GOLD) which classified COPD patients according to spirometry results as: GOLD 1- Mild: Forced expiratory volume in 1 second (FEV1) ≥80%, GOLD 2- Moderate: FEV1≤80 %, GOLD 3- Severe: FEV1≤50 % and FEV1<30 %**:**GOLD 4- Very severe

**ICU admission for:** Oxygen therapy, ventilator support via NIMV or IMV, hemodynamic instability, arterial blood gases (ABG) showing acidosis or hypercapnia and failure to improve after empiric treatment before ICU admission.

**Exclusion criteria:** Patients with bronchial asthma, cystic fibrosis or severely immunocompromised patients, new infiltration in chest x-ray on admission, vasculitis or other causes that increase CRP as inflammatory bowel disease (IBD), rheumatoid arthritis and systemic lupus and clinical suspicion of left sided heart failure or ischemic heart disease.

**History**

**Personal data:** name, age and sex. **Present history of medical illness including the following:** Duration of the symptoms (cough & dyspnea) and change of color & amount of sputum.

The smoking index ***(Leffondré et al., 2006)*** (a unit for measuring cigarettes consumption over a long period and was calculated using the following formula: smoking index = cigarettes per day × years of tobacco use).

**Drug history** including previous antibiotics, domiciliary oxygen therapy and number of annual exacerbation especially in the last year.

**Clinical examination.**

**Complete physical examination performed with emphasis on:** Vital signs: (heart rate, blood pressure, respiratory rate and temperature), mental status according to Glasgow Coma Score (GSC) and chest examination.

**Laboratory evaluation:**

**The following investigations were performed to all patients on admission (5ml of blood was needed):** Complete blood picture (CBC), including differential White Blood Cells, serum levels of urea and Creatinine, to exclude renal failure, aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin, sodium (Na) and potassium (K), ABG, to set base line and to diagnose hypoventilation and hypoxemia, culture of sputum, tracheal aspirate or bronchial lavage (if available) and determination of CRP concentration by enzyme linked immunosorbent assay (ELISA).

**Radiological investigation:** Chest X ray or CT chest to exclude presence of pneumonia.

**Interventions *(Global Initiative for Chronic Obstructive Lung disease; Accessed on 20 Sebtember, 2021)***

**All patients were subjected to treatment and management of ARDS which is summarized as follows:** Oxygen therapy included supplemental oxygen titrated according to ABG aiming SaO2 of 88-92% in the form of nasal cannula from 1-2L/minute or Venturi mask at 24% (2-3 L/minute) or at 28%(4L/minute), indications of NIMV were moderate to severe dyspnea with use of accessory muscles and paradoxical abdominal motion, moderate to severe acidosis (pH ≤ 7.35) and/ or hypercapnia (PaCO2 > 6.0 kPa, 45 mm Hg), respiratory frequency > 25 breaths per minute, Indications of IMV were inability to tolerate NIV or NIV failure, severe dyspnea with use of accessory muscles and paradoxical abdominal motion, respiratory frequency > 35 breaths per minute, life-threatening hypoxemia, severe acidosis (pH < 7.25) and/or hypercapnia (PaCO2 > 8.0 kPa, 60 mm Hg), respiratory arrest, somnolence, impaired mental status, cardiovascular complications (hypotension, shock) and other complications (metabolic abnormalities, sepsis,