"EFFICACY OF CRP IN GUIDING ANTIBIOTIC USAGE IN PATIENTS WITH ACUTE EXACERBATION OF COPD: A RANDOMISED CONTROLLED TRIAL"

By

Reg. No. BR0119002

Dissertation

Submitted to the:

KLE Academy of Higher Education and Research, Belagavi, Karnataka.

In partial fulfilment of the requirements for the degree of

M.D.

IN

RESPIRATORY MEDICINE

Department of Respiratory Medicine

Jawaharlal Nehru Medical college Belagavi,

Karnataka.

APRIL 2022

KLE Academy of Higher Education and Research, Belagavi, Karnataka

Endorsement by Head of the Department, Principal / Head of the Institution

This is to certify that the thesis **"EFFICACY OF CRP IN GUIDING ANTIBIOTIC USAGE IN PATIENTS WITH ACUTE EXACERBATION OF COPD: A RANDOMISED CONTROLLED TRIAL"** is a bonafide research work done by **Dr. R.Nikhilesh** (Reg. No.BR0119002) under the guidance of **Dr. Bhagyashri B. Patil MD** Professor and Head Department Respiratory Medicine J.N. Medical College, Belagavi.

Dr. Bhagyashri B. Patil MD
Professor and Head,
Department of Respiratory Medicine
J.N. Medical College,
Belagavi – 590 010. Karnataka.

Date:
Place: Belagavi

Dr. (Mrs.) N S Mahantashetti MD (Paed.)
Principal
J.N. Medical College,
Nehru Nagar,
Belagavi – 590 010. Karnataka.

Date:
Place: Belagavi

LIST OF ABBREVIATIONS

COPD	-	Chronic Obstructive Pulmonary Disease
AECOPD	-	Acute Exacerbation of Chronic Obstructive Pulmonary Disease
CRP	-	C-Reactive Protein
PCT	-	Procalcitonin
GOLD	-	Global Initiative of Chronic Obstructive Lung Diseases
FEV1	-	Forced Expiratory Volume in 1 second
FVC	-	Functional Vital Capacity
BMI	-	Body Mass Index
ICU	-	Intensive Care Unit
CPAP	-	Continous Positive Airway Pressure
IMV	-	Invasive Mechanical Ventilation
ERS	-	European Respiratory Society
ATS	-	American Thoracic Society
WHO	-	World Health Organization

ABSTRACT

Introduction- Acute exacerbations of COPD (AECOPD) has a significant impact on the quality of life, morbidity and mortality. Infection being the primary etiology, antibiotic use plays a major role in the treatment of these patients. CRP, one of the serum biomarkers aids in initiating antibiotic use in these patients. Hence, the present study is aimed to know the CRP directed prescription of antibiotic in patients with COPD in acute exacerbation.

Materials and Methods- The study was conducted in tertiary care hospital for 1 year. 90 patients were enrolled in the study, and randomized into CRP group and Standard Care group. CRP group had 40 patients and 50 patients were included in the Standard Care group. Outcomes of CRP guided antibiotic use in COPD patients were compared in both the groups.

Results- The use of antibiotics in CRP group was significantly less compared to Standard Care Group(65% vs. 88%, p= 0.0091). The mean duration of hospital stay was 7.50 ± 2.91 days, while 10.12 ± 3.91 days in the Standard Care group.(p= 0.0006). The mean length of ICU stay was 3.50 ± 1.05 days in the CRP group and 9.80 ± 3.59 days in the Standard Care group.(p= 0.0005). The rate of mortality was similar in the groups, having no significance.

Conclusion- CRP guided antibiotic use resulted in reduced use of antibiotics, reduced length of ICU stay and lessened duration of hospital stay in patients with acute exacerbation of COPD.

LIST OF CONTENTS

LIST OF TABLES

LIST OF GRAPHS

LIST OF FIGURES

INTRODUCTION

COPD constitutes a global health burden.[1] Acute exacerbations of COPD (AECOPD) has a significant impact on the quality of life, morbidity and mortality.[2,3] Established causes for AECOPD include infections of the respiratory tract due to bacterial and/or viral etiology and air pollution, which makes up a major portion of the cases of acute exacerbation of COPD[4]. Wherein individuals with characteristics of bacterial infection and severe exacerbation, have benefitted from use of antibiotics,[5,6] initiating antibiotics for viral infections or other causes of COPD exacerbation is futile. This might increase the risk of harmful effects and the occurrence of drug resistance[7].

Serum biomarkers such as Procalcitonin (PCT) and C- reactive Protein(CRP) may help in narrowing down patients who would benefit from antibiotic therapy. CRP is an acute phase reactant synthesized by the liver in response to cytokines released by the damaged tissue. It is generally measured to screen for infection or inflammation. The levels of CRP shows a marked elevation especially in infections due to bacterial etiology. A study done by Hurst[8] et. al which evaluated 36 biomarkers had concluded CRP was the most discerning biomarker to validate AECOPD, revealing its diagnostic efficacy. Elevated CRP levels is associated with purulent sputum production and increase total blood counts[9,10].

In comparison to Procalcitonin, CRP levels are especially elevated, in the event of infection, bacteria in particular, at the time of admission to the hospital, by which, the beneficial effect of antibiotics is more with higher values of CRP.[11] Hence, CRP levels play a vital role in initiating antibiotics in patients with acute exacerbation of COPD.[12]

CRP levels alone, differentiates between pneumonia and other causes of exacerbations in patients admitted to the hospital with asthma and COPD.

The rampant utilization of antibiotics in patients with COPD exacerbation contributes to high medical costs and risk of adverse drug reactions. CRP is a more accessible and feasible biomarker in contrast to PCT, which may avoid unnecessary antibiotic use and as well reduce hospital stay in patients with acute exacerbation of COPD.

Hence the present study is aimed to know the CRP directed prescription of antibiotic in patients with COPD in acute exacerbation.

OBJECTIVE OF THE STUDY

To determine the efficacy of C-Reactive Protein (CRP) in guiding antibiotic prescription in patients with acute exacerbation of COPD.

REVIEW OF LITERATURE

1. DEFINITION OF COPD

GOLD – 2021 (Global Initiative for Chronic Obstructive Lung Disease) defined COPD as " a common preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases.

Parenchymal destruction and disease of smaller airways in combination causes chronic airflow limitation, which is variable among different individuals. While in general there is correlation between the extent of airflow obstruction and the smoking history, it differs significantly across individuals.[13] On an average there is fall in FEV1 of higher than 60 mL/year among smokers who contract COPD. However, just a small section of smokers progress to a COPD of a clinically significant level.

Small airways become more narrow and structural changes occur due to persistent inflammation that results from small airway disease. When the lung parenchyma is destroyed by inflammatory processes, oxidative stress, or protease/antiprotease imbalance, lung elastic recoil and the number of alveolar attachments on the small airways get reduced and airflow gets restricted. Systemic consequences occur when the inflammation extends beyond the lungs. Therefore COPD is a complex, heterogenous disease, comprising multiple components and involving many complications. Even if some individuals suffer from airflow limitation that are similar in severity, the clinical and radiological presentation of the disease may be different.[14]

COPD is a heterogenous disease that causes pathologic changes in the large and small airways (chronic bronchitis and bronchiolitis) and lung parenchyma (emphysema); these conditions have widely differing manifestation across different patients.[15] The clinical definition of chronic bronchitis is "the presence of cough and sputum production for most days over 3 months for 2 consecutive years". The definition of emphysema is "enlargement of the airspaces distal to the terminal bronchioles", as a result of the alveolar walls getting destroyed. Such enlargement of distal airspace and alveolar destruction decreases maximal expiratory airflow by reducing the lung elastic recoil.

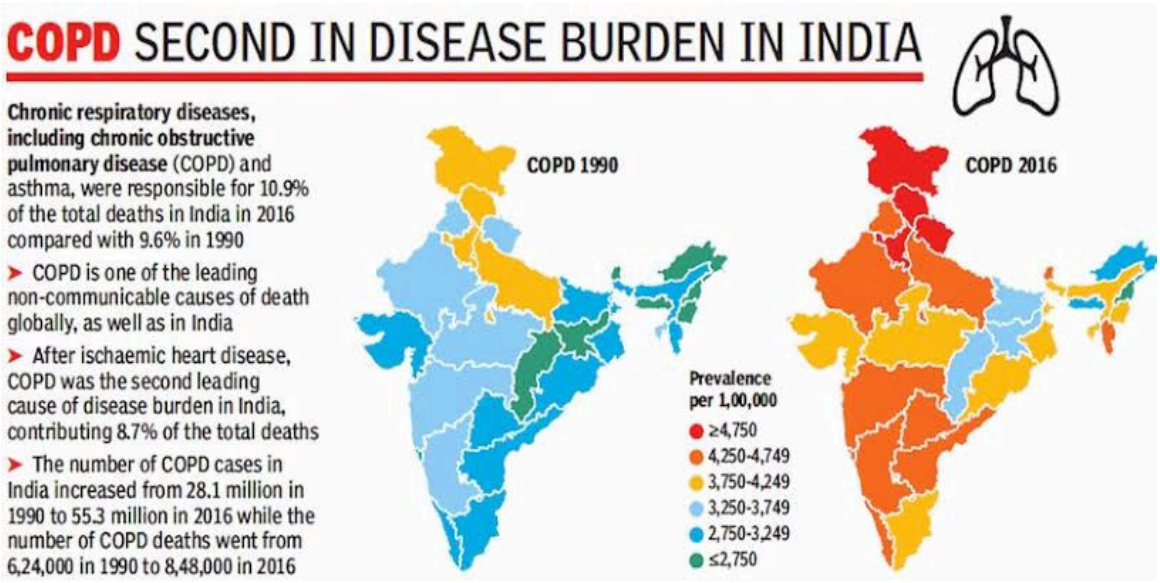
2. EPIDEMIOLOGY OF COPD

Worldwide there were 251 million COPD cases in 2016 according to a report of the Global Burden of Disease. Approximately 3.17 million deaths resulted in 2015 from COPD, out of which more than 85% occurred in third-world countries. When assessing the global economic burden of COPD the two major aspects to be taken into account are underdiagnosis and comorbidities. In many countries, COPD is underdiagnosed. Studies determining the global economic burden of COPD are conducted based on the number of patients diagnosed with COPD. Therefore the computation of the overall economic burden of COPD is inaccurate since such studies omit the burden of undiagnosed COPD.[16]

A study by the Burden of Obstructive Lung Disease (BOLD) revealed a prevalence of 10.1% globally. Men were found to have a prevalence of 11.8% and women 8.5%. The number of prevalent cases differs across various regions of the world. Cape Town, South Africa, has the highest prevalence of 22.2% of men and 16.7% of

women suffering from COPD, while Hanover, Germany, reported the lowest prevalence of 8.6% for men.

Figure 1: COPD PREVALENCE IN INDIA



The WHO has calculated that mortality rates due to COPD will rise in the Southeast Asian region by around 160% over the next 20 years. In India, about 50 lakhs people are expected to perish due to COPD annually being the largest number in the world only second to China. Multiple studies conducted by Murthy, Sastry and Jindal have indicated that approximately 5% of adults suffer mortality due to COPD, depending upon factors such as biomass fuel use, socioeconomic status etc. Sections like smokers, males and rural population record higher rates of mortality.[17]

Rough estimates indicate that there are about 3 crore patients of COPD in India. COPD prevalence in our country, varies from 2.12% to 9.4% in men and it varies between 1.33% to 1.49% in women.[18] Another challenge to community health is emerging in the form of the extent of elderly population. The number of senior

citizens is increasing by 2% annually. This contributes to a frightening increase in the number of prevalent cases of COPD.

Morbidity of COPD

COPD is a common and primary cause of morbidity which is associated with the worsening quality of life. Doctors report that 80% of COPD patients hospitalised following an increase in severity suffer a health condition rated worse than death. It is estimated that 50% of patients who are discharged from their first COPD-related hospitalization get readmitted within six months. Available statistics show a higher incidence of morbidity in males as compared to females; morbidity also increases as age progresses. It is likely that morbidity is also impacted by other comorbid conditions which are not directly linked with COPD but still act as a bottleneck in the treatment of COPD or adversely impact the patient's health.[19]

Mortality of COPD

In the year 1990, COPD was labelled the sixth leading cause for death globally; Nonetheless, with improvement in life expectancy and increase in cigarette smokers in developing nations, it is likely that in future COPD may become the third most common cause for death. Total deaths from COPD are expected to increase by more than 30% in the coming 10 years from the figure of 3.17 million approximately in 2015.

In accordance with a study done by University of Washington's Global Burden of Disease in 2018, COPD was the second significant cause of death in India in 2017 after acute coronary syndrome, resulting in the death of nearly 1 million (958,000) Indians. The aggregate mortality rate ranges from 3 to 111 per 100,000

population and is higher in males than females. The rising epidemic of smoking and increase in longevity also play an important part.

Financial burden of COPD

COPD causes a huge financial loss for both the patients and the nation. The economic burden of COPD is approximately US$38.8 billion in US and US$38.6 billion in Europe. The approximate economic burden due to COPD is US$7.5 billion for India. Of the direct costs associated with COPD, about 84% is due to hospital admissions. It is also estimated that lost productivity due to COPD accounts for about 40% to 67% of the overall costs worldwide. Hence it is observed that COPD imposes a significant financial burden on countries across the world.

3. Risk factors

a. Genetics

In smokers with COPD, there is a considerable familial likelihood of airflow limitation in their siblings.[20] Therefore, genetic, alongside environmental elements, could also be associated in the development of the disease. The most acclaimed hereditary cause for the development of emphysema is the Alpha 1 antitrypsin deficiency, a serine-protease inhibitor.[21] Other genes having an impact on the probability of developing COPD, includes the alpha nicotinic acetylcholine receptor, in addition to the gene encoding MMP12, hedgehog interacting protein gene, and the FAM13 gene.

b. Smoking

Worldwide, cigarette smoking is the most common risk factor associated with COPD. Cigarette smokers have a higher prevalence of respiratory symptoms, reduced lung function, a higher rate of decline in FEV1, diminution of lung density, along with a higher mortality rate than people who do not smoke.[22] The deciding features being the number of cigarettes smoked as well as the duration of inhalation. In addition to filtered cigarettes, consumption of tobacco and marijuana are the other elements posing a threat to the occurrence of COPD.[23] Several studies have shown discontinuation of smoking, to result in lower frequency of respiratory manifestations along with gradual drop in FEV1, in patient cohorts as well as population studies.[24]

c. Air pollution

Dyspnea, cough, expectoration and reduced lung functions are a common phenomena secondary to high levels of air pollutants. Impaired pulmonary function in adulthood and decreased lung development in children is seen in individuals exposed to high levels of particulate matter and nitrogen oxide in the air. Biomass fuel use in poorly ventilated homes has been reported to be a common cause of COPD among women in third world countries.[25] Exposure to sulphur dioxide is also associated with chronic bronchitis. The World Health Organization approximated that indoor air pollution was one of the leading factors for death in more than 10 lakh individuals suffering from COPD.[26]

d. Asthma and hyperreactivity

Asthma is too, considered a threat for the evolution of COPD. A study done in Netherlands among asthmatic patients reported irreversible impediment of airflow

in 20% of patients.[27] while, a longitudinal population study conducted in Denmark, showed "self-reported asthma" was related to an increased drop in FEV1[28]. In the European Community Respiratory Health Survey, hyperresponsiveness of bronchi was second, with smoking of cigarettes being the primary causation for COPD, taking the population attributable risk to upto 15%.[29] This is in agreement with earlier reports that showed, even in non asthmatic individuals there was a major influence on the drop in FEV1, due to hyperresponsive activity of the bronchi.

e. Infection

An account of childhood pulmonary infection is correlated with decreased lung function and enhanced respiratory manifestations in adult life.[30] Susceptibility to infections is vital in COPD exacerbation, thereby causing further diminution in FEV1, even though the actual impact may be decent.[31]

f. Occupational exposure

Occupational exposures is an important etiological agent for COPD.[32] NHANES III survey suggested that occupational exposure contributes to 19% overall and 31% of non smokers who develop COPD.[33]

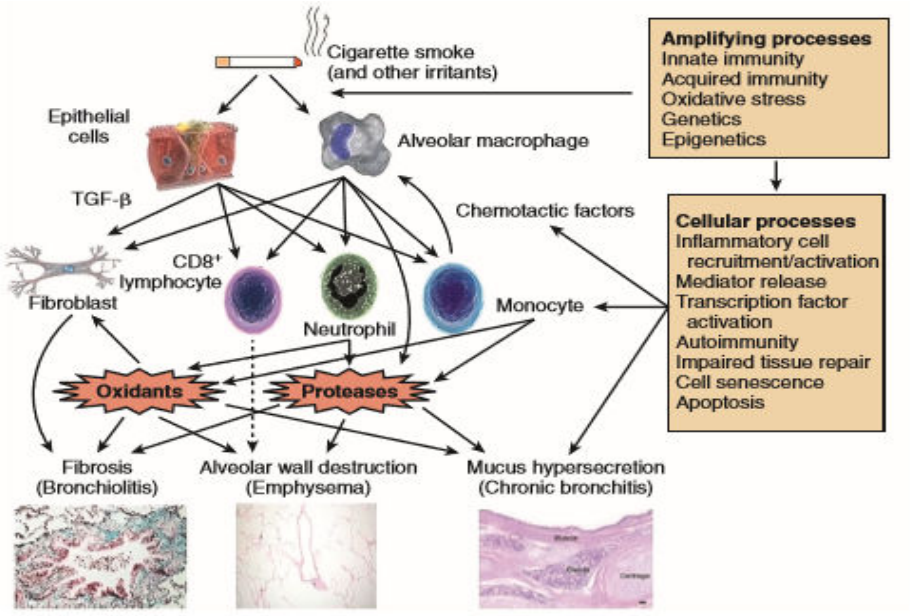
g. Socioeconomic status

Poor socioeconomic status alone, is a threat for COPD and is supposedly typical of various components particularly intrauterine growth retardation, malnutrition (antioxidant- deficient diet), personal hygiene, childhood pulmonary infections, subjection to tobacco smoke, biomass smoke and other indoor air contaminants. These factors might cumulatively promote to COPD. Socioeconomic status should hence, be regarded as an independent menace for developing COPD.[34]

4. Pathogenesis of COPD

As mentioned in the description of COPD, inflammation occupies a principal part in its pathogenesis. The inflammation prototype is that smoking and other forms of inhaled irritants mobilizes the innate inflammatory cells to the lungs and respiratory tract. Thus, resulting in injury to the lung tissue and disruption of normal pathways of lung repair. Cellular and humoral immunity also have a vital role to play in its pathogenesis

Figure 2: Pathogenesis of COPD



In COPD, there is accumulation of CD4+ and CD8+T cells and B cells the walls of small airways, giving rise to the bronchus-associated lymphoid tissue(BALT) .[35] The higher measures of BALT in the airways is directly correlates to the severity of GOLD stage.

In COPD patients, the bronchial epithelium and submucosa is primarily inhabited by monocytes alongside a few neutrophils.[36] With respect to monocytes, T lymphocytes dominate, essentially CD8+ cells (T-cytotoxic lymphocytes) together

with macrophages. Thereby, elevating the quotient of CD8+/CD4+ in COPD.[37] The amount of macrophages in the lung parenchyma, airways and BAL increases as much as 10 times. Macrophage measures in the airways associates with the intensity of the airflow impediment in COPD. Macrophages get activated by cigarette smoke to release inflammatory mediators, such as TNF-α, IL-8, and other CXC chemokines.[38]

Cytokines and chemokines

In patients suffering from advanced emphysema, there is an intense expression of TH1 cytokines by the lymphocytes in the pulmonary tract, resulting in elevated measures of CXCR3, CCR5 and interferon (IFN)-γ. Hence, it is understood that severe emphysema is predominated by the colligation of alveolar lymphocytes in the TH1 phenotype. Smoking induced emphysema is also associated with increased levels of TNF-α . Exaggerated inflammatory responses of alveoli has been noted in patients with overexpression of TNF-α. IL-1β has also been implicated in the pathogenesis of emphysema.

Airway remodelling and limitation

The important sites of prominent opposition to airflow in COPD are the small airways (bronchioles < 2 mm in diameter) High number of inflammatory cells and structural changes, such as epithelial goblet cell metaplasia, airway wall fibrosis, and smooth muscle hypertrophy are the major changes seen in the small airways.[39]

Protease/antiprotease imbalance

A disparity is created due to the enhanced production of proteases or the diminished activity of anti-proteases. This concept is derived from studies exhibiting the deficiency of major anti-elastase α1-antitrypsin (A1AT) in patients developing early-

onset emphysema.[40] Oxidative stress secondary to cigarette smoking and inflammation, conditions several inflammatory cells to release a combination of proteases and inactivate several antiproteases by oxidation. The major proteases involved in the pathogenesis of COPD are the serine proteases produced by neutrophils, cysteine proteases and matrix metalloproteases (MMPs) produced by macrophages. The major antiproteases involved in the pathogenesis of emphysema include α-1-antitrypsin, secretory leukoproteinase inhibitor and tissue inhibitors of MMP

Oxidative stress

Cigarette smoke induces release of reactive oxygen and nitrogen species from inflammatory cells. This causes a disproportion between oxidants and antioxidants, developing oxidative stress, thus, establishing various pathogenic pathways of the disease.[41] Oxidative stress can lead to inactivation of anti proteinases and stimulation of mucous production. It further enhances inflammation by activating many intercellular pathways, including kinases (e.g. P38 mitogen-activated protein (MAP) kinase) enhancing transcription factor activation (e.g. nuclear factor-κB(NF-κB)) and epigenetic events that lead to increased gene expression of proinflammatory mediators.

Mucous hypersecretion

A variety of elements such as IL-1β, TNF-α, cigarette smoke, lipopolysaccharides (LPSs), neutrophil elastase and oxidative stress ensue goblet cell metaplasia and mucus hypersecretion.[42] ROS produced by cigarette smoke, induces activation of vascular endothelial growth factor receptor (VEGFR) and initiates the TACE(TNFα converting enzyme) causing mucus production. This is followed by loss

of TGF-α in the epithelium of the respiratory tract.[43] COPD patients with a history of smoking manifest heightened levels of FGF in the airways. This establishes the role of FGF in mucous hypertension in these patients.[44]

Pulmonary Hypertension

This may develop later during the course of COPD. It is mainly due to the hypoxic vasoconstriction of small pulmonary arteries resulting in structural changes including intimal hyprerplasia, progressing to hypertrophy[45]. An inflammatory response in vessels, coupled with endothelial cell dysfunction is also quite commonly seen. The loss of pulmonary capillary bed in emphysema further contributes to increased pressure in pulmonary circulation.

Progressive pulmonary hypertension eventually results in right ventricular hypertrophy and right sided cardiac failure. The diameter of pulmonary arteries as measured on CT scans of chest, has been associated with increased risk of exacerbations[46]. This suggests that pulmonary vasculature by itself is a major risk factor for exacerbation.

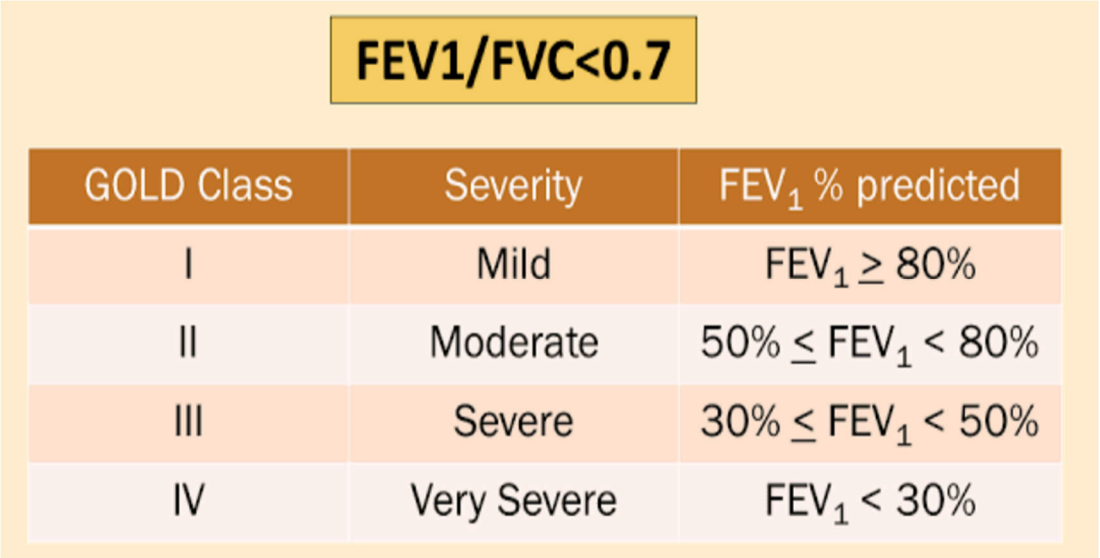
Gas Exchange Abnormalities

This results in hypoxemia and hypercapnia, contributing to pathogenesis in COPD. Reduced ventilation is primarily due to decreased drive of ventilation or raised dead space ventilation.[47]The abnormalities in the alveolar ventilation coupled with decreased pulmonary vascular blood flow, results in worsening of Ventilation Perfusion ratio.[48]

5. Classification of COPD

A post bronchodilator assessment of FEV1/FVC<0.7 is taken into account, keeping in line with the GOLD protocol 2021 for the diagnosis of COPD. The intensity of obstruction of airflow is categorized on the basis of post bronchodilator FEV1/FVC assessment. The categorization is given below:

Figure 3: Classification of airflow limitation intensity in COPD



6. COPD Exacerbation

COPD in acute exacerbation is interpreted as the sudden deterioration of pulmonary symptoms requiring supplemental therapy.[49]

Such exacerbations are generally characterized by marked airway inflammation, excessive mucus production and significant gas trapping. Patients usually present with sudden onset breathlessness and wheeze, cough with increased sputum production.

Exacerbation can be categorized as-

Mild- That requires treatment with short acting beta 2-agonist alone

Moderate- That requires treatment with short acting beta 2-agonist in conjuction with oral corticosteroid use and antibiotic therapy.

Severe- Requiring hospital admission. Patients having severe exacerbations usually have acute respiratory failure associated with it.

The most common triggering factor being viral infections of the respiratory tract, usually in the winter season, it can also be secondary to bacterial infection or environment pollution. Exposure to particulate matter(PM 2.5) for a short period can also precipitate exacerbation, leading to increased hospital admissions and high mortality of COPD patients.[50] Various studies have shown increased presence of sputum eosinophils in COPD patients.[51] This coupled with neutrophils and other inflammatory cells make the patient susceptible to viral infections.[52] Some patients have more frequent exacerbations(two or more in a year). These patients usually have poor health conditions and increased morbidity in comparison to patients with less frequent exacerbations.[53] A major predictor in the patient's exacerbator frequency primarily depends on the number of exacerbations he/she has had in the previous year.[54]

Other factors that may be associated with increased risk of acute exacerbations/severity of exacerbation include higher ratio of the pulmonary artery to aorta cross section dimension(ratio more than 1), usually seen in emphysema, as is measured by CT scan of the thorax.[55]

Deficiency of nutrients, primarily Vitamin D has also shown to be a causative agent for exacerbations. Studies have proved that Vitamin D supplementation in these patients aids in reducing the frequency of episodes as well as the hospital admissions as much by 50%.[56] Hence, it is advised that all patients admitted with exacerbation of

COPD should be evaluated for severe deficiency(less than 10ng/ml) and supplementation to be given if necessary.

Antibiotic use in COPD Exacerbation

There exists a controversy in the use of antibiotics in patients with acute exacerbation of COPD[57], despite knowledge of the fact that an infection by viruses or bacteria[58]could be the etiological agent. In order to initiate antibiotic in COPD patients, they must have the three chief symptoms of-

a. Increased dyspnoea
b. Increased sputum volume
c. Increased sputum purulence.

If sputum purulence alone is present, or the patient requires intensive care unit(ICU) admission[59], the proprosed duration of antibiotic use is between 5 days to 7 days.[60]

The selection of antibiotics is determined by the resistance pattern of the local bacterial agent. Patients presenting with frequent exacerbations, severe obstruction of airways,[61] requirement of mechanical ventilation,[62] sputum or any other substance from the respiratory tract has to be subjected to culture and sensitivity. This will help in identifying any gram negative bacteria(Pseudomonas aeruginosa) or any other resistant bacteria that may have colonized the airways. A favourable outcome is reported on the basis of amelioration of sputum purulence and breathlessness.

C- Reactive Protein

CRP is an acute phase serum protein produced in blood secondarily by inflammatory cytokines particularly Interleukin IL-6. [63] It belongs to the pentraxin family of proteins which is produced by liver.[64] CRP is synthesized by cells in the vascular wall namely, endothelial cells, smooth muscle cells, and by adipose tissue. [65]

Discovered by Tillett and Francis in 1930, CRP gene is located on chromosome 1[66]. It is a 224- residue protein with a molecular weight of 25106 Da. It was named due to its capacity to precipitate the somatic C-polysaccharide of Streptococcus pneumonia.[67]

It sets in motion the complement system and attaches to Fc receptors. [68]

Considerable rise in CRP levels suggest clinically significant inflammation, whereby, the absence of a raised CRP aids in the exclusion of probable infection/inflammation.[69]

Serial CRP values may provide a more precise analysis of inflammatory changes in response to treatment. CRP is very helpful in labelling a non-inflammatory cause to a significantly elevated ESR.

CRP values usually peak within 48 hours of hospital admission, in an acute phase reaction. The normal values are below 10mg/l.[70]Any values higher than 10mg/L is indicative of probable inflammatory disorders. Raised CRP values have low diagnostic variables, since a variety of conditions cause elevation of CRP levels.

CRP values are affected by the gender and racial characteristics of the patients. Men have lower values than women, while Caucasians have higher values than Afro-americans.[71]

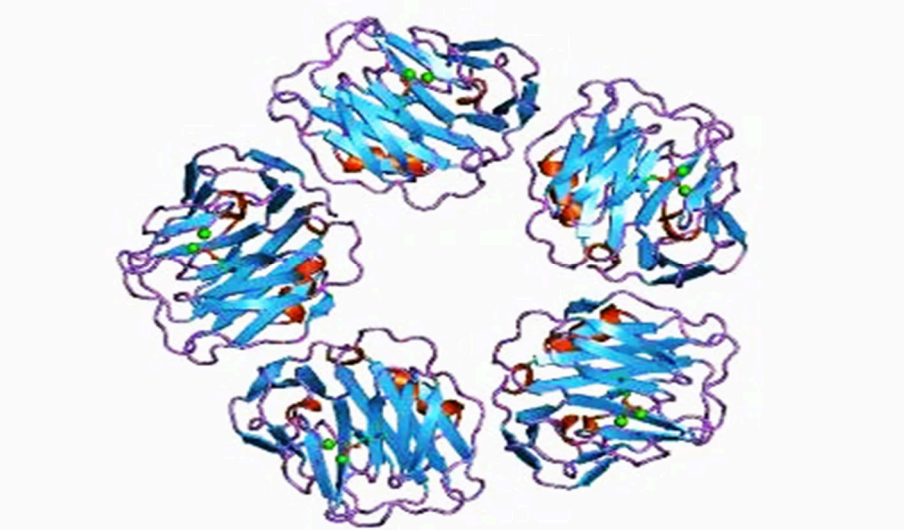


Figure 4: C-Reactive protein, pentraxin related

C- Reactive Protein in association with COPD Exacerbations

A study was conducted by Butler et al[72]. in United Kingdom for C-Reactive Protein testing to predict antibiotic use for COPD exacerbations. A multicentre , randomised controlled trial was performed. The study patients were allocated to receive standard therapy based on CRP testing (CRP-guided group) or standard care alone (usual-care group). The primary outcome variables were antibiotic use for COPD exacerbations within 1 month post randomization and disease-related health condition at 15 days post randomization, as evaluated on basis of Clinical COPD Questionnaire, a 10-item scale with scores ranging from 0 (very good COPD health status) to 6 (extremely poor COPD health status). A total of 653 patients were analysed. Fewer patients in the CRP group stated antibiotic use than in the usual-care group (57.0% vs. 77.4%). The mean difference in the total score on the Clinical COPD Questionnaire at 15 days was in favor of the CRP-guided group. Hence, it was concluded that a lesser percentage of patients in the CRP-guided group than in the usual-care group received an antibiotic prescription at the initial consultation with no documented adverse reactions.

A study conducted by Prins et al.[73], in Netherlands, to assess the CRP guided antibiotic usage in hospitalized patients with COPD exacerbation. They were randomised to obtain antibiotics based either on the GOLD guidelines or according to the CRP values. About 220 patients underwent randomization. Less patients in the CRP group received antibiotics in comparison to the GOLD group (31.7% vs. 46.2%, p=0.028). The 1-month failure to treatment rate was almost similar (44.5% in the CRP group versus 45.5% in the GOLD-group, p=0.88), as was the time to next exacerbation (32 days in the CRP group versus 28 days in the GOLD group, p=0.713). Hospital stay duration was almost same in both groups (7 days in the CRP group versus 6 days in the GOLD group, p=0.206). It was concluded that CRP guided antibiotic usage in patients, resulted in considerable reduction in antibiotic prescription.

A study was conducted by Bates et al[74]. in Cardiff university, United Kingdom on the use of CRP to guide antibiotic usage in COPD patients admitted with exacerbation. It was a multi-centre randomized controlled trial which included 650 participants. It suggested CRP is a reliable and cost effective biomarker to guide in prescribing antibiotics to patients with acute exacerbation of COPD.

Another study done by Daniels et al.[75] in Netherlands on the use of C Reactive protein vs. Procalcitonin as predictive markers of response to antibiotic therapy in acute exacerbation of COPD. A total of 205 patients were enrolled for this placebo-controlled trial. Clinical and pathogenic parameters, serum C-reactive protein (CRP) level (cutoffs 5 and 50 mg/L), and serum procalcitonin level (PCT) (cut-offs 0.1 and 0.25 mg) were assessed. A positive association between PCT and CRP (R= 0.46, P =

.001) was found. A large portion of patients (75%) had elevated CRP levels with low PCT levels. Although CRP levels were increased in the presence of bacteria, PCT levels were similar. PCT and CRP, both had similar effect on the clinical response, and a clinical success rate of 90% in patients with CRP less 5 mg/L was shown. A slow rising therapeutic outcome of antibiotics usage (6%, 10%, and 18%), was observed for individuals with values f C-reactive protein of less than 5, 6-50, and more than 50 mg/L, respectively, which was not significant. As against the existing information, this analysis recommended that cases with low procalcitonin values had benefitted from antibiotic therapy. C-reactive protein is a better marker in such patients.

A study was conducted by Carl Llor et al.[76] in Spain to explore the influence of CRP rapid test in antibiotics prescribing rate in patients with acute exacerbation of COPD. This was a multi-centered, double blinded, randomized controlled trial. A total of 310 patients were randomized. The primary outcome measure was clinical cure at end of therapy visit(i.e 9-11 Days). The median time to the next exacerbation was significantly longer in patients receiving antibiotic compared with placebo (233 d compared with 160 d). The best C-reactive protein serum cut-off for predicting clinical failure with placebo was 40 mg/L. It concluded the patients with mild to moderate COPD exacerbations, who were treated with antibiotics, had a considerably longer period to the next exacerbation as compared to placebo group.

A prospective non-randomised interventional pilot study conducted by Soler et al[77]. in Barcelona, Spain, to investigate association of purulent expectoration and serum biomarkers in prescribing antibiotics for COPD patients in exacerbation. 73 in hospital patients were include, of which 34 had purulent expectoration. The chief

outcome was scale of treatment failure during hospital admission. Minor outcomes were elements reflecting brief and prolonged results. No variations were noted on treatment failure yardstick(9% non-purulent versus 10% purulent (p=0.51). Serum C-reactive protein (CRP) was markedly raised in the purulent group at time of admission (11.6 versus 5.3, p=0.006) and at 3rd day (2.7 versus 1.2, p=0.01). Levels of serum Procalcitonin were identical between the two groups. No changes were noted in brief outcomes. The proportion of exacerbation at 6 months was more in the purulent group. It, therefore, concluded that serum CRP levels were raised in comparison to PCT, and maybe used as a useful parameter to determine antibiotic use in such patients.

Another study was conducted by Colak et al[78]. in Turkey to compare two biomarkers Procalcitonin and CRP in prescribing antibiotics in patients with acute exacerbation of COPD. A total of 116 participants were included in the study. Median serum CRP level was 44 mg/L value of serum PCT was estimated to be 0.07 in these patients. It concluded that CRP values was a better marker in comparison to PCT in these patients to help reduce antibiotic usage, and consecutively hospital stay.

Another study conducted by Strykowski et al[79]. in Copenhagen, Denmark, to evaluate changes in over and under-prescribing antibiotics in patients with acute exacerbation of COPD by using CRP values as an intervention in determining antibiotic usage. 952 patients with AECOPD were included in the study. Two types of intervention were conducted: Full intervention group (FIG) were exposed to a compound intervention and antibiotics started on basis of C-reactive protein (CRP) testing; partial-intervention group (PIG) was only exposed to the compound intervention. Overuse was described as antibiotic used in a patient having type III exacerbation (≤ one Anthonisen Criteria); Under-utilization was defined as no antibiotic initiated, in a

patient having type I exacerbation (three Anthonisen Criteria). It was inferred that CRP was a handy investigation to curtail the excessive use of antibiotics.

The rampant utilization of antibiotics in patients with COPD exacerbation contributes to high medical costs and risk of adverse drug reactions. CRP is a more accessible and feasible biomarker in contrast to PCT, which may avoid unnecessary antibiotic use and as well reduce hospital stay in patients with acute exacerbation of COPD.

Hence the present study has been taken up to know the CRP directed prescription of antibiotic in patients with COPD in acute exacerbation.

METHODOLOGY

A 12 month randomized controlled trial was conducted in KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi.

Study Design

It is a randomized controlled trial.

Study Period and Duration

The study was conducted between January 2020 to December 2020, for 1 year.

Study Location

The study was conducted in the Department of Respiratory Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi.

Sample Size

The minimum sample size formula based on two proportions is

$$n = \frac{(z_\alpha + z_\beta)^2 \bar{p}(1-\bar{p})}{d^2}$$

where p_1 and p_2 are the proportions of the two groups.

$$p = \frac{p_1 + p_2}{2} \text{ and } d = p_1 - p_2$$

z_α is linked with the level of significance and z_β is linked with the power of the test. For 5% level of the significance $z_\alpha = 1.96$ and $z_\beta = 0.84$ for 80% power of the test.

Ref:

By taking proportion of success, p_1 = 37.7% and p_2 = 69.7% the sample size obtained is 38.

There would be two groups with minimum size of 38.

A total of 90 patients were included in the study.

Source of Data

Data was culminated from all the patients admitted with COPD in acute exacerbation, under the Department of Respiratory Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi, for a period of 12 months.

Outcome

Reduction in antibiotic usage through CRP guidance was the primary outcome.

Duration of hospital stay, duration of ICU stay, duration of treatment with non-invasive ventilation, duration of treatment with invasive mechanical ventilation, rate of mortality and the total hospital expenditure were the secondary outcomes.

Inclusion Criteria

Patients getting admitted to the hospital with acute exacerbation of COPD.

Exclusion Criteria

1) Infection at another site(eg. UTI, cellulitis, brain abscess) that may likely produce a systemic response.

2) Currently taking antibiotics for AECOPD.

3) Acute inflammatory conditions (Rheumatoid arthritis, gout, or polymyalgia rheumatica)

4) Immunocompromised patients like HIV, patients on chemotherapy, patients on steroid, patients on immunosuppressive therapy

5)Active case of Tuberculosis, lung abscess, bronchiectasis with secondary infection.

6) Septicemia due to other causes.

Method of data Collection

All patients with COPD in acute exacerbation, getting admitted to the hospital were included in the study.

A diagnosis of COPD was made based on GOLD 2021 criteria which mandates a post bronchodilator FEV1/FVC of < 0.70. The pulmonary function values used in this study was obtained from patients before the study and not in the course of the exacerbation.

The classification of patients was based on Anthonisen's criteria for COPD Exacerbation.

Figure 5: Anthonisen's Classification of COPD exacerbation

TYPE I(Most Severe)	TYPE II	TYPE III
All three symptoms(Increased dyspnoea, Increased sputum volume, Increased sputum purulence)	Any of the two symptoms	One symptom with atleast one of the below- a. An upper respiratory tract infection in the past 5 days, b. increased wheezing, c. increased cough d. fever without obvious source e. A 20% increase in the respiratory rate and heart rate above baseline

A detailed history will be taken in the form of a systematic proforma regarding patient age, sex, past medical/surgical history. After considering inclusion and exclusion criteria the patients were taken for the study.

- Patients were randomized into two groups, following consent, by simple random sampling.
- In the Standard Care group, the patient is initiated on antibiotic therapy regardless of CRP values.
- In the Intervention group, the patient is started on antibiotic treatment based on the CRP values.

The CRP values are interpreted as follows-

- CRP<20- Antibiotics are unlikely to be beneficial and usually should not be prescribed.
- CRP = 20-40- Antibiotics maybe be beneficial- Mainly if purulent sputum is present, after taking into account the patient's underlying health condition and features of current exacerbation.
- CRP> 40- Antibiotics likely to be beneficial.

Due to the availability of HsCRP in our hospital laboratory, HsCRP values were taken and converted to CRP by a factor of 10.

Investigations

1. Complete Haemogram
2. Highly sensitive C-Reactive Protein (HsCRP)
3. Renal and Hepatic Profile
4. Chest X-Ray
5. Sputum for Gram stain, culture and Sensitivity
6. Viral Markers- HIV, HBsAg, HCV

Ethical Clearance

The ethical clearance was obtained from the Ethical and Research Committee, KLE Academy of Higher Education and Research centre, Belagavi, prior to the commencement of the study.

Informed Consent

All the participants who had fulfilled the above criteria, were duly informed about the proceedings of the study and their written consent was obtained before their inclusion into the study.

Statistical Analysis

The study is focused on comparison of two groups. For the continuous quantitative variables mean and standard deviation will be calculated. The inter group continuous variables will be compared using suitable tools of statistics like unpaired student's t test. Two quantitative variables, within a group, will be compared using student's paired t test.

Discrete variables will be represented by median. Suitable graphs will be used to depict the comparison.

The categorical data will be expressed in terms of rates, ratios and percentages. The association between the outcome, clinical and demographic characteristics will be tested using Chi-square test or Fisher's exact test. Nonparametric tests will be used for discrete variables.

For all the tests the value of p less than 5% (0.05) will be considered significant.

RESULTS

This prospective observational study for 1 year was conducted in KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi.

106 patients with COPD in acute exacerbation were included in the study. 12 patients were removed in view of other chronic lung diseases. 4 patients were discharged against medical advice. Hence, 90 patients were assessed in the final analysis.

All the patients were randomly distributed into two groups(Simple Random Sampling), the CRP group(Intervention Group) and Standard Care group. CRP group comprised 40 patients and Standard Care group comprised 50 patients for the final analysis.

The mean age in CRP group was 60.30±7.80 and in Standard Care group was 61.32±7.46. Most of the study patients were primarily in the age group of 50-59 years comprising of 42.50% patients in the CRP group and 43.33% patients in the Standard Care group.

Majority of the patients were male comprising of 66.67% of the overall patients. In the CRP group, there were 26 males(65%) and in the Standard Care group, there were 34 males(68%). The mean BMI of overall patients was 22.82.

The number of smokers in the Standard Care group accounted to 50% as against 45% in the CRP group. The mean number of smokers in both groups were 47.5%.

The mean FEV1% in the CRP group was 59.74% ± 11.86% while it was 55.37% ± 8.86% in the Standard Care group. The mean FEV1/FVC ratio was 0.56 ± 0.13 in the CRP group while it was 0.55 ± 0.10 in the Standard Care group.

The mean duration of symptoms prior to hospital admission in both groups was 7.62 ± 0.34 days.

The primary cause of exacerbation accounted for infection, presenting in 14(35%) patients in the CRP group, while in 13(26%) of the patients in the Standard Care group. The overall cause of exacerbation in both groups was due to infection, seen in 27(30.5%)patients. The other causes of exacerbation included indoor pollution(14.5%), outdoor pollution(15.5%), irregular inhaler use(9.75%) and unknown(26.5%).

A greater portion of the patients among both groups belonged to the class II of Anthonisen's classification comprising upto 38(42%) patients. The Standard Care group consisted of more patients in class I comprising upto 18(36%) patients. While CRP group comprising upto 12(30%) patients.

The mean CRP values in all patients of both groups was 43.28 ± 8.82. In the CRP group, it was 39.68 ± 12.22 while in the Standard Care group, it was 46.88 ± 5.42.

Table 1: Baseline Characteristics Of Study Patients

BASELINE CHARACTERISTICS	**TOTAL(N=90)**	**CRP GROUP(N=40)**	**GOLD GROUP(N=50)**	**P VALUE**
AGE(in years)	60.87 ± 7.59	60.30 ± 7.46	61.32 ± 7.46	0.52
SEX(Males)	60(66.67%)	26(65%)	34(68%)	0.76
BMI (Kg/m^2)	22.82 ± 3.50	22.82 ± 3.96	22.83 ± 3.04	0.90
MEAN DAYS WITH SYMPTOMS	7.62 ± 2.25	7.85 ± 2.73	7.40 ± 1.78	0.34
FEV1%	57.50 ± 10.2	59.74 ± 11.63	55.37 ± 8.86	0.08
FEV1/FVC	0.55 ± 0.12	0.56 ± 0.13	0.55 ± 0.10	0.699
CURRENT SMOKER	43(47.78%)	18(45%)	25(50%)	0.63
HYPERTENSION	41(45.56%)	18(45%)	23(46%)	0.92
TYPE II DIABETES MELLITUS	30(33.33%)	14(35%)	16(32%)	0.76
IHD	18(20%)	8(20%)	10(20%)	1.00
OTHER CO-MORBIDITIES	11(12.22%)	5(12.50%)	6(12.00%)	0.94
O2 SATURATION AT ADMISSION(%)	85.9 ± 5.32	86.20 ± 4.95	85.7 ± 5.70	0.66
WBC COUNTS(IN 10^9 CU.MM)	12.67 ± 2.24	12.29 ± 2.21	13.13 ± 2.27	0.08
CRP VALUES	43.24 ± 8.8	39.68 ± 12.22	46.88 ± 5.42	0.0003
CRP VALUES>40	48(53.3%)	21(52.5%)	27(54%)	0.98
OXYGEN MASK	54(61%)	28(70%)	26(52%)	0.29
CPAP	16(17%)	4(10%)	12(24%)	0.56
INVASIVE MECHANICAL VENTILATION	8(8.5%)	2(5%)	6(12%)	0.20
NO. OF EXACERBATIONS IN THE LAST YEAR				
NONE	73(81%)	33(82.5%)	40(80%)	0.743
ONE	10(11.11%)	5(12.5%)	5(10%)	
TWO	6(6.67)	4(8%)	2(5%)	
THREE	1(1%)	0	1(2%)	

Figure: Flowchart Of Study Patients

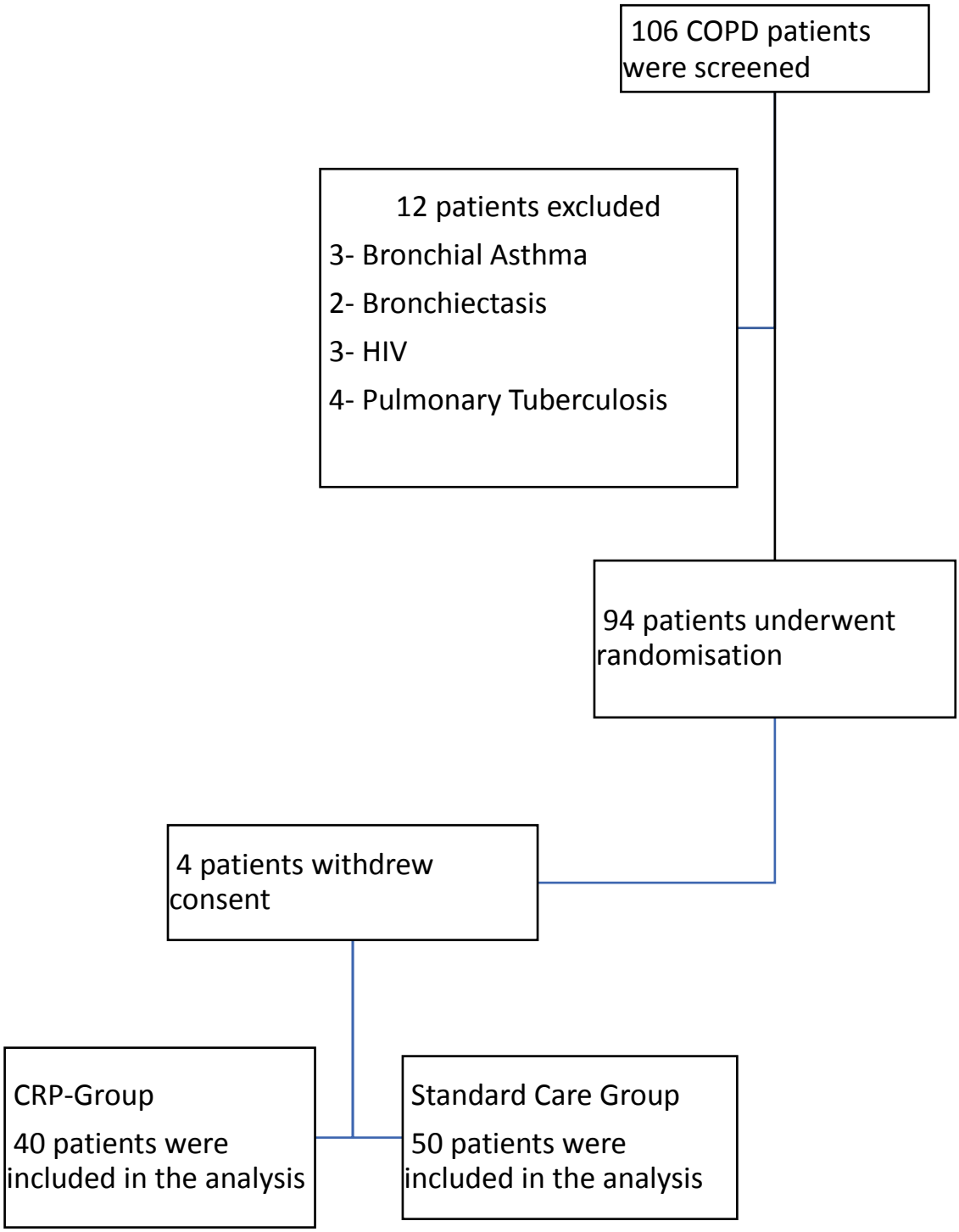
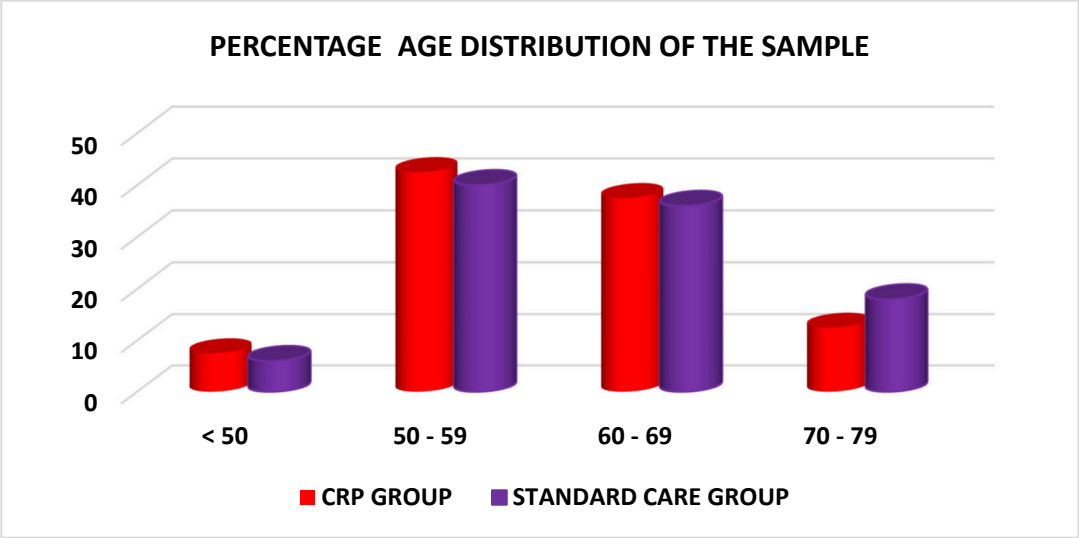


Table 2: Comparison of age among the two groups

	CRP GROUP		STANDARD CARE GROUP	
AGE (YEARS)	**NUMBER**	**PERCENTAGE**	**NUMBER**	**PERCENTAGE**
< 50	3	7.50	3	6.00
50 - 59	17	42.50	20	40.00
60 - 69	15	37.50	18	36.00
70 - 79	5	12.50	9	18.00
TOTAL	40	100.00	50	100.00

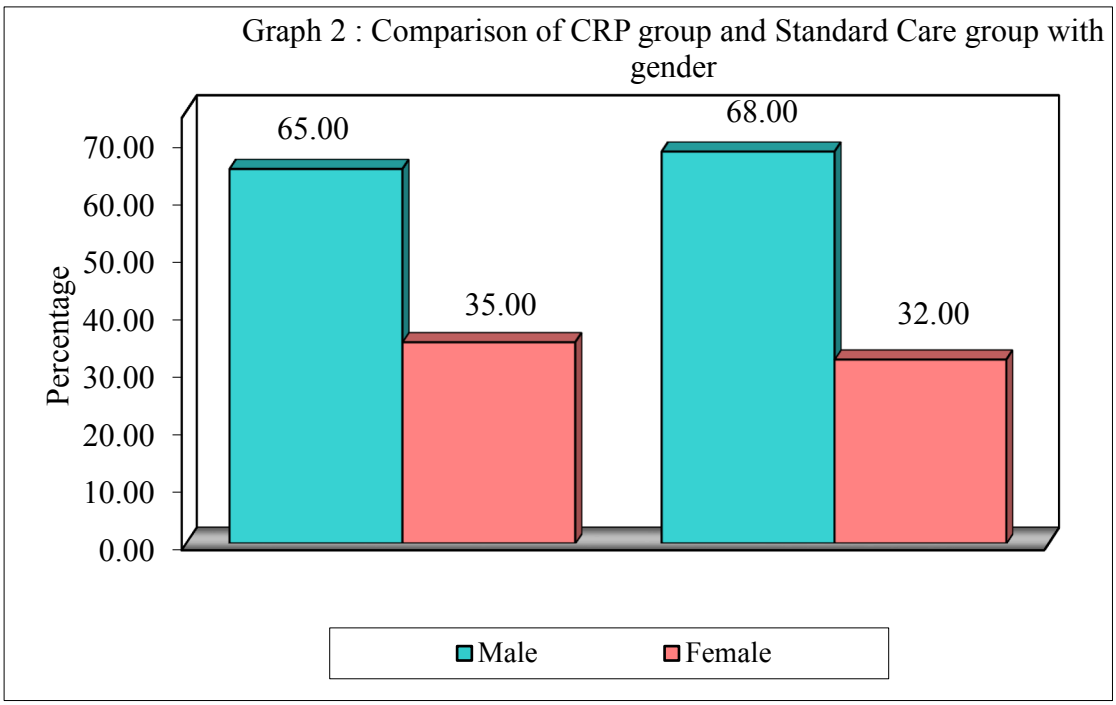
Graph 1: Comparison of age among the two groups



The greater portion of patients were in the age group 50-59 amounting to 17(42.50%) patients in CRP group while there were 22(44%) patients in the GOLD group. In the age group 60-69, there were 15(37.50%) patients in CRP group, while Standard Care group consisted of 17(34%) patients.

Table 3 : Comparison of CRP group and Standard Care group with gender

GENDER	CRP GROUP	%	STANDARD CARE GROUP	%	TOTAL	%
MALE	26	65.00	34	68.00	60	66.67
FEMALE	14	35.00	16	32.00	30	33.33
TOTAL	40	100.00	50	100.00	90	100.00



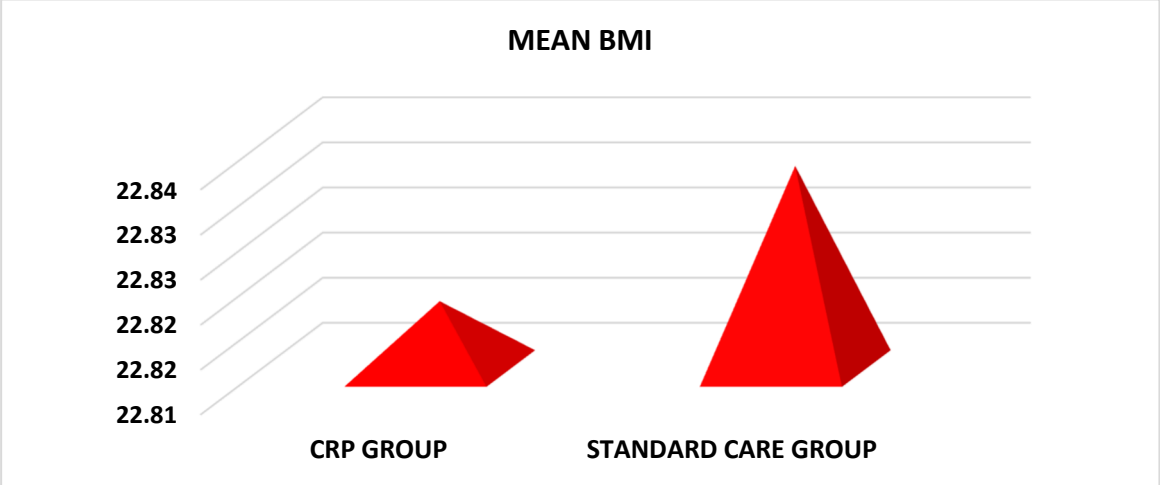
Majority of the patients were male comprising of 66.67% of the overall patients. In the CRP group, there were 26 males(65%) and in the GOLD group, there were 34 males(68%).

Table 4: Comparison mean BMI among the two groups

	CRP GROUP		STANDARD CARE GROUP	
	MEAN	**S.D.**	**MEAN**	**S.D.**
BMI	22.82	3.96	22.83	3.04

p= 0.90, Not significant

Graph 3: Comparison mean BMI among the two groups



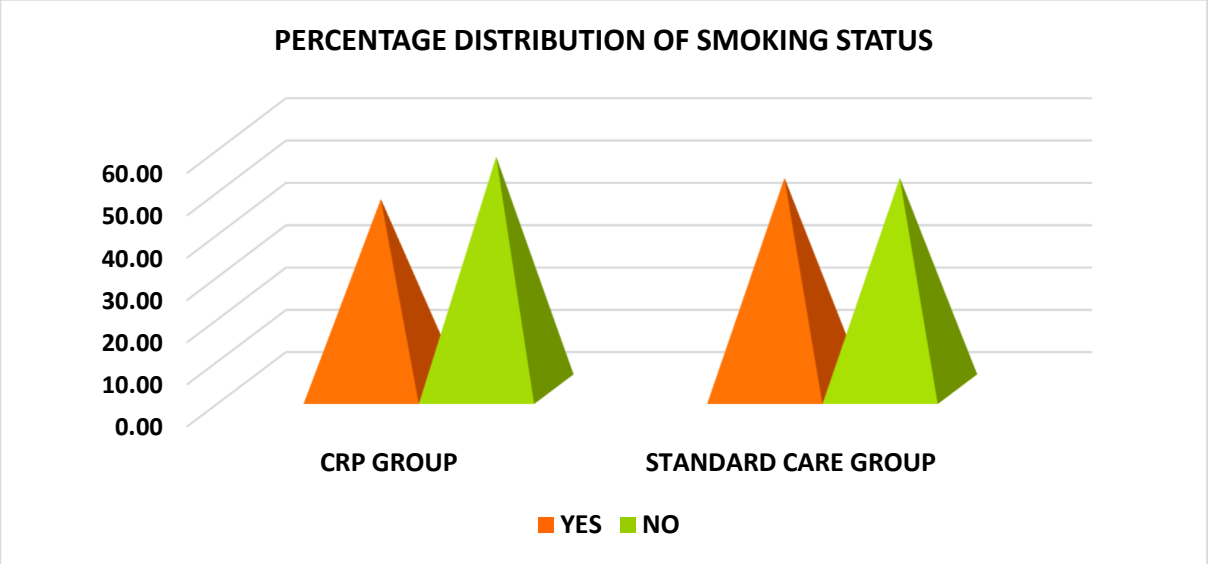
The mean BMI of patients in CRP group was 22.82 ± 3.96 and in Standard care group was 22.83 ± 3.04. The mean BMI of overall patients was 22.82 ± 3.50. The p value was 0.90, which is not statistically significant.

Table 5: Comparison of Smoking status among the two groups

	CRP GROUP		STANDARD CARE GROUP	
SMOKING STATUS	**NUMBER**	**PERCENTAGE**	**NUMBER**	**PERCENTAGE**
YES	18	45.00	25	50.00
NO	22	55.00	25	50.00
TOTAL	40	100.00	50	100.00

p= 0.63, Not significant

Graph 4: Comparison of Smoking status among the two groups



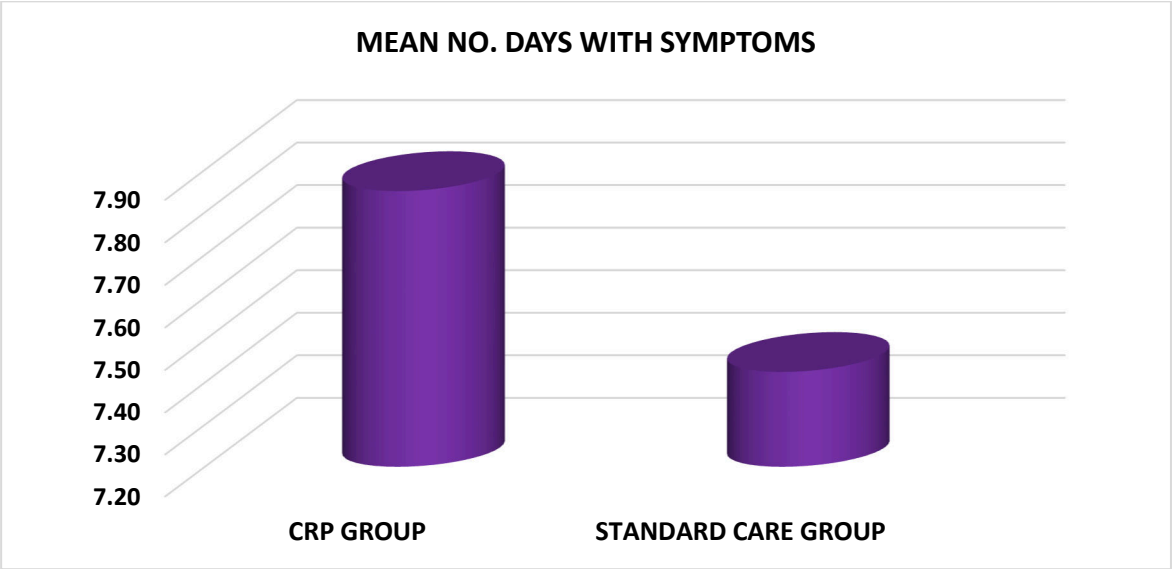
The number of smokers in the Standard Care group accounted to 50% as against 45% in the CRP group. The mean number of smokers in both groups were 47.5%. The p value was 0.63, which is not statistically significant.

Table 6: Comparison of mean no. of days with symptoms

GROUPS	N	MEAN	SD
CRP GROUP	40	7.85	2.73
STANDARD CARE GROUP	50	7.40	1.78

p value= 0.47, Not significant

Graph 5: Comparison of mean no. of days with symptoms

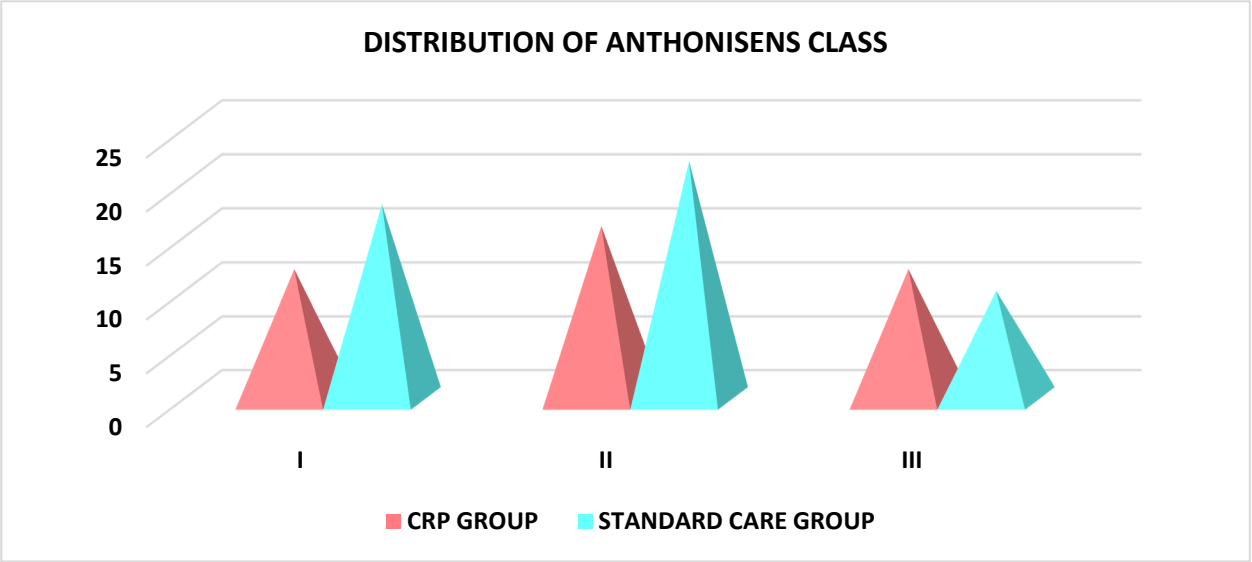


The mean duration of symptoms prior to hospital admission in the CRP group was 7.85 ± 2.73 days, while in the Standard Care group, it was 7.40 ± 1.78 days. The overall mean duration of symptoms in both groups was 7.62 ± 0.34 days.

Table 7: Comparison of Anthonisen's class in both the groups

	CRP GROUP		STANDARD CARE GROUP	
ANTHONISENS CLASS	**NUMBER**	**PERCENTAGE**	**NUMBER**	**PERCENTAGE**
I	12	30.00	18	36.00
II	16	40.00	22	44.00
III	12	30.00	10	20.00
TOTAL	40	100.00	50	100.00
P= 0.53, Not Significant				

Graph 6: Comparison of Anthonisen's class in both the groups



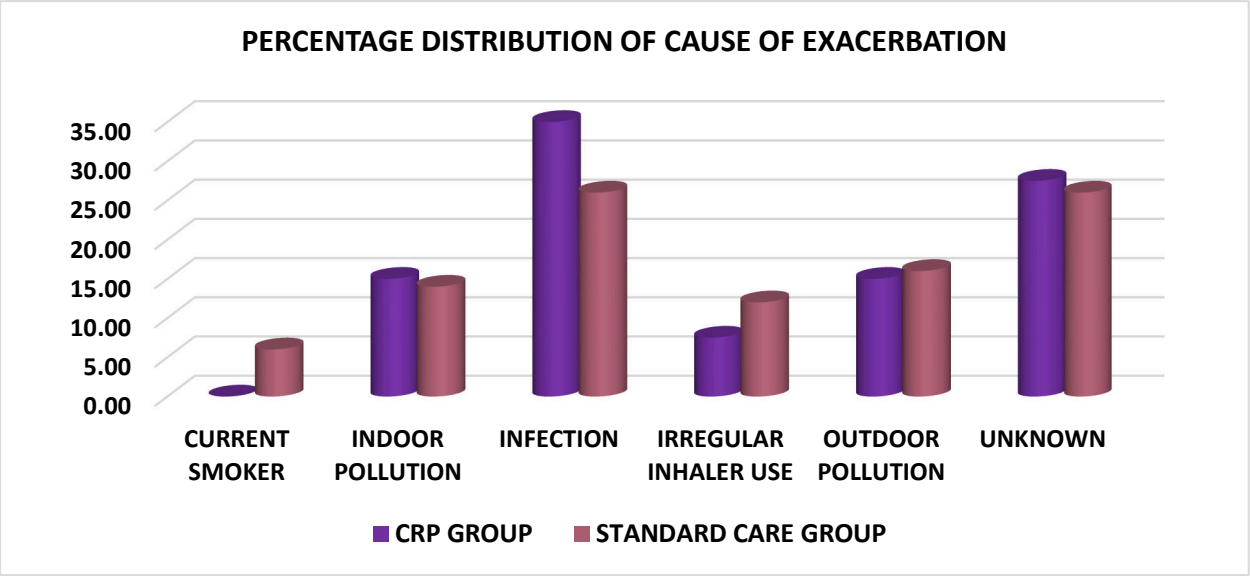
A greater portion of the patients among both groups belonged to the class II of Anthonisen's classification comprising upto 38(42%) patients. The Standard Care group consisted of more patients in class I comprising upto 18(36%) patients, while the CRP group was comprising upto 12(30%) patients.

Table 8: Causes of Exacerbation among study patients

	CRP GROUP		STANDARD CARE GROUP	
CAUSE OF EXACERBATION	NUMBER	PERCENTAGE	NUMBER	PERCENTAGE
CURRENT SMOKER	0	0.00	3	6.00
INDOOR POLLUTION	6	15.00	7	14.00
INFECTION	14	35.00	13	26.00
IRREGULAR INHALER USE	3	7.50	6	12.00
OUTDOOR POLLUTION	6	15.00	8	16.00
UNKNOWN	11	27.50	13	26.00
TOTAL	40	100.00	50	100.00

p=0.62, Not Significant

Graph 7: Causes of Exacerbation among study patients



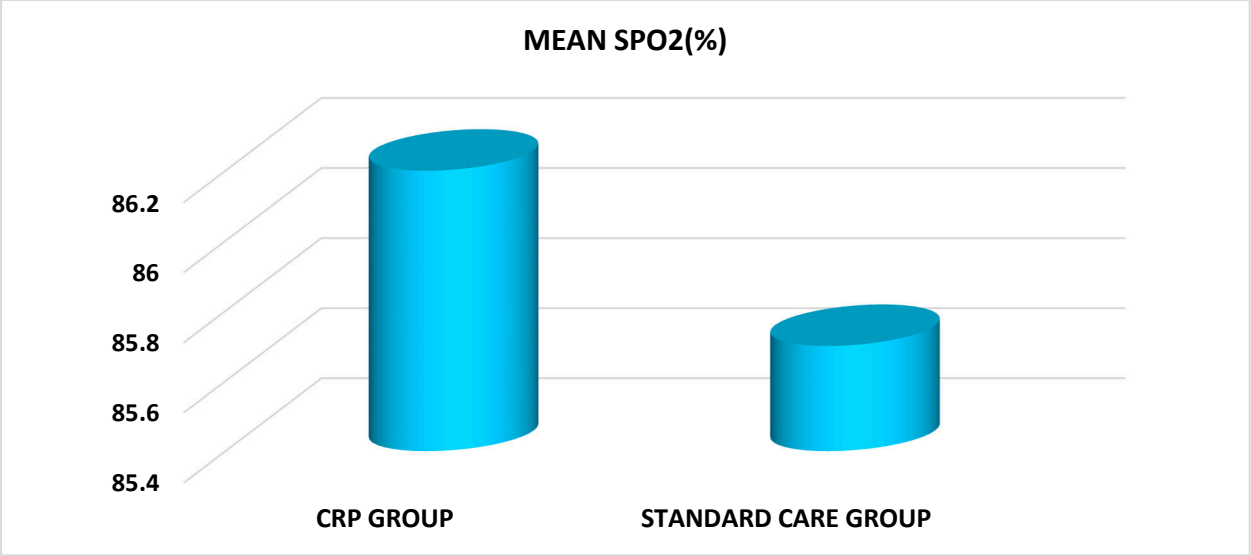
The primary cause of exacerbation accounted for infection, presenting in 14(35%) patients in the CRP group, while in 13(26%) of the patients in the Standard Care group. The overall cause of exacerbation in both groups was due to infection, seen in 27(30.5%)patients. The other causes of exacerbation included indoor pollution(14.5%), outdoor pollution(15.5%), irregular inhaler use(9.75%) and unknown(26.5%).

Table 9: Comparison of mean oxygen saturation(SPO2) on admission between the groups

	CRP GROUP		STANDARD CARE GROUP	
	MEAN	**S.D.**	**MEAN**	**S.D.**
SPO2(%)	86.2	4.95	85.70	5.79

p= 0.62, Not significant

Graph 8: Comparison of mean oxygen saturation(SPO2) on admission between the groups



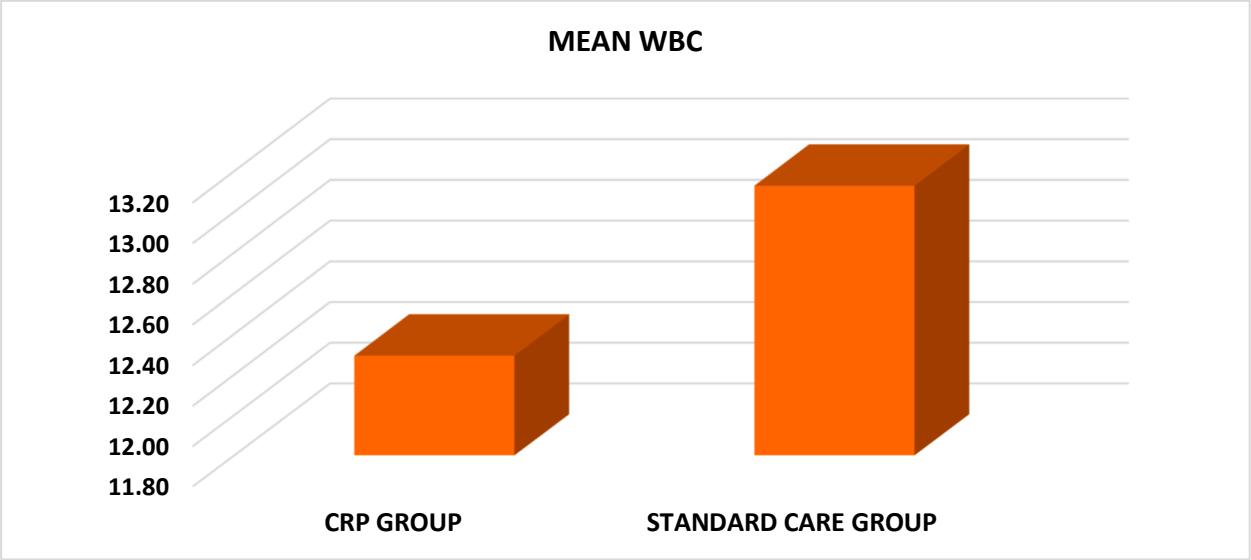
The mean SPO2% at admission was 86.2 ± 4.95 in the CRP group, while it was 85.70 ± 5.79 in the Standard Care group. The p value was 0.62, which was not significant.

Table 10: Comparison of mean WBC between the two groups

GROUPS	N	MEAN	SD
CRP GROUP	40	12.29	2.21
STANDARD CARE GROUP	50	13.13	2.27

p= 0.08, Not significant

Graph 9: Comparison of mean WBC between the two groups



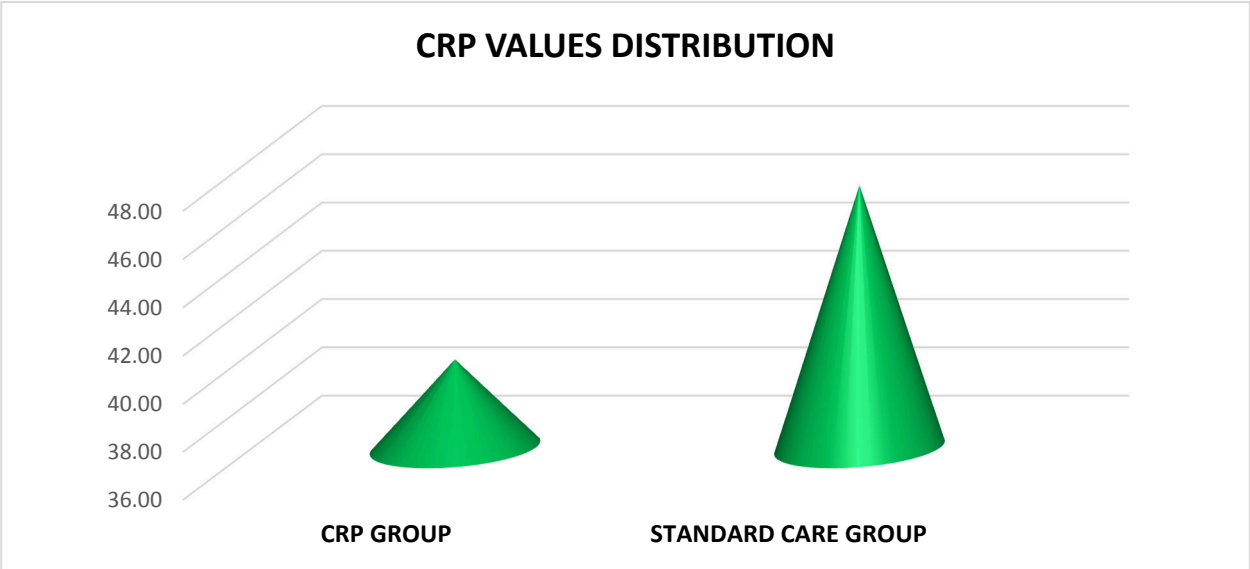
The mean WBC in the CRP group was 12.29 ± 2.21, while the mean value in the Standard Care group was 13.13 ± 2.27. The p value was 0.08 which was not significant.

Table 11: Comparison of mean CRP values between the two groups

	CRP GROUP		STANDARD CARE GROUP	
	MEAN	**S.D.**	**MEAN**	**S.D.**
CRP	39.68	12.22	46.88	5.42

p= 0.0003, Highly significant

Graph 10: Comparison of mean CRP values between the two groups



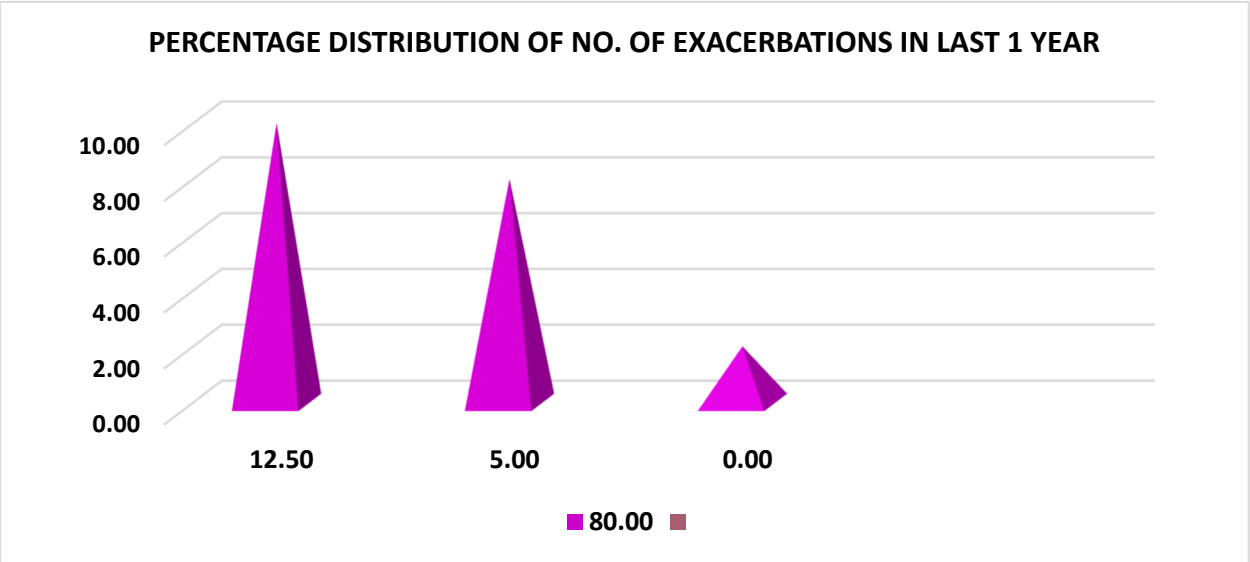
In the CRP group, the CRP value was 39.68 ± 12.22 while in the GOLD group, it was 46.88 ± 5.42. The mean CRP values in all patients of both groups was 43.28 ± 8.82. The p value was 0.0003, which was statistically significant.

Table 12: Comparison of CRP group and Standard care group with No. of exacerbations in last 1year

	CRP GROUP		STANDARD CARE GROUP	
NO. OF EXACERBATIONS IN LAST 1 YEAR	**NUMBER**	**PERCENTAGE**	**NUMBER**	**PERCENTAGE**
0	33	82.50	40	80.00
1	5	12.50	5	10.00
2	2	5.00	4	8.00
3	0	0.00	1	2.00
TOTAL	40	100.00	50	100.00

p= 0.74, Not significant

Graph 11: Comparison of CRP group and Standard Care group with No exacerbations in last 1year



The number of exacerbations in both groups are similar, in the past 1 year. The p value is 0.74, which is not significant.

Table 13: Comparison of microorganisms grown in sputum culture among the study patients

	CRP GROUP		STANDARD CARE GROUP		TOTAL	
SPUTUM C/S	**NUMBER**	**PERCENTAGE**	**NUMBER**	**PERCENTAGE**	**NUMBER**	**PERCENTAGE**
ACINETOBACTER BAUMANNI	1	2.50	3	6.00	4	4.25
COMMENSALS	5	12.50	3	6.00	8	9.25
HAEMOPHILUS INFLUENZA	7	17.50	8	16.00	15	16.75
KLEIBSELLA PNEUMONIAE	10	40.00	22	44.00	38	42.00
MORAXELLA CATRAHALLIS	1	2.50	2	4.00	3	3.25
NO GROWTH	4	10.00	3	6.00	7	8.00
PSEUDOMONAS AERUGINOSA	0	0.00	2	4.00	2	2.00
STREP PNEUMONIAE	6	15.00	7	14.00	13	14.50
TOTAL	40	100.00	50	100.00	90	100

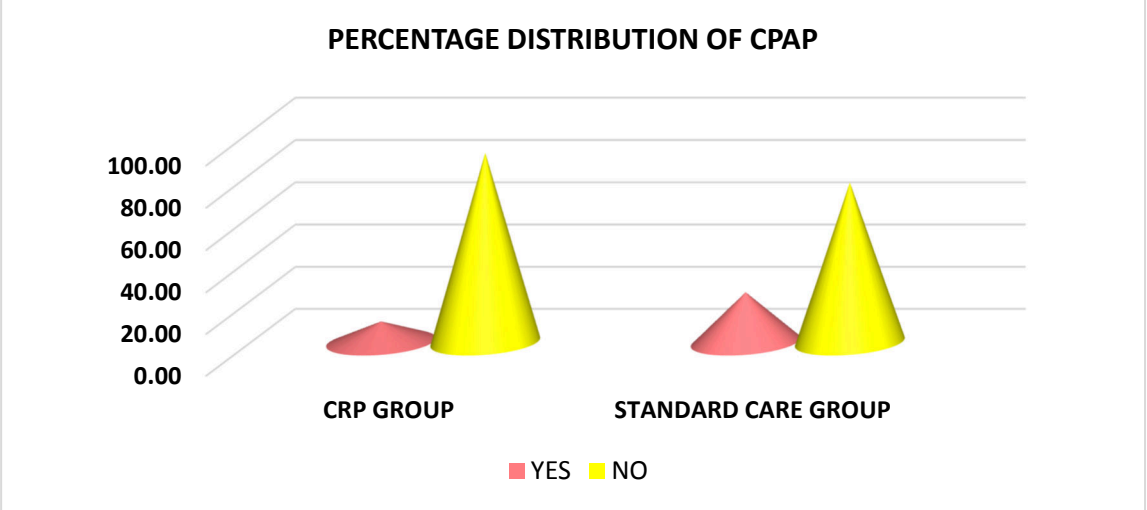
In the sputum culture, the most frequently isolated organism was Kleibsella pneumoniae, seen in 38(42%) patients of the study population . This was followed by Haemophilus influenzae and Streptococcus pneumoniae, isolated in 15(16.75%) patients and 13(14.50%) patients respectively.

Table 14: Comparison of patients on CPAP among the two groups

	CRP GROUP		STANDARD CARE GROUP	
CPAP	**NUMBER**	**PERCENTAGE**	**NUMBER**	**PERCENTAGE**
YES	4	10.00	12	24.00
NO	36	90.00	38	76.00
TOTAL	40	100.00	50	100.00

p=0.08, Not significant

Graph 12: Comparison of patients on CPAP among the two groups



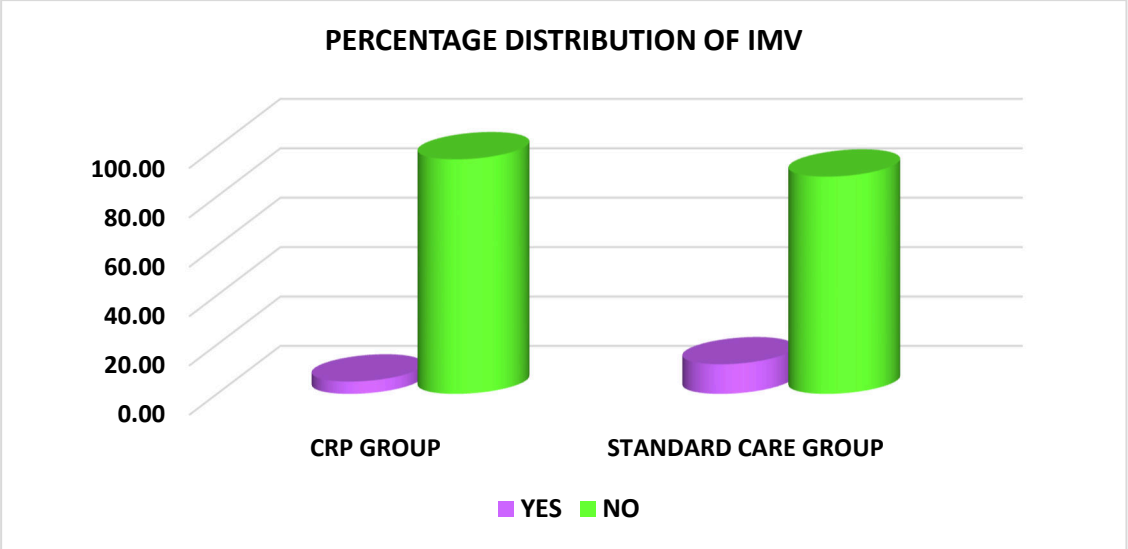
In the CRP group, 4(10%) patients required non-invasive ventilatory support, while in the Standard Care group, 12(24%) patients had to be connected to CPAP. The p value was 0.08, which was not statistically significant.

Table 15: Comparison of patients on IMV among the two groups

	CRP GROUP		STANDARD CARE GROUP	
IMV	**NUMBER**	**PERCENTAGE**	**NUMBER**	**PERCENTAGE**
YES	2	5.00	6	12.00
NO	38	95.00	44	88.00
TOTAL	40	100.00	50	100.00

p= 0.24, Not significant

Graph 13: Comparison of patients on IMV among the two groups



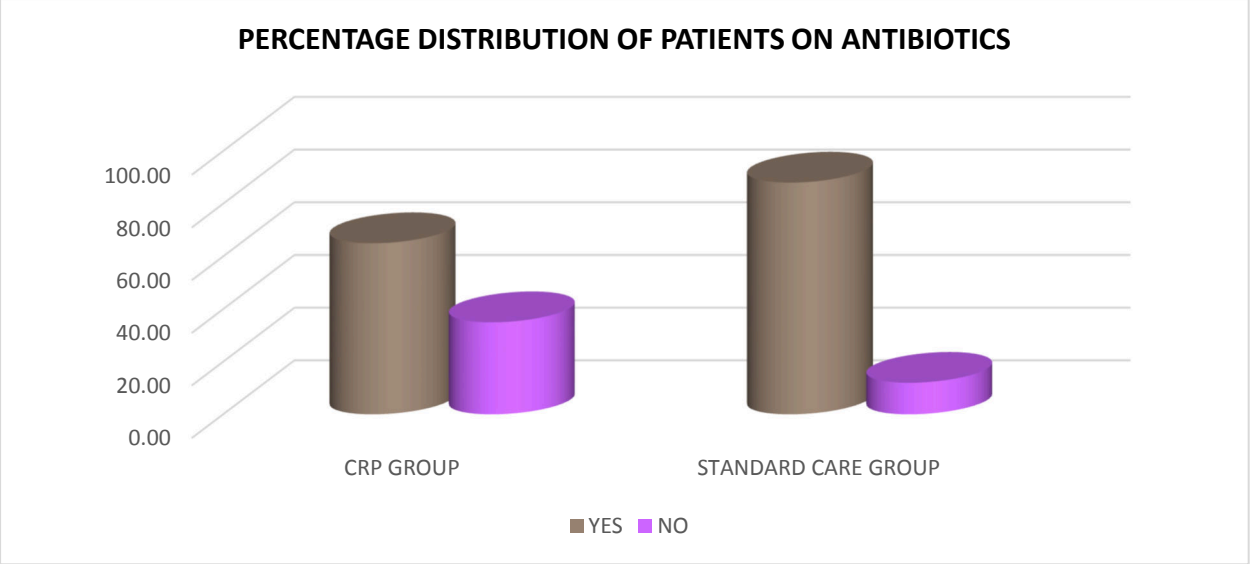
In the CRP group, 2(5%) patients required invasive mechanical ventilation, while in the Standard Care group, 6(12%) patients required endotracheal intubation. The p value was 0.24, which was not statistically significant.

Table 16: Comparison of patients on antibiotics among the two groups

	CRP GROUP		STANDARD CARE GROUP	
	NUMBER	PERCENTAGE	NUMBER	PERCENTAGE
YES	26	65.00	44	88.00
NO	14	35.00	6	12.00
TOTAL	40	100.00	50	100.00

p=0.0091, Very significant

Graph 14: Comparison of patients on antibiotics among the two groups



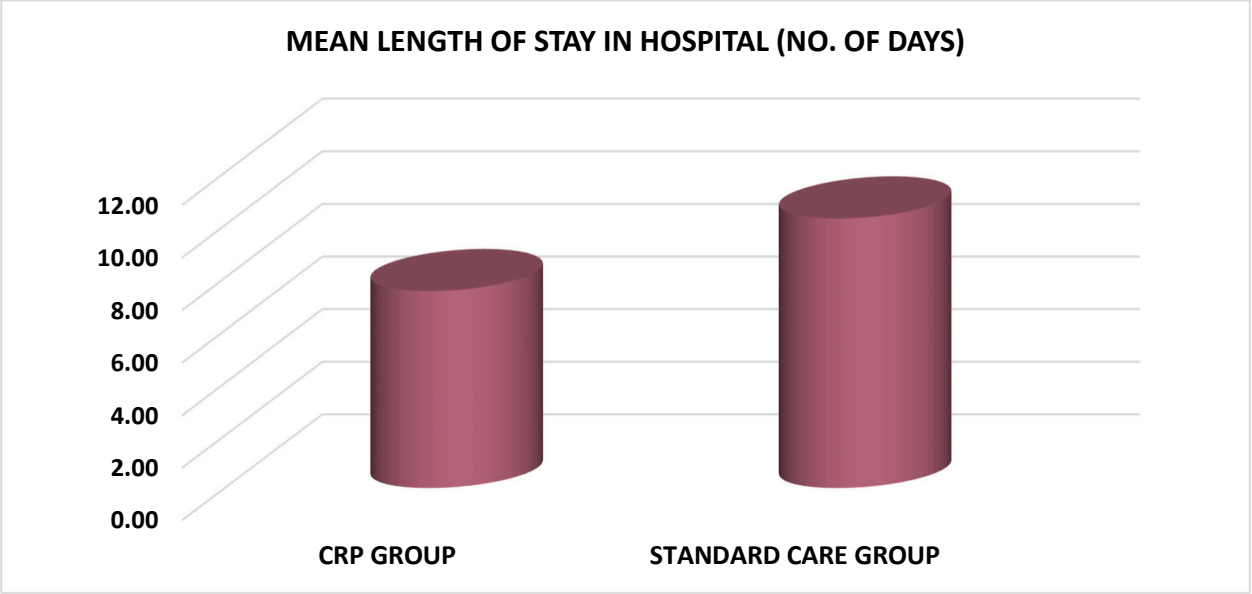
In the CRP group, 26(65%) patients were on antibiotic treatment, whereas in the Standard Care group, 44(88%) patients were started on antibiotic therapy. The p value was 0.0091, which was statistically very significant.

Table 17: Comparison of Length of Hospital stay among patients in the two groups

Groups	N	MEAN	SD
CRP GROUP	40	7.50	2.87
STANDARD CARE GROUP	50	10.12	3.91

p= 0.0006, Highly significant

Graph 15: Comparison of Length of Hospital stay among patients in the two groups



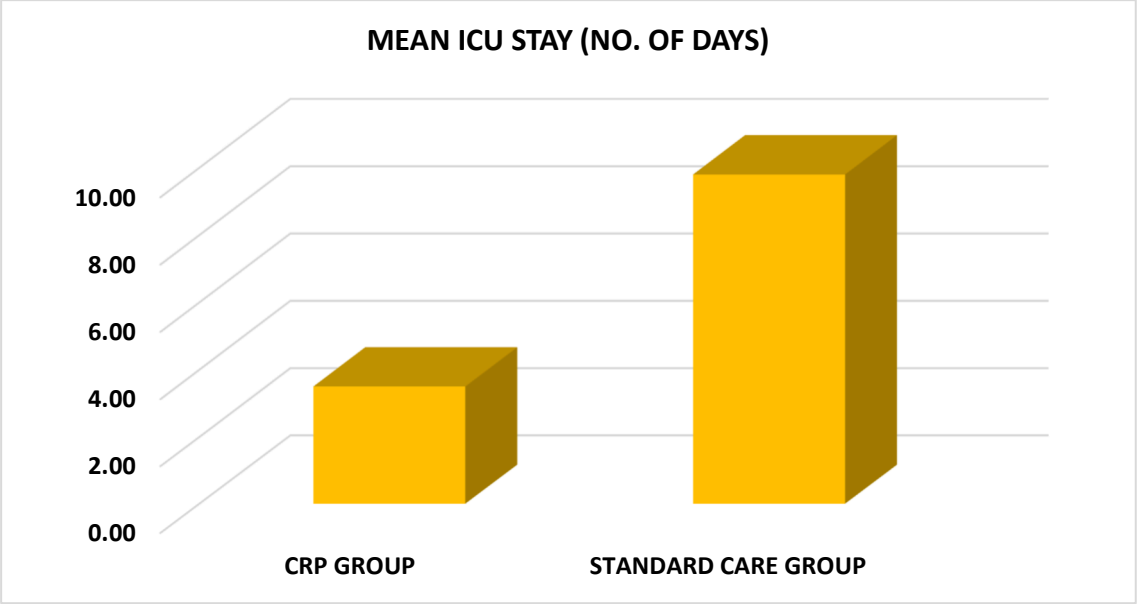
In the CRP group, the mean length of hospital stay is 7.50 ± 2.87 days, while in the Standard Care group, it is 10.12 ± 3.91 days. The p value is 0.0006, which is statistically highly significant.

Table 18: Comparison of Length of ICU stay among the two groups

	CRP GROUP		STANDARD CARE GROUP	
	MEAN	**S.D.**	**MEAN**	**S.D.**
ICU STAY (NO. OF DAYS)	3.50	1.05	9.80	3.59

p= 0.0005, Highly significant

Graph 16: Comparison of Length of ICU stay among the two groups



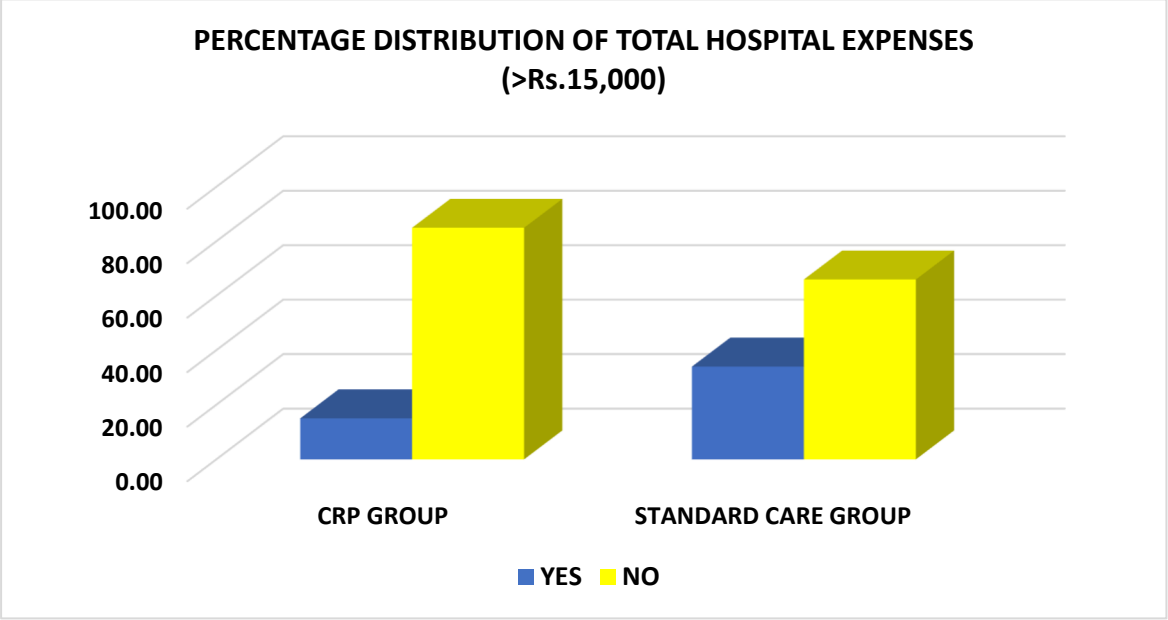
In the CRP group, the mean length of ICU stay is 3.50 ± 1.05 days, while in the Standard Care group, the mean length of ICU stay is 9.80 ± 3.59 days. The p value is 0.0005, which was statistically highly significant.

Table 19: Comparison of Hospital expenditure between the two groups

TOTAL HOSPITAL EXPENSES (>Rs.15,000)	CRP GROUP		STANDARD CARE GROUP	
	NUMBER	PERCENTAGE	NUMBER	PERCENTAGE
YES	6	15.00	17	34.00
NO	34	85.00	33	66.00
TOTAL	40	100.00	50	100.00

p= 0.04, Significant

Graph 17: Comparison of Hospital expenditure between the two groups



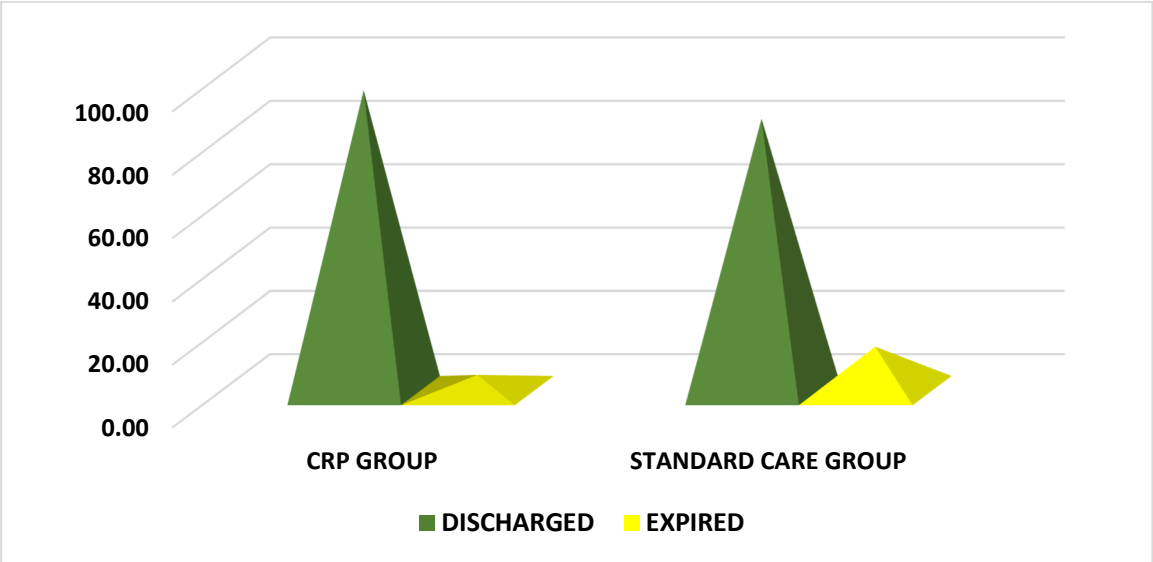
In the CRP Group, it is seen that 6% of the patients had a total hospital expenditure of more than Rs. 15,000, while in the Standard care group, 34% of the patients had a total hospital expenditure of more than Rs. 15,000. The p value is 0.04, which is significant.

Table 20: Comparison of rate of mortality among the patients in the two groups

	CRP GROUP		STANDARD CARE GROUP	
OUTCOME	NUMBER	PERCENTAGE	NUMBER	PERCENTAGE
DISCHARGED	38	95.00	43	86.00
EXPIRED	2	5.00	7	14.00
TOTAL	40	100.00	50	100.00

p= 0.15, Not significant

Graph 18 : Comparison of rate of mortality among the patients in the two groups



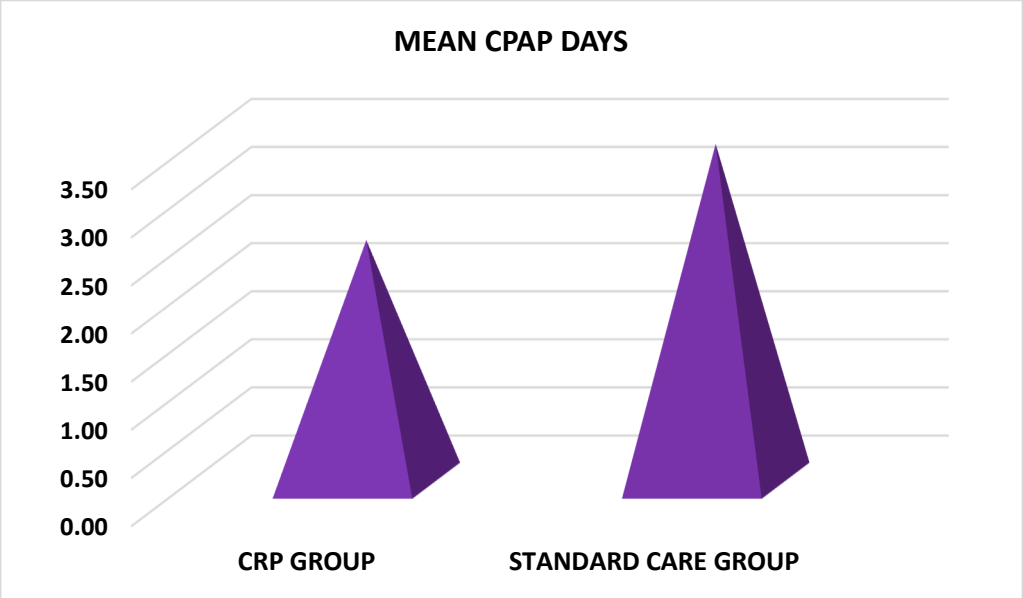
In the CRP group, 2(5%) patients expired during the period of study, while in the Standard Care group, 7(14%) patients died during the course of study. The p value was 0.15, which is not statistically significant.

Table 21: Comparison of mean duration of CPAP days among the patients in the two groups

	CRP GROUP		STANDARD CARE GROUP	
	MEAN	**S.D.**	**MEAN**	**S.D.**
CPAP DAYS	2.50	0.58	3.50	2.12

p= 0.02, Significant

Graph 19: Comparison of mean duration of CPAP days among the patients in the two groups



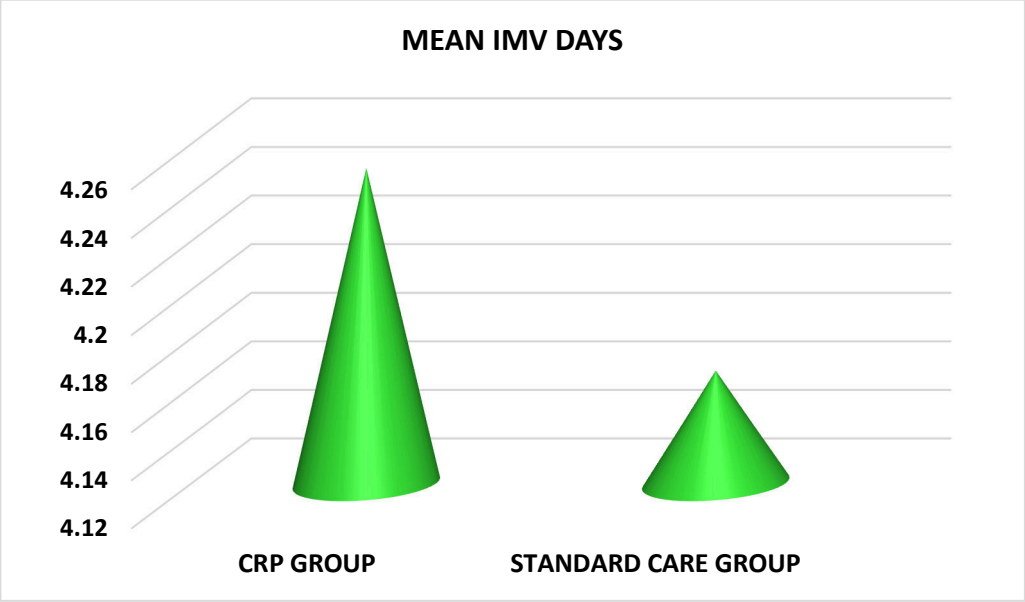
In the CRP group, the mean duration of CPAP was 2.50 ± 0.58 days, while in the Standard Care group, it was 3.50 ± 2.12 days. The p value was 0.02, which was statistically significant.

Table 22: Comparison of mean duration of IMV days among the patients in the two groups

	CRP GROUP		STANDARD CARE GROUP	
	MEAN	**S.D.**	**MEAN**	**S.D.**
IMV DAYS	4.25	1.36	4.17	1.72

p= 0.66, Not significant

Graph 20: Comparison of mean duration of IMV days among the patients in the two groups



In the CRP group, the mean duration of IMV requirement was 4.25 ± 1.36 days, while in the Standard Care group, it was 4.17 ± 1.72 days. The p value was 0.66, which was not significant.

DISCUSSION

The aim of this study was to determine the efficacy of CRP in reducing antibiotic usage in patients admitted with acute exacerbation of COPD.

It was conducted over a period of 12 months in Department of Respiratory Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi.

The study participants were randomized into two groups ie. The CRP group and Standard Care group by simple random sampling. The results of the study was assessed between both the groups.

A greater portion of the patients in the study, about 41.25% patients were between the age group 50-59 years, followed by 36.75% patients were between the age group 60-69 years. The severity of COPD is higher in the older individuals. There was a male predominance in the study with male to female ratio being 2:1.

Cigarette smoking is a well established risk factor in the development of exacerbation in COPD patients. The postulated mechanism being airway inflammation, inducing macrophages to release neutrophil chemotactic factors and elastases. In our study, 47.5% of the patients were smokers, with 50% in the Standard care group and 45% in the CRP group. A case controlled study done by Korani et. al[80] on fifty eight stable COPD patients (26 smokers and 32 non-smokers) showed that smoking was an independent risk factor associated with development of exacerbation.

Badaran and colleagues[81] studied 196 in-hospital patients admitted due to exacerbation of COPD. They found that 26.5% of the patients were smokers, while 65% of them had a history of smoking in the past. Compared to the above mentioned studies, there was no difference in smokers in both the groups in our study.

Exacerbations are a significant component of the clinical course in COPD patients. As the disease progresses frequent exacerbations are commonly seen. In our study, 17.5%

of patients had an exacerbation in the previous one year as against 20.5% of patients who had an exacerbation in the Standard care group. Paggiaro et al.[82]reported that patients with GOLD stage II had a lower risk of frequent exacerbation as compared to GOLD stage I. Donaldson[83] and colleagues had shown that patients with severe COPD a higher exacerbation as compared to moderate COPD patients. Compared to the above studies, the exacerbation risks were similar in both groups.

Exacerbation of COPD usually results, primarily by infections of the airways, by bacteria and viruses and other environment factors, including smoking and air pollution.[84] COPD exacerbation is usually characterized by systemic inflammation and the rise in inflammatory mediators, namely C-Reactive protein, serum procalcitonin and others[85]. Raised serum biomarkers is also an indicator of severity of the disease.[86]

In this study, CRP values were markedly raised(CRP>40), in 48(53.25%) patients of the study population, similar to other studies. Many studies[87]measuring CRP values in COPD patients had shown they were more raised in patients with acute exacerbation in comparison to stable COPD patients. Dev et al.[88]had demonstrated that CRP maybe a marker of COPD exacerbation, but not very sensitive in detecting bacterial infection. Hurst et al[89] had demonstrated that among the array of markers, CRP was found to be the most precise in determining COPD exacerbation, though it was not neither sensitive nor specific. A prospective cohort study conducted by Thomsen et al.[90] on 3083 COPD patients had showed elevated levels of CRP, along with fibrinogen and total leukocyte count were associated with increased risk of exacerbation.

Infections of the respiratory tract have always been the primary cause of COPD exacerbations, and bacteria are the most commonly observed culprits. As a matter of

fact, in patients with COPD, the lower respiratory is usually colonized by bacteria, even in the stable state. Hence, it often becomes difficult to pin-point on infection as the cause for exacerbation on routine sputum bacteriological culture specimens. It is also associated with increased eosinophil levels along with neutrophils and other inflammatory cells.[91]

In this study, we found infection to be the most common cause of exacerbation, seen in 27(30.5%) patients of the study population. The most frequently isolated organism from sputum culture being Kleibsella pneumoniae, followed by Haemophilus influenzae and Streptococcus pneumoniae.

Kawamatawong et al.[92] conducted a similar study in Thailand, where they had reported Kleibsella pneumoniae to be the most common organism seen in patients admitted with acute exacerbation of COPD. Hui et al.[93] performed a multicentre study on various bacterial etiologies in patients with exacerbation of chronic bronchitis. He had concluded Kleibsella to be the frequently isolated organism, followed by Haemophilus influenza species. Many studies conducted earlier have even shown the presence of atypical organisms such as Chlamydia pneumonia as the primary agent in the exacerbation of COPD patients.[94]

Regardless of the infectious agents being viral or bacterial in exacerbation of COPD, antibiotics do play an essential role in treatment of exacerbations.[95] The recent GOLD protocol supports the use of antibiotics in patients with COPD exacerbation on the basis of sputum purulence. Nonetheless, sputum purulence alone cannot serve as a yardstick to direct antibiotic prescription in these patients. Several placebo trials have shown that antibiotic use reduce the short term consequences, irrespective of the purulence of the sputum.[96]

The current protocol as per the European Respiratory Society (ERS)/American Thoracic Society (ATS) advocates the antibiotic use in COPD patients with acute exacerbation, though this was provided for only ambulant patients.[97] The antibiotic use might result in marginal improvement, but is often associated with a high morbidity. Commonly observed adverse effects seen with antibiotic use include diarrhoea, allergic drug reactions, and increased drug resistance.[98]

In this study, we found that CRP guided antibiotic prescription had ensued a lower percentage of patients received antibiotics. In the Standard Care group, 44(88%) patients received antibiotics, while in the CRP group, only 26(65%) patients were initiated on antibiotic therapy.

Various inflammatory markers have been considered in the diagnostic evaluation of COPD exacerbation. C-Reactive protein, being one among them, has not rendered any promising results in previously conducted trials. Recently, Butler et al.[99] conducted a randomized controlled in England on antibiotic usage in COPD out-patients, visiting the hospital following an exacerbation event. The antibiotic use was based on CRP values evaluated during the visit. They reported a marked reduction in prescribing antibiotics to patients, whose antibiotic therapy was based on CRP testing.

Another randomized controlled trial lead by Prins et al.[100] in Netherlands on patients admitted to the hospital with exacerbation of COPD had demonstrated similar results, without a rise in treatment failure. Weis et al.[101] had conducted a randomized controlled trial in Copenhagen on in-hospital patients of acute exacerbation of COPD. It was found that CRP can be used as potential marker of significant bacterial infection. Llor et al.[102] had studied 310 COPD patients in exacerbation, to explore the influence of CRP rapid test in prescribing antibiotics. He reported that patients with mild to moderate COPD exacerbation had a longer period to next exacerbation.

Daniel[103] and colleagues had conducted a study on 205 patients, on the use of CRP vs PCT as predictive markers of response to antibiotic therapy in acute exacerbation of COPD. It was seen that CRP and PCT levels had similar effect on the clinical response. This study suggests the patients with low PCT levels benefit from antibiotics, CRP maybe a more valuable marker in these patients for initiation of antibiotic treatment. Hence, the results of this study are concurrent with the reports of the previous trials.

We also found that CRP guided antibiotic use had resulted in the reduced length of ICU stay, and the overall duration of hospital stay. This can be supported by the prompt use of corticosteroids and nebulisation in these patients. However, there were no differences in duration of treatment with non-invasive or invasive mechanical ventilation. The rate of mortality also remained similar in both the groups. Brochard[104] et. al had conducted a randomized controlled trial on patients admitted to the intensive care unit with acute exacerbation of COPD. He observed that use of non-invasive ventilation in these patients had reduced the need for endotracheal intubation with reduced length of hospital stay and reduced mortality rate.

Lindenauer[105]et. al studied 25628 patients in a large cohort study admitted to the intensive care unit with acute exacerbation of COPD. It was reported treatment with non invasive ventilatory support was associated with lesser risk of nosocomial pneumonia, lesser length of hospital stay. This in turn resulted in lower costs and reduced mortality rate.

A systematic review and meta analysis conducted by Leuzzi et. al[106]showed that raised CRP values on admission was associated with a raised mortality rate. A study done by Miniati[107] et. al on 200 COPD patients with 200 controls, had shown that rate

of hospital admission was higher in patients with raised CRP, which also served as an essential marker of risk of mortality in COPD patients.

Management of acute exacerbation of COPD(AECOPD) is essential, as it has a serious negative impact on the lung function, quality of life and economic status of the patient.[108] Out patient management of COPD exacerbations could significantly reduce the humungous expenses incurred in the form of hospital care, drugs and medical equipment cost, need for ICU admission, daily activities of medical personnel etc. In our study, we found that total hospital expenditure(including antibiotic costs) was an average of Rs.15,000. The total medical expenses amounting to more than Rs. 15,000 seen in 15% of patients in the CRP group, while 34% of patients in the Standard Care group. Francis[109] et. al had conducted a Point-of-care testing of CRP on 650 COPD patients admitted with exacerbation, to guide antibiotic therapy. He reported that CRP values helped in reducing the antibiotic usage by £70(approx. Rs.7000) in the patients which in turn decreased the financial stress on the patient.

Another observational analysis was conducted by Ronaldson[110] et al. based on CPRD on data on 45375 patients. It was based on the cost effectiveness of antibiotics in COPD exacerbation. They showed that 'no antibiotic use' in COPD exacerbations resulted in poor outcomes and higher medical costs(£1900, approx. Rs. 2 lac.) as against 'antibiotic use' in COPD exacerbations.(£750 approx Rs. 75000).Therefore, our results are in agreement with the other studies.

Serum Procalcitonin(PCT) is another well established biomarker used in the diagnostic evaluation of COPD patients in acute exacerbation. It is a polypeptide normally produced in the neuroendocrine cells of thyroid and the lungs, is a marker of systemic inflammation and bacterial infection. Bafadhel[111] et al. in their study said

that using PCT threshold levels of >0.25 ng/ml to guide antibiotic usage in COPD patients, could bring down the use from 76% to 7%. Halim and Sayyed[112] in their study showed that at cut-off 1.49 ng/ml, PCT had 83.7% sensitivity and specificity of 78.3% for predicting acute exacerbation of COPD patients who require ventilator support. A recently done meta-analysis had reported a 35.5% reduction in antibiotic use based on PCT guidance. However, it did not a report a reduction in length of stay in the hospital or any other unfavourable outcomes.[113] This considerable decrease in the antibiotic use can be described by the fact that 80.1% of the patients in the control group in the incorporated studies were on antibiotic therapy.

A pilot study was conducted by Soler et al.[114], to investigate relationship between sputum purulence and biomarkers in prescribing antibiotics for patients with acute exacerbations of COPD. It was reported that serum CRP levels were raised in comparison to PCT, and maybe used as a useful parameter to determine antibiotic use in such patients. Another study conducted by Colak et al.[115] to compare two biomarkers Procalcitonin and CRP in prescribing antibiotics in patients with acute exacerbation of COPD. A total of 116 participants were included in the study. It was inferred that CRP values was a better marker in comparison to PCT in these patients to help reduce antibiotic usage, and consecutively hospital stay. Thus, the above mentioned studies hold evidence to the fact that CRP is a biomarker, superior to PCT in predicting antibiotic usage in patients of COPD with acute exacerbation.

Using CRP as a biomarker in guiding antibiotic use in COPD patients has several benefits. First, serum CRP may better represent the bacterial pathogens in the lower respiratory tract(as indicated by sputum purulence) while serum Procalcitonin may not.[116] Secondly, CRP is an inexpensive and feasible investigation in all hospitals globally. While serum Procalcitonin is highly priced and is suitable for research

purposes. Hence, application of CRP guided antibiotic usage is an economical method without any changes in laboratory settings.

The main purpose of this study was to determine a definite technique to minimize the excessive use of antibiotics in COPD patients admitted with exacerbation. The unnecessary and over utilization of antibiotics poses a dreadful threat to mankind in the form of antibiotic resistance. Thus, antibiotic resistance directly corresponds to the use of antibiotics in different countries across the world.[117] The antibiotic resistance can be kept under check for upto 30%, by executing certain guidelines that prevent antibiotic use.[118] According to a study done recently, across 13 European nations on the proper use of antibiotics in COPD patients admitted with exacerbation, it was found that 86% of admitted patients received antibiotic therapy, wherein only 61.4% of the patients had met the criteria for antibiotic use as per GOLD guidelines.[119] The abuse of antibiotics can be attributed to the fact that physicians initiate antibiotics based on sputum purulence as reported by the patient, which cannot be completely relied upon.[120] Pertaining to these factors, biomarkers may be useful in antibiotic guidance in treating COPD patients coming in exacerbation.

The strengths of our study were randomized controlled trial is that, it is one of the first Indian studies to evaluate the efficacy of CRP in the determining antibiotic usage in COPD patients with acute exacerbation.

The limitations of our study include

1. The study sample size was small, being conducted in a tertiary care hospital. Hence, it may not be a complete representation of the overall population.
2. More number of patients in the Standard care group received antibiotics. This may have influenced the results of the study
3. The safety of the antibiotic use was not analysed in this study.

CONCLUSION

- In summary, the current survey showed that antibiotic prescription through CRP guidance, in patients with exacerbation of COPD, significantly reduces their use.
- There is also a reduction in hospital duration of stay on the judicious use of antibiotic use.
- Further studies need to performed to provide a concrete evidence on CRP guidance to initiate antibiotic therapy on COPD patients.
- In the CRP group, 4(10%) patients required non-invasive ventilatory support, while in the Standard Care group, 12(24%) patients had to be connected to CPAP.

SUMMARY

- The study was conducted in a tertiary care hospital in Belagavi
- The enrolled patients were divided into two groups on the basis of simple random sampling. 40 patients included in CRP group and 50 patients included in the Standard care group.
- The mean age in CRP group was 60.30±7.80 and in Standard Care group was 61.32±7.46.
- Majority of the patients were male comprising of 60 patients(66.67%) of the overall patients
- The mean number of smokers in both groups were 47.5%.
- The mean FEV1% in the CRP group was 59.74% ± 11.86% while it was 55.37% ± 8.86% in the Standard Care group.
- The mean FEV1/FVC ratio was 0.56 ± 0.13 in the CRP group while it was 0.55 ± 0.10 in the Standard Care group.
- The mean duration of symptoms prior to hospital admission in both groups was 7.62 ± 0.34 days.
- The primary cause of exacerbation accounted for infection, presenting in 30.5% of the study patients.

- The mean CRP values in all patients of both groups was 43.28 ± 8.82. In the CRP group, it was 39.68 ± 12.22 while in the Standard Care group, it was 46.88 ± 5.42.
- In the CRP group, 26(65%) patients were on antibiotic treatment, whereas in the Standard Care group, 44(88%) patients were started on antibiotic therapy, which was statistically significant.

- In the CRP group, the mean length of hospital stay is 7.50 ± 2.87 days, while in the Standard Care group, it is 10.12 ± 3.91 days, which is statistically highly significant
- In the CRP group, the mean length of ICU stay is 3.50 ± 1.05 days, while in the Standard Care group, the mean length of ICU stay is 9.80 ± 3.59 days, which was statistically highly significant.
- In the CRP group, the mean duration of CPAP was 2.50 ± 0.58 days, while in the Standard Care group, it was 3.50 ± 2.12 days.
- In the CRP group, the mean duration of IMV requirement was 4.25 ± 1.36 days, while in the Standard Care group, it was 4.17 ± 1.72 days
- In the CRP group, 2(5%) patients expired during the period of study, while in the Standard Care group, 7(14%) patients died during the course of study.
- This study highlights the reduced use of antibiotics based on CRP guidance and thereby, the reduction in length of hospital stay in patients of acute exacerbation of COPD.

BIBLIOGRAPHY

1. Murray CJ. Lopez AD. Evidence-based health policy- lessons from Global Burden of Disease Study. *Science.* 1996;274(5288): 740-743.
2. Seemungal TA, Donaldson GC, Bhowmik A. Time course and recovery of exacerbations in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 2000; 161(5):1608- 1613.
3. Fletcher CM, Peto R, Charles. Natural history of chronic bronchitis and emphysema. *The British Medical Journal 1,* no.6077(1977): 1645-48.
4. White AJ, Gompertz S, Stockley RA. Chronic obstructive pulmonary disease: the etiology of exacerbations of chronic obstructive pulmonary disease. *Thorax* 2003;58(1): 73-80.
5. Ram FS, Rodriguez- Roisin R, Granados-Navarrete A. Antibiotics for exacerbation of chronic obstructive pulmonary disease. *Cochrane database Syst. Rev.* 2006;19(2): CD004403.
6. Anthonisen NR, Manfreda J, Warren CP. Antibiotic therapy in exacerbation of chronic obstructive pulmonary disease. *Ann Intern Med.* 1987;106(2): 196-204.
7. World Health Organisation (WHO). WHO Report on Infectious Disease: Overcoming Antimicrobial Resistance. Geneva, Switzerland: WHO;2000.
8. Hurst JR, Donaldson GC, Perera RW. Use of plasma biomarkers at exacerbation of chronic obstructive pulmonary. *Am J Respir Crit Care Med*. 2006;174(8):867-74.
9. Llor C, Moragas A, Hernandez S. Efficacy of antibiotic therapy for acute exacerbation of mild to moderate chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 2012;186(8):716-23.
10. Garcha DS, Thurston SJ . Changes in prevalence and load of airway bacteria using quantitative PCR in stable and exacerbated COPD. *Thorax*, 2012;67(12):1075-80.
11. Daniels JMA, Schoorl M, Snijders D. Procalcitonin Vs C- Reactive protein as predictive markers of response to antibiotic therapy in acute exacerbation of COPD. *Chest* 2010;138(5):1108-15.
12. David F Strykowski, Anni B S Nielsen, Llor C. C-reactive protein reduces antibiotic overprescribing in acute exacerbation of chronic bronchitis and COPD. *Family Practice* 2015;32(4):395-400.

13. Burrows B, Knudson RJ, Cline MG. Quantitative relationships between cigarette smoking and ventilator function. *Am Rev Respir Dis* 1977; 115:195–205.

14. Agusti AG. COPD , a multicomponent disease: implications for management. *Respir Med.* 2005;99:670-682.

15. Hogg JC, Timens W: The pathology of chronic obstructive pulmonary disease. *Ann Rev Pathol Mech Dis* 2009; 4:435–459.

16. Soriano JB, Zielinski J, Price D. Screening for and early detection of chronic obstructive pulmonary disease. *Lancet* 2009; 374: 721–732.

17. Jindal SK . Emergence of chronic obstructive pulmonary disease as an epidemic in India. *Indian J Med Res* 2006;124:619–30.

18. Murthy KJR, Sastry JG. Economic burden of COPD. In: Burden of diseases in India. Published by National Commission on Macroeconomic and Health, Ministry of Health and Family Welfare, Govt. of India, New Delhi, 2005: 264-74.

19. Schellevis FG, Van de L. Consultation rates and incidence of intercurrent morbidity among patients with chronic disease in general practice. *Br J Gen Pract* 1994; 44:259-62.

20. McCloskey SC, Patel BD, Hinchliffe SJ. Siblings of patients with severe chronic obstructive pulmonary disease have a significant risk of airflow obstruction. *Am J Respir Crit Care* Med 2001; 164:1419–1424.

21. Brode SK, Ling SC, Chapman KR: Alpha-1 antitrypsin deficiency: a commonly overlooked cause of lung disease. *Can Med Assoc J* 2012; 184:1365–1371.

22. Anto JM, Vermeire P, Vestbo J. Epidemiology of chronic obstructive pulmonary disease. *Eur Respir J* 2001; 17:982–994.

23. WHO Study Group on Tobacco Product Regulation: Water Pipe smoking: health effects, research needs, and recommended actions by regulators, 2005, World Health Organization Publication.

24. Vestbo J, Edwards LD, Scanlon PD. For the ECLIPSE Investigators: change in forced expiratory volume in 1 second over time in COPD. *N Engl J Med* 2011; 365:1184–1192.

25. Ozbay B, Uzun K, Arslan H. Functional and radiological impairment in women highly exposed to indoor biomass fuels. *Respirology.* 2001; 6: 255–8.

26. Smith-Sivertsen T, Diaz E, Pope D. Effect of reducing indoor air pollution on women's respiratory symptoms and lung function: the RESPIRE Randomized Trial, Guatemala. *Am J Epidemiol*. 2009;170:211.

27. Vonk JM, Jongepier H, Panhuysen CI: Risk factors associated with the presence of irreversible airflow limitation and reduced transfer coefficient in patients with asthma after 26 years of follow up. *Thorax* 2003; 58:322–327.

28. Lange P, Parner J, Vestbo J: A 15-year follow-up study of ventilatory function in adults with asthma. *N Engl J Med* 2008; 339:1194– 1200.

29. de Marco R, Accordini S, Marcon A: Risk factors for chronic obstructive pulmonary disease in a European cohort of young adults. *Am J Respir Crit Care Med* 2011;183:891–897.

30. Barker DJ, Godfrey KM, Fall C: Relation of birth weight and childhood respiratory infection to adult lung function and death from chronic obstructive airways disease. *BMJ* 1991; 303:671–675.

31. Vestbo J, Edwards LD, Scanlon PD: for the ECLIPSE Investigators: change in forced expiratory volume in 1 second over time in COPD. *N Engl J Med* 2011; 365:1184–1192.

32. Lange P, Groth S, Nyboe J: Effects of smoking and changes in smoking habits on the decline of FEV1. *Eur Respir J* 1989; 2:811–816.

33. Hnizdo E, Sullivan PA, Bang KM, et al: Association between chronic obstructive pulmonary disease and employment by industry and occupation in the US population: a study of data from the Third National Health and Nutrition Examination Survey. *Am J Epidemiol* 2002;156:738–746.

34. Burrows B, Kellogg AL, Buskey J. Relationship of symptoms of chronic bronchitis and emphysema to weather and air pollution. *Arch Environ Health*. 1968; 16(3):406-13.

35. Hogg JC, Chu F, Utokaparch S. The nature of small-airway obstruction in chronic obstructive pulmonary disease. *N Engl J Med.* 2004;350:2645.

36. Di Stefano A, Caramori G, Ricciardolo FL. Cellular and molecular mechanisms in chronic obstructive pulmonary disease: an overview. *Clin Exp Allergy* 2004; 34:1156–67.

37. Saetta M, Di Stefano A, Maestrelli P. Activated T-lymphocytes and macrophages in bronchial mucosa of subjects with chronic bronchitis. *Am Rev Respir Dis* 1993; 147:301–06.

38. Russell RE, Culpitt SV, DeMatos C. Release and activity of matrix metalloproteinase-9 and tissue inhibitor of metalloproteinase-1 by alveolar macrophages from patients with chronic obstructive pulmonary disease. *Am J Respir Cell Mol Biol* 2002; 26:602–09.

39. Saetta M, Turato G, Luppi F. Inflammation in the pathogenesis of chronic obstructive pulmonary disease. In Voekel NF, MacNee W, editors: Chronic obstructive lung disease, Ontario, 2002; 114–26.

40. Stoller JK, Aboussouan LS. Alpha1-antitrypsin deficiency. *Lancet* 2005;365:2225–36.

41. MacNee W: Oxidative stress and chronic obstructive pulmonary disease. *Eur Respir Mon* 2006; 11:100–129.

42. Voynow JA, Gendler SJ, Rose MC. Regulation of mucin genes in chronic inflammatory airway diseases. *Am J Respir Cell Mol Biol* 2006; 34:661–665.

43. Casalino-Matsuda SM, Monzon ME, Forteza RM. Epidermal growth factor receptor activation by epidermal growth factor mediates oxidant-induced goblet cell metaplasia in human airway epithelium. *Am J Respir Cell Mol Biol* 2006; 34:581–91.

44. Guddo F, Vignola AM, Saetta M. Upregulation of basic fibroblast growth factor in smokers with chronic bronchitis. *Eur Respir J* 2006;27:957–963.

45. Sakao S, Voelkel NF, Tatsumi K. The vascular bed in COPD: pulmonary hypertension and pulmonary vascular alterations. *Eur Respir Rev* 2014; 23(133): 350-5.

46. Wells JM, Washko GR, Han MK. Pulmonary arterial enlargement and acute

exacerbations of COPD. *N Engl J Med* 2012; 367(10): 913-21.

47. Elbehairy AF, Ciavaglia CE, Webb KA. Pulmonary Gas Exchange Abnormalities in Mild Chronic Obstructive Pulmonary Disease. Implications for Dyspnea and Exercise Intolerance. *Am J Respir Crit Care Med* 2015; 191(12): 1384- 94.

48. Rodriguez-Roisin R, Drakulovic M, Rodriguez DA. Ventilation-perfusion imbalance and chronic obstructive pulmonary disease staging severity. *J Appl Physiol* 2009; 106(6): 1902-8.

49. Wedzicha JA, Seemungal TA. COPD exacerbations: defining their cause and prevention. *Lancet* 2007; 370(9589): 786-96.

50. Li MH, Fan LC, Mao B. Short-term Exposure to Ambient Fine Particulate Matter Increases Hospitalizations and Mortality in COPD: A Systematic Review and Meta-analysis. *Chest* 2016; 149(2): 447-58.

51. Papi A, Bellettato CM, Braccioni F. Infections and airway inflammation in chronic obstructive pulmonary disease severe exacerbations. *Am J Respir Crit Care Med* 2006; 173(10): 1114-21.

52. Bafadhel M, McKenna S, Terry S. Acute exacerbations of chronic obstructive pulmonary disease: identification of biologic clusters and their biomarkers. *Am J Respir Crit Care Med* 2011; 184(6): 662-71.

53. Seemungal TA, Donaldson GC, Paul EA. Effect of exacerbation on quality of life in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998; 157(5 Pt 1): 1418-22.

54. Hurst JR, Vestbo J, Anzueto A. Susceptibility to exacerbation in chronic obstructive pulmonary disease. *N Engl J Med* 2010; 363(12): 1128-38.

55. Wells JM, Washko GR, Han MK, et al. Pulmonary arterial enlargement and

acute exacerbations of COPD. *N Engl J Med* 2012; 367(10): 913-21.

56. Jolliffe DA, Greenberg L, Hooper RL. Vitamin D to prevent exacerbations of COPD: systematic review and meta- analysis of individual participant data from randomised controlled trials. *Thorax* 2019; 74(4): 337-45.

57. Seemungal T, Harper-Owen R, Bhowmik A. Respiratory viruses, symptoms, and inflammatory markers in acute exacerbations and stable chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001; 164(9): 1618-23.

58. Vollenweider DJ, Jarrett H, Steurer-Stey CA. Antibiotics for exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2012; 12: CD010257.

59. Anthonisen NR, Manfreda J, Warren CP. Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. *Ann Intern Med* 1987; 106(2): 196-204.

60. Masterton RG, Burley CJ. Randomized, double-blind study comparing 5- and 7-day regimens of oral levofloxacin in patients with acute exacerbation of chronic bronchitis. *Int J Antimicrob Agents* 2001; 18(6): 503-12.

61. Adams S, J. M, Luther M. Antibiotics are associated with lower relapse rates in outpatients with acute exacerbations of chronic obstructive pulmonary disease. *Chest* 2000; 117: 1345-52.

62. Soler N, Torres A, Ewig S. Bronchial microbial patterns in severe exacerbations of chronic obstructive pulmonary disease (COPD) requiring mechanical ventilation. *Am J Respir Crit Care Med* 1998; 157(5 Pt 1): 1498-505.

63. McPherson RA, Matthew R., Pincus MR. Henry's Clinical Diagnosis and management by Laboratory Methods. 22nd Ed. Elsevier Saunders: Philadelphia 2011. 254-5.

64. Devaraj S, Singh U, Jialal I. Human C-reactive protein and the metabolic syndrome. *Curr Opin Lipidol* 2009; 20(3): 182-9.

65. McPherson RA, Matthew R., Pincus MR. Henry's Clinical Diagnosis and management by Laboratory Methods. 22nd Ed. Elsevier Saunders: Philadelphia 2011. 254-5.

66. Williamson MA, Snyder LM, Wallach JB. Wallach's Interpretation of diagnostic tests. 9th Ed. Phialdelphia:Wolters Kluwer/Lippincott Williams & Wilkins Health; 2011.

67. Casas JP, Shah T, Hingorani AD. C-reactive protein and coronary heart disease: a critical review. *J Intern Med.* 2008; 264(4): 295-314.

68. McPherson RA, Matthew R., Pincus MR. Henry's Clinical Diagnosis and management by Laboratory Methods. 22nd Ed. Elsevier Saunders: Philadelphia 2011. 254-5.

69. McPherson RA, Matthew R., Pincus MR. Henry's Clinical Diagnosis and management by Laboratory Methods. 22nd Ed. Elsevier Saunders: Philadelphia 2011. 254-5.

70. Pepys MB, Hirschfield GM. C-reactive protein: a critical update. *J Clin Invest.* 2003; 111(12): 1805-12.

71. Burris CA, Ashwood ER, Burns DE. Tietz Textbook of Clinical Chemistry and Molecular Diagnosis. 4th Ed. St. Louis: Elsevier Saunders; 2006; 1633: 962-67.

72. Bulter C, Gillespie D, White P. C-Reactive protein Testing to guide Antibiotic Prescribing for COPD Exacerbations. *N Engl J Med* 2019; 381(2): 111-120.

73. Prins HJ, Dujikers R, van der Valk P. CRP Guided antibiotic treatment in acute exacerbations of COPD in hospital admissions. *Eur Respir J* 2019;53(1802014): 01-10

74. Bates J, Francis NA, White P. General practitioner use of a C-Reactive protein point-of-care test to help target antibiotic prescribing in patients with acute exacerbation of chronic obstructive pulmonary disease(the PACE study) *BioMed Central* 2017;18(442): 01-15.

75. Daniels JMA, Schoorl M, Snijders D. Procalcitonin Vs C-Reactive protein as predictive markers of response to antibiotic therapy in acute exacerbation of COPD. *Chest* 2010;138(5):1108-15.

76. Llor C, Moragas A, Hernandez S. Efficacy of antibiotic therapy for acute exacerbation of mild to moderate chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 2012;186(8):716-23.

77. Soler N, Esperatti M, Ewig S. Sputum purulence-guided antibiotic use in hospitalized patients with exacerbation of COPD. *Eur Respir J* 2012; 40(6): 1344-53.

78. Colak A, Yilmaz C, Toprak B. Procalcitonin and CRP as biomarkers in determination of community-acquired pneumonia and exacerbation of COPD. *J Med Biochem* 2017; 36: 122-26.

79. Strykowski DF, Nielsen BS, Llor C. C-reactive protein reduces antibiotic overprescribing in acute exacerbation of chronic bronchitis and COPD. *Family Practice* 2015;32(4):395-400.

80. Korani YA, Hassan AT, Tony AE. The impact of smoking on inflammatory biomarkers in patients with chronic obstructive pulmonary disease. *Egyptian Journal of Chest Diseases and Tuberculosis* 2016; 65: 597-603.

81. Badaran E, Ortega E, Bujalance C. Smoking and COPD exacerbations. *Eur Respir J* 2012; 40: 1055.

82. Paggiaro PL, Dahle R, Bakran I. Multicentre randomized placebo-controlled trial of inhaled fluticasone propionate in patients with chronic obstructive pulmonary disease. *Lancet* 1998;351: 773-80.

83. Donaldson GC, Seemungal TA, Bhowmik A. Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease. *Thorax* 2002; 57: 847-52.

84. Woodhead M, Blasi F, Ewig S. Guidelines for the management of adult lower respiratory tract infections. *Eur Respir J* 2005; 26(6): 1138-80.

85. Papi A, Bellettato CM, Braccioni F. Infections and airway inflammation in chronic obstructive pulmonary disease severe exacerbations. *Am J Respir Crit Care Med.* 2006;173(10):1114-1121.

86. Chen H, Wang D, Bai C. Proteomics-based biomarkers in chronic obstructive pulmonary disease. *J Proteome Res.* 2010;9(6);2798-2808.

87. Bircan A, Gokirmak M, Kilic O. C-reactive protein levels in patients with chronic obstructive pulmonary disease: Role of infection. *Med Princ Pract* 2008;17: 202-08.

88. Dev D, Wallace E, Sanrakan R.Value of C-Reactive protein measurements in chronic obstructive pulmonary disease. *Respir Med* 1998; 92:664-67.

89. Hurst JR, Perera WR, Wilkinson TMA. Inflammatory changes, recovery and recurrence at COPD exacerbation. *Eur Respir J* 2007;29: 527-34.

90. Thomsen M, Ingebrigtsen TS, Marott JL. Inflammatory biomarkers and exacerbations in chronic obstructive pulmonary disease. *JAMA* 2013;309: 2353-61.

91. Bafadhel M, McKenna S, Terry S. Acute exacerbations of chronic obstructive pulmonary disease: identification of biologic clusters and their biomarkers. *Am J Respir Crit Care Med* 2011; 184(6): 662-71.

92. Kawamatawong T, Apiwattanaporn A, Siricharoonwong W. Serum inflammatory biomarkers and clinical outcomes of COPD exacerbation caused by different pathogens. *Int J Chron Obstruct Pulmon Dis.* 2017;12: 1625-30.

93. Hui DS. Margaret IP, Ling T. A multicentre surveillance study on the characteristics, bacterial etiologies and in vitro antibiotic susceptibilities in patients with acute exacerbation of chronic bronchitis. *Respirology* 2011;16: 532-39.

94. Blasi F, Legnani D, Lombardo VM. Chlamydial pneumoniae infection in acute exacerbations of COPD. *Eur Respir J 1993;*6: 19-22.

95. Seemungal T, Harper-Owen R, Bhowmik A. Respiratory viruses, symptoms, and inflammatory markers in acute exacerbations and stable chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001; 164(9): 1618-23.

96. Ram FS, Rodriguez-Roisin R, Granados-Navarrete A. Antibiotics for exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2006; (2): CD004403.

97. Wedzicha JA, Miravitlles M, Hurst JR. Antibiotics for exacerbation of chronic obstructive pulmonary disease. A European Respiratory Society/American Thoracic guideline. *Eur Respir J* 2017; 49: 1600791.

98. Desai H, Richter S, Doern G. Antibiotic resistance in sputum isolates of Streptococcus pneumoniae ion chronic obstructive pulmonary disease is related to antibiotic exposure. *COPD* 2010; 7: 337-344.

99. Bulter C, Gillespie D, White P. C-Reactive protein Testing to guide Antibiotic Prescribing for COPD Exacerbations. *N Engl J Med* 2019; 381(2): 111-120.

100. Prins HJ, Dujikers R, van der Valk P. CRP Guided antibiotic treatment in acute exacerbations of COPD in hospital admissions. *Eur Respir J* 2019;53(1802014): 01-10.

101. Weis N, Almdal T. C-reactive protein- can it be used as a marker of infection in patients with exacerbation of chronic obstructive pulmonary disease? *European Journal of Internal Medicine* 2006;17: 88-91.

102. Llor C, Moragas A, Hernandez S. Efficacy of antibiotic therapy for acute exacerbation of mild to moderate chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 2012;186(8):716-23.

103. Daniels JMA, Schoorl M, Snijders D. Procalcitonin Vs C-Reactive protein as predictive markers of response to antibiotic therapy in acute exacerbation of COPD. *Chest* 2010;138(5):1108-15.

104. Brochard L, Mancebo J, Wysocki M. Non invasive ventilation for acute exacerbations of chronic obstrucyive pulmonary disease. *N Engl J Med*. 1995; 333(13): 817-22.

105. Lindenauer PK, Stefan MS, Shieh MS. Outcomes associated with invasive and non-invasive ventilation among patients hospitalized with exacerbations of chronic obstructive pulmonary disease. *JAMA Intern Med.* 2014; 174(12): 1982-93.

106. Leuzzi G, Galeone C, Taverna F. C-reactive protein level predicts mortality in COPD: a systematic review and meta- analysis. *Eur Respir Rev* 2017; 26: 160070.

107. Miniati M, Monti S, Bottai M. Prognostic value of C-reactive protein in chronic obstructive pulmonary disease. *Intern Emerg Med.* 2011; 6(5): 423-30.

108. Anzueto A. Impact of exacerbations on COPD. *Eur Res Rev* 2010;19: 113-18.

109. Francis NA, Gillespie D, Wootton M. Clinical features and C-reactive protein as predictors of bacterial exacerbations of COPD. *Int J Chron Obstruct Pulmon Dis* 2020;15: 3147-58.

110. Ronaldson SJ, Raghunath A, Togerson DJ. Cost effectiveness of antibiotics for COPD management :observational analysis using CRPD data. *ERJ Open Res.* 2017; 3(2): 00085-2016.

111. Bafadhel M, Clark TW, Reid C. Procalcitonin and C-Reactive protein in hospitalised adult patients with community acquired pneumonia or exacerbation of asthma or COPD. *CHEST* 2011;139: 1410-8.

112. Halim AA, Sayed M. The value of serum procalcitonin among exacerbated COPD patients. *Egypt J Chest Dis Tuberc*. 2015; 64: 821-7.

113. Mathioudakis AG, Chatzimavridou-Grigoriadou V, Corlateanu A. Procalcitonin to guide antibiotic administration in COPD exacerbations: a meta-analysis. *Eur Respir Rev* 2017; 26: 160073.

114. Soler N, Esperatti M, Ewig S. Sputum purulence-guided antibiotic use in hospitalized patients with exacerbation of COPD. *Eur Respir J* 2012; 40(6): 1344-53.

115. Colak A, Yilmaz C, Toprak B. Procalcitonin and CRP as biomarkers in determination of community-acquired pneumonia and exacerbation of COPD. *J Med Biochem* 2017; 36: 122-26.

116. Daniels JMA, Schoorl M, Snijders D. Procalcitonin Vs C-Reactive protein as predictive markers of response to antibiotic therapy in acute exacerbation of COPD. *Chest* 2010;138(5):1108-15.

117. Goosens H, Ferech M, Vander SR. Outpatient antibiotic use in Europe and association resistance: a cross-national database study. *Lancet* 2005; 365: 579-87.

118. Seppala H, Klaukka T, Vuopio- Varkila J. The effect of changes in the consumption of macrolide antibiotics on erythromycin resistance in group A Streptococci in Finland. Finnish Study Group for Antimicrobial Resistance. *N Engl J Med* 1997; 337: 441-46.

119. Lopez-Campos JL, Hartl S, Pozo-Rodriguez F. Antibiotic prescription for COPD exacerbations admitted to hospital: European COPD audit. *PLos One* 2015;10:e0124374.

120. Daniels JM, de Graff CS, Vlaspolder F. Sputum colour reported by patients is not a reliable marker of the presence of bacteria in acute exacerbations of chronic obstructive pulmonary disease. *Clin Microbiol Infect* 2010;16: 583-88.

ANNEXURE I

ETHICAL CLEARANCE CERTIFICATE

K.L.E. ACADEMY OF HIGHER EDUCATION AND RESEARCH
(Deemed – to- be- University)
Accredited 'A' Grade by NAAC (2nd Cycle) Placed in Category 'A' by MHRD (GoI)
JAWAHARLAL NEHRU MEDICAL COLLEGE,
NEHRU NAGAR, BELAGAVI-590010 (KARNATAKA-INDIA)
Website: http//www.jnmc.edu
E-Mail : dome@jnmc.edu
Phone: (+ 91-(0)831 Office : 2472550
Principal: 2471701
Fax No. +91 (0)831 – 2470759

Ref: MDC/DOME/ 275. Date: 24/12/2019

To,

BR0119002
PG student in Respiratory Medicine,
J.N.Medical College,
BELAGAVI.

Sub: Institutional Ethical Clearance for the study.

With reference to the above, we wish to inform you that your proposed research project titled **"EFFICACY OF CRP IN GUIDING ANTIBIOTIC USAGE IN PATIENTS WITH ACUTE EXACERBATION OF COPD: A RANDOMISED CONTROLLED TRIAL"**, is ethical and justifiable. The proposed research project has been cleared by the JNMC Institutional Ethics Committee on Human Subjects Research.

(Dr. Anita Dalal)
Member Secretary
JNMC Institutional Ethics Committee
on Human Subjects Research,
J.N.Medical College, Belagavi.

(Dr. Roopa M Bellad)
Chairman,
JNMC Institutional Ethics Committee
on Human Subjects Research,
J.N.Medical College, Belagavi.

ANNEXURE II

INFORMED CONSENT

EFFICACY OF CRP IN GUIDING ANTIBIOTIC USAGE IN PATIENTS WITH ACUTE EXCACERBATION OF COPD

PRINCIPAL INVESTIGATOR

GUIDE:

INTRODUCTION AND PURPOSE:

The present study is conducted among patients with acute exacerbation of chronic obstructive pulmonary disease(AECOPD) getting admitted under Department of Respiratory Medicine at KLE's Dr.Prabhakar Kore Charitable Hospital and Medical Research Centre, Belagavi. You are requested to participate in the study and your participation is completely voluntary. The purpose of this study is to determine the use of C-Reactive protein (CRP) in antibiotic prescription in patients with acute exacerbation of COPD.

CRP is a cheap, common and reliable biomarker in determining severity of infection in patients with acute exacerbation of COPD at the time of hospital admission.

This study aids in reduction in unnecessary use of antibiotics in patients admitted with acute exacerbation of COPD, thereby cutting down high medical costs and prolonged hospital stay.

PROCEDURE:

If you agree to participate in this study, the relevant data will be collected as per proforma and final diagnosis made.

After getting inducted in the study, you will be asked questions regarding your past and present medical history and randomly allocated to either of the study groups, and subjected to HsCRP estimation (costing Rs. 270/-), in addition to the usual treatment. Based on the HsCRP levels, the antibiotic prescription will be assessed.

BENEFITS:

Patient will not be eligible for any kind of monetary benefits or free services by virtue of your participation in the study.

RISKS:

Methods applied to do the study are safe.

COST OF PARTICIPATION:

The cost of the Investigation will be borne by the Study Subject. The other indirect expenses will be borne by the Investigator.

PRIVACY AND CONFIDENTIALITY:

The results of the study may be published in journals for scientific purposes. However, your identity will not be revealed. All information collected will be coded so that no one other than the investigator will know your identity.

WITHDRAWAL FROM THE STUDY:

You can withdraw from the study at any time if you wish to do so.

ALTERNATIVES:

In case you opt out of the study, it will not affect your relationship with KLES Dr. Prabhakar Kore Hospital.

AUTHORIZATION TO PUBLISH THE RESULTS:

The results of the study will be forwarded to KAHER, Belagavi as a part of the requirement towards the completion of MD degree, review and publishing. The researcher may also use the information gathered from this study for presentation in scientific meetings. However, your identity will not be revealed.

CONSENT TO PARTICIPATE IN A RESEARCH STUDY

I, voluntarily agree to take part in this study, by signing this consent form I am not giving up my legal rights. I may withdraw at any time. I am signing after having read, or been read to me in the vernacular language including risks and the benefits and having all queries cleared.

Signature of the study patient :

Name of Study patient :

Name of the Witness :

Signature of the Witness :

Name of Investigator :

Signature of the Investigator :

Date :

Place :

ANNEXURE III

PROFORMA

Name: BMI:

Age: IP. NO :

Sex:

Chief Complaints

Past History:

Anthonisen's Class- I / II / III

Current Smoker:

No. of exacerbations in the previous year:

Cause of exacerbation:

Current use of inhalers:

Clinical Examination:

Pulse rate: BP:

Spo2 at room air: RS:

Resp rate:

Investigations:

Total WBC count:

HsCRP:

Sputum C/S:

Length of hospital stay:

Length of ICU stay:

Duration of CPAP:

Duration of IMV:

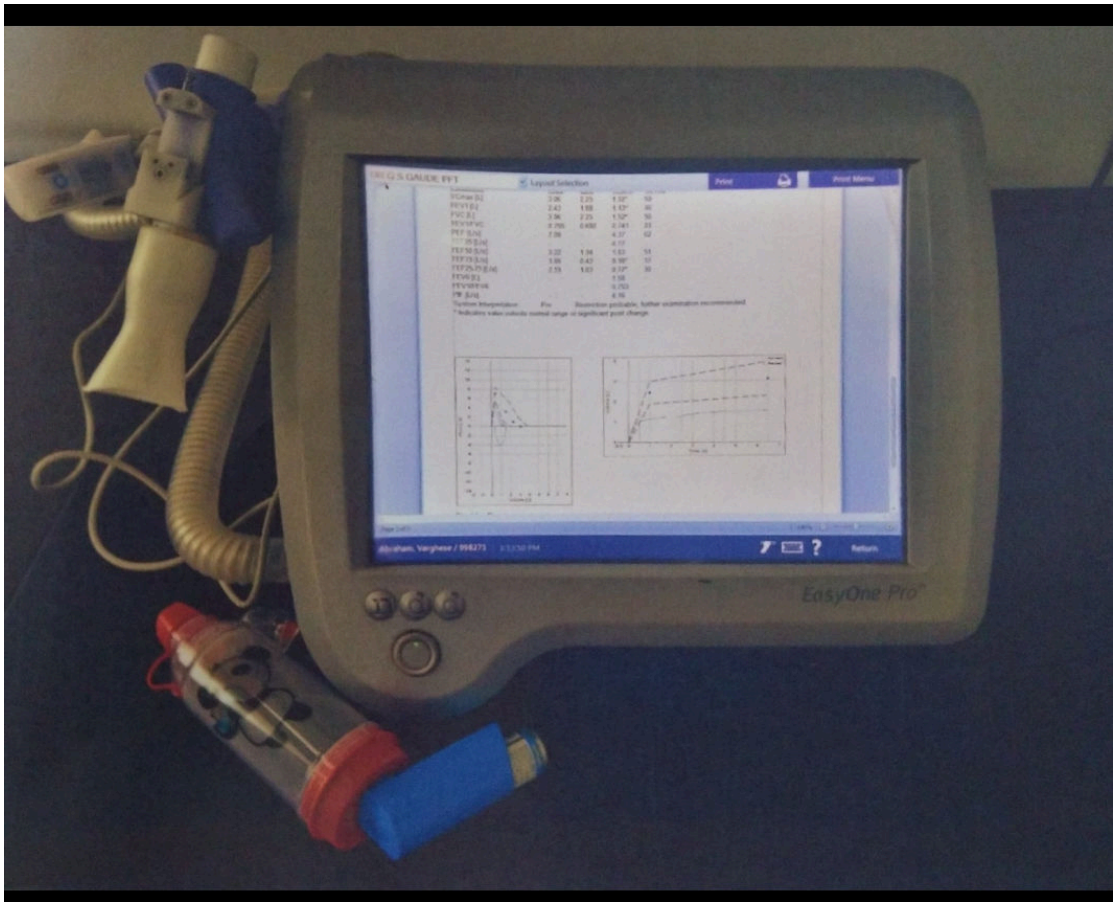
Total hospital expenditure:

Outcome:

ANNEXURE IV

PHOTOGRAPH

1. SPIROMETER



ANNEXURE V
MASTER CHART – CRP GROUP

Sl.No.	IP. NO.	AGE	SEX	BMI	HONISENS C/S WITH SYN	CAUSE OF E	INHALER US	SMOKING S	HYPERTENS	TYPE 2 DIAB	IHD	OTHER COM	RESP RATE	SPO2(%)	WBC	SPUTUM C/	ET C/S	CRP	CRP>40	XYGEN MAS	CPAP	IMV	cerbations i	/ IN HOSPITA	CPAP DAYS	IMV DAYS	TAY(NO. OF	NT ON ANTIE	1 ANTIBIOT	OUTCOME	AL EXPENSES(> Rs.15,000)			
1	1022626	52	M	24.2	II	7	INFECTION	Y	Y	Y	Y	N	N	26	86	11.7	COMMENSALS	37	N	Y	N	N	0	5	NO	NO	0	Y	N	DISCHARGED	N			
2	1022974	74	M	18.2	I	15	UNKNOWN	N	Y	N	Y	N	N	32	84	15.2	MORAXELLA CATARRHAL	63	Y	N	Y	N	1	10	2	NO	2	Y	Y	DISCHARGED	Y			
3	1024732	69	M	20.2	I	12	INFECTION	N	Y	Y	N	Y	N	24	87	12	NO GROWTH	42	Y	Y	N	N	0	7	NO	NO	0	Y	N	DISCHARGED	N			
4	1040599	55	F	17.6	III	8	INFECTION	N	N	Y	N	N	HYPOTHYRO	34	91	8.7	NO GROWTH	25	N	Y	N	N	0	5	NO	NO	0	N	N	DISCHARGED	N			
5	1027727	48	M	27.2	I	8	IRREGULAR	N	Y	Y	N	N	N	32	90	14.7	COMMENSALS	34	N	Y	N	N	0	5	NO	NO	0	N	N	DISCHARGED	N			
6	1022157	66	M	19.3	III	10	UNKNOWN	N	N	N	Y	N	Y	22	84	11.8	NO GROWTH	16	N	N	N	N	0	5	NO	NO	0	N	N	DISCHARGED	N			
7	1023801	59	M	21.3	II	15	OUTDOOR F	N	Y	Y	Y	Y	CABG	30	80	12.8	STREP PNEUMONIAE	55	Y	Y	N	N	2	10	NO	NO	0	Y	N	DISCHARGED	N			
8	1023706	62	F	22.4	II	7	UNKNOWN	Y	N	Y	N	N	N	26	86	14.8	COMMENSALS	52	Y	Y	N	N	1	7	NO	NO	0	Y	N	DISCHARGED	N			
9	1020079	50	F	25.2	I	5	INFECTION	N	N	N	N	N	N	24	92	7.5	NO GROWTH	NO GROWTH	30	N	N	N	Y	0	5	NO	5	5	N	Y	DIED	Y			
10	1020066	63	F	23.3	III	10	INDOOR PO	N	N	Y	N	N	N	32	82	13.9	NO GROWTH	58	Y	Y	N	N	2	14	NO	NO	0	Y	N	DISCHARGED	N			
11	1022570	59	M	19.4	II	8	UNKNOWN	Y	Y	Y	N	Y	N	27	84	12.9	COMMENSALS	47	Y	Y	N	N	0	7	NO	NO	0	Y	N	DISCHARGED	N			
12	1022264	64	M	20.3	III	6	OUTDOOR F	Y	N	N	Y	Y	N	22	90	10.9	NO GROWTH	32	N	Y	N	N	0	5	NO	NO	0	N	N	DISCHARGED	N			
13	1023046	73	M	17.3	I	10	CURRENT SM	N	Y	Y	N	Y	N	38	75	12.9	KLEIBSELLA PNEUMONIA	64	Y	N	Y	N	1	15	3	NO	4	Y	Y	DISCHARGED	Y			
14	1041201	47	M	28.3	III	15	UNKNOWN		N	N	N	N	N	25	89	14.8	NO GROWTH	28	N	N	N	N	0	5	NO	NO	0	N	N	DISCHARGED	N			
15	1041191	53	F	18.3	II	5	INFECTION	Y	N	Y	N	N	HYPOTHYRO	31	83	13.8	COMMENSALS	40	Y	Y	N	N	0	7	NO	NO	0	Y	N	DISCHARGED	N			
16	1041248	65	M	24.5	II	7	UNKNOWN	Y	Y	Y	Y	Y	N	28	90	10.7	COMMEYSALS	44	Y	Y	N	N	0	7	NO	NO	0	Y	N	DISCHARGED	N			
17	1021366	77	M	32.1	I	10	CURRENT SM	N	Y	Y	Y	N	N	36	72	15.9	KLEIBSELLA PNEUMONIA	62	Y	N	Y	N	1	15	3	NO	4	Y	Y	DIED	Y			
18	1022968	54	M	19.3	III	5	INFECTION	N	N	Y	N	N	N	23	92.0	9	COMMENSALS	32	N	Y	N	N	0	5	NO	NO	0	N	N	DISCHARGED	N			
19	1023730	64	F	23.8	II	10	UNKNOWN	N	N	Y	Y	N	N	28	83	12.7	COMMENSALS	50	Y	Y	N	N	0	7	NO	NO	0	Y	N	DISCHARGED	N			
20	1028681	70	F	24.2	III	7	INDOOR PO	N	N	N	N	N	N	29	85	10.4	NO GROWTH	26	N	Y	N	N	0	7	NO	NO	0	N	N	DISCHARGED	N			
21	1028210	55	M	20.8	III	5	OUTDOOR F	N	Y	Y	N	Y	N	28	94	10.3	NO GROWTH	32	N	N	N	N	0	5	NO	NO	0	N	N	DISCHARGED	N			
22	1023248	65	M	18.6	I	7	INFECTION	N	N	Y	Y	N	N	32	85	14.2	HAEMOPHILUS INFLUEN	38	N	Y	N	N	0	7	NO	NO	0	Y	N	DISCHARGED	N			
23	1018364	56	M	18.7	II	8	OUTDOOR F	N	N	N	Y	N	N	27	88	12.5	COMMENSALS	42	Y	Y	N	N	0	7	NO	NO	0	Y	N	DISCHARGED	N			
24	1011432	74	M	21.2	I	4	CURRENT SM	N	Y	Y	Y	Y	N	37	76	14.9	ACINETOBACTER BAUMA	54	Y	N	Y	N	1	15	2	NO	3	Y	Y	DISCHARGED	Y			
25	1024332	54	F	27.3	II	7	INFECTION	N	N	N	Y	N	N	26	89	13.2	NO GROWTH	47	Y	Y	N	N	0	7	NO	NO	0	Y	N	DISCHARGED	N			
26	1023274	65	F	31.2	III	7	INDOOR PO	N	N	Y	N	N	N	28	88	12.3	NO GROWTH	45	Y	Y	N	N	0	5	NO	NO	0	Y	N	DISCHARGED	N			
27	1024732	53	F	21.2	II	5	UNKNOWN	N	N	N	N	N	N	32	85	14.9	COMMENSALS	39	N	Y	N	N	0	7	NO	NO	0	Y	N	DISCHARGED	N			
28	1024046	58	M	23.3	I	7	INFECTION	N	Y	N	N	N	N	27	86	12.7	COMMENSALS	23	N	Y	N	N	0	5	NO	NO	0	N	N	DISCHARGED	N			
29	1025518	61	F	28.3	I	5	UNKNOWN	Y	N	N	N	N	HYPOTHYRO	28	87	11.6	NO GROWTH	PSEUDOMO	38	N	N	N	Y	0	8	NO	2	3	Y	Y	DISCHARGED	Y			
30	1028143	53	M	27.3	II	6	INFECTION	N	Y	N	N	N	N	32	84	12.9	COMMENSALS	45	Y	Y	N	N	0	10	NO	NO	0	Y	N	DISCHARGED	N			
31	1025856	64	M	23.9	II	7	IRREGULAR	N	Y	N	Y	N	N	23	88	13.2	NO GROWTH	35	N	Y	N	N	0	7	NO	NO	0	Y	N	DISCHARGED	N			
32	1027974	49	M	30	III	6	OUTDOOR F	N	N	N	Y	N	N	22	96	7.9	NO GROWTH	19	N	N	N	N	0	5	NO	NO	0	N	N	DISCHARGED	N			
33	1026222	51	F	21.2	II	7	INFECTION	N	N	N	N	N	N	32	85	10.7	COMMENSALS	26	Y	Y	N	N	0	7	NO	NO	0	N	N	DISCHARGED	N			
34	1024983	58	M	18.9	II	8	IRREGULAR	N	Y	N	N	N	N	30	84	13.8	COMMENSALS	48	Y	Y	N	N	0	7	NO	NO	0	Y	N	DISCHARGED	N			
35	1024772	60	F	17.7	I	5	INFECTION	N	N	N	N	N	N	34	86	12.8	COMMENSALS	45	Y	Y	N	N	0	10	NO	NO	0	Y	N	DISCHARGED	N			
36	1023891	65	M	19.7	III	6	INFECTION	N	Y	N	N	N	N	29	88	8.9	NO GROWTH	25	N	Y	N	N	0	8	NO	NO	0	N	N	DISCHARGED	N			
37	1010511	54	M	21.7	II	8	INFECTION	N	Y	N	N	N	N	30	85	12.9	COMMENSALS	45	Y	Y	N	N	0	7	NO	NO	0	Y	N	DISCHARGED	N			
38	1010921	69	F	24.7	III	10	UNKNOWN	N	N	N	N	N	N	28	87	14.8	COMMENSALS	43	Y	N	N	N	0	7	NO	NO	0	Y	N	DISCHARGED	N			
39	1000542	57	M	26.2	I	8	OUTDOOR F	N	N	N	N	N	N	31	86	12.5	COMMENSALS	38	N	Y	N	N	0	8	NO	NO	0	Y	N	DISCHARGED	N			
40	1002125	67	M	24.4	II	8	UNKNOWN	N	Y	N	N	N	N	32	96	7.6	NO GROWTH	23	N	N	N	N	0	5	NO	NO	0	N	N	DISCHARGED	N			

ANNEXURE V
MASTER CHART – STANDARD CARE GROUP

Sl.No.	IP. NO.	AGE	SEX	BMI	ANTHONISE	NO. DAYS W	CAUSE OF E	INHALER US	SMOKING STAT	HYPERTENSIO	TYPE 2 DIABET	IHD	OTHER CON	RESP RATE	SPO2(%)	WBC	SPUTUM C/	ET C/S	CRP	CRP>40	OXYGEN MA	CPAP	INVASIVE M	No. of exac	LENGTH OF	CPAP DAYS	IMV DAYS	ICU STAY(N	PATIENT ON	> 1 ANTIBIO	OUTCOME	TOTAL HOSPITAL EXPENSES(>Rs. 50,000)
1	1009814	53	M	32.3	I	7	INFECTION	N	Y	Y	Y	Y	N	34	80	12.5	STREP PNEU	N	32	N	N	Y	N	2	10	6	NO	8	Y	Y	DISCHARGE	Y
2	1009871	65	M	23.3	I	10	IRREGULAR	N	Y	Y	N	N	N	36	75	17.2	KLEIBSELLA	N	49	Y	N	Y	N	0	15	6	NO	12	Y	Y	EXPIRED	Y
3	1009986	45	M	21.2	II	6	INFECTION	Y	N	N	N	N	N	28	90	11.7	NO GROWT	N	30	N	Y	N	N	0	7	NO	NO	0	Y	N	DISCHARGE	N
4	1010218	48	M	24.3	II	8	INFECTION	N	N	Y	N	N	N	26	83	14.8	COMMENSA	N	45	Y	N	Y	Y	0	5	4	1	5	Y	N	EXPIRED	Y
5	1000797	56	F	19.2	III	6	INFECTION	N	N	N	Y	N	N	32	86	13.2	COMMENSA	N	26	N	Y	N	N	1	13	NO	NO	0	Y	N	DISCHARGE	Y
6	1000842	72	M	17.8	I	7	IRREGULAR	N	Y	Y	N	Y	CVA	38	75	18.5	NO GROWT	STREP PNEU	62	Y	N	Y	Y	3	20	4	5	15	Y	N	EXPIRED	Y
7	999105	69	F	21.2	II	10	IRREGULAR	N	N	N	Y	N	HYPOTHROI	28	83	14.8	NO GROWT	N	35	N	N	Y	N	1	14	5	NO	10	Y	N	DISCHARGE	Y
8	999767	54	M	24.7	II	8	IRREGULAR	N	Y	N	Y	N	N	34	86	15.9	KLEIBSELLA	N	43	Y	Y	N	N	0	13	NO	NO	0	Y	Y	DISCHARGE	N
9	1002130	63	F	20.1	I	5	UNKNOWN	Y	N	Y	N	N	N	37	75	14.2	COMMENSA	N	54	Y	N	Y	N	2	16	5	NO	13	Y	Y	EXPIRED	Y
10	1002237	57	F	21.2	II	6	OUTDOOR F	N	N	Y	N	N	N	31	87	16.5	HAEMOPHII	N	48	Y	Y	N	N	1	15	NO	NO	0	Y	Y	DISCHARGE	Y
11	1001329	62	F	23.3	III	8	INDOOR PO	Y	N	N	N	N	N	32	90	9.3	NO GROWT	N	48	N	N	N	N	0	5	NO	NO	0	Y	N	DISCHARGE	N
12	1001539	75	M	18.2	I	15	UNKNOWN	N	Y	Y	N	Y	N	39	64	15.5	NO GROWT	MORAXELLA	48	Y	N	N	Y	2	21	NO	6	15	Y	Y	EXPIRED	Y
13	1000376	54	M	26.2	II	6	INFECTION	Y	Y	N	Y	Y	N	32	85	14.9	COMMENSALS		48	Y	Y	N	N	0	10	NO	NO	0	Y	N	DISCHARGE	N
14	1002119	65	M	27.9	I	8	UNKNOWN	N	Y	Y	N	N	N	36	78	15.9	NO GROWT	ACINETOBA	48	Y	N	Y	Y	2	15	2	4	13	Y	Y	DISCHARGE	Y
15	1038749	59	M	28.3	II	8	UNKNOWN	N	Y	Y	Y	Y	CABG	34	87	12.9	COMMENSA	N	48	Y	Y	N	N	0	10	NO	NO	0	Y	Y	DISCHARGE	Y
16	1012737	65	M	30.2	I	10	INFECTION	N	N	Y	N	Y	N	38	79	17.3	NO GROWT	STREP PNEU	48	Y	N	N	Y	1	14	NO	4	12	Y	Y	EXPIRED	Y
17	1010611	59	F	23.2	I	8	INDOOR PO	Y	Y	N	Y	N	N	36	76	16.3	NO GROWT	KLEIBSELLA	48	Y	N	N	Y	1	15	NO	5	12	Y	Y	EXPIRED	Y
18	1012752	74	M	17.5	II	7	UNKNOWN	N	Y	Y	N	N	N	27	86	14.9	COMMENSA	N	48	N	Y	N	N	0	5	NO	NO	0	Y	N	DISCHARGE	N
19	1019005	61	M	19.3	II	6	INFECTION	N	Y	Y	N	N	N	32	86	14.6	COMMENSA	N	48	Y	Y	N	N	0	7	NO	NO	0	Y	N	DISCHARGE	N
20	1018945	58	M	21.2	II	8	IRREGULAR	N	N	N	Y	N	N	31	85	12.8	COMMENSA	N	48	N	N	Y	N	0	7	3	NO	5	Y	Y	DISCHARGE	Y
21	1018728	64	M	20.2	III	6	OUTDOOR F	N	Y	N	N	N	N	32	93	9.7	NO GROWT	N	48	Y	N	N	N	0	5	NO	NO	0	N	N	DISCHARGE	N
22	1012380	57	M	23.4	III	7	INFECTION	N	N	N	N	N	N	26	92	12.3	NO GROWT	N	48	N	N	N	N	0	7	NO	NO	0	Y	N	DISCHARGE	N
23	1018364	72	M	18.5	II	6	IRREGULAR	N	Y	Y	Y	Y	CABG	29	86	14.8	HAEMOPHII	N	48	Y	Y	N	N	0	7	NO	NO	0	Y	Y	DISCHARGE	N
24	1018122	67	F	19.7	III	8	INDOOR PO	N	N	Y	Y	N	N	26	94	9.7	NO GROWT	N	48	N	N	N	N	0	7	NO	NO	0	N	N	DISCHARGE	N
25	1017370	73	M	18.2	II	10	CURRENT SI	N	Y	Y	N	Y	N	34	87	16.3	COMMENSA	N	48	N	Y	N	N	0	7	NO	NO	0	Y	N	DISCHARGE	N
26	1021525	65	M	25.8	II	8	OUTDOOR F	N	N	N	N	N	N	27	89	12.8	COMMENSA	N	48	Y	Y	N	N	0	10	NO	NO	0	Y	N	DISCHARGE	N
27	1008957	59	F	24.8	II	7	INFECTION	N	N	N	Y	N	N	28	88	10.8	NO GROWT	N	48	N	Y	N	N	0	7	NO	NO	0	Y	N	DISCHARGE	N
28	1011709	60	M	23.4	II	8	UNKNOWN	N	Y	Y	N	N	N	32	84	13.9	KLEIBSELLA	N	48	Y	N	Y	N	0	12	2	NO	5	Y	Y	DISCHARGE	Y
29	1012169	53	M	24.7	II	7	OUTDOOR F	N	Y	Y	N	N	N	34	86	12.7	NO GROWT	N	48	Y	Y	N	N	0	10	NO	NO	0	Y	N	DISCHARGE	N
30	1011991	64	F	22.8	II	7	INFECTION	Y	N	N	N	N	N	28	88	11.4	NO GROWT	N	48	N	Y	N	N	0	8	NO	NO	0	Y	N	DISCHARGE	N
31	1011969	74	M	20.1	III	10	UNKNOWN	N	Y	N	Y	Y	N	30	91	12.5	NO GROWT	N	48	Y	Y	N	N	0	7	NO	NO	0	Y	N	DISCHARGE	N
32	1041180	58	M	23.3	II	8	INFECTION	N	Y	N	N	N	N	28	88	14.2	COMMENSA	N	48	Y	Y	N	N	0	10	NO	NO	0	Y	N	DISCHARGE	N
33	1011155	70	M	19.3	III	5	UNKNOWN	N	Y	N	N	N	N	26	93	11.5	NO GROWT	N	48	N	N	N	N	0	10	NO	NO	0	N	N	DISCHARGE	N
34	1011882	54	F	21.6	I	8	INDOOR PO	Y	N	N	Y	N	N	35	84	12.3	PSEUDOMO	N	48	Y	N	Y	N	0	12	5	NO	8	Y	Y	DISCHARGE	Y
35	1028443	68	F	25.9	I	10	INDOOR PO	N	N	Y	N	N	HYPOTHROI	28	88	13.2	COMMENSA	N	48	N	Y	N	N	0	10	NO	NO	0	Y	N	DISCHARGE	N
36	1012346	71	M	18.6	I	6	UNKNOWN	N	Y	N	N	N	N	32	86	11.9	COMMENSA	N	48	N	Y	N	N	0	10	NO	NO	0	Y	N	DISCHARGE	N
37	1018636	53	M	21.7	III	6	OUTDOOR F	N	N	Y	N	N	N	25	94	8	NO GROWT	N	48	N	N	N	N	0	7	NO	NO	0	N	N	DISCHARGE	N
38	1017472	64	M	22.9	II	5	INFECTION	N	Y	N	N	N	N	29	85	11.7	NO GROWT	N	48	Y	Y	N	N	0	12	NO	NO	0	Y	N	DISCHARGE	N
39	1008947	60	F	24.8	II	6	UNKNOWN	N	N	Y	N	N	N	27	88	12.6	COMMENSA	N	48	Y	N	N	N	0	10	NO	NO	0	Y	N	DISCHARGE	N
40	1008957	53	M	23.9	I	7	UNKNOWN	N	N	N	N	N	N	28	86	13.6	COMMENSA	N	48	Y	Y	N	N	0	10	NO	NO	0	Y	N	DISCHARGE	N
41	1009166	48	F	20.8	III	5	OUTDOOR F	N	N	Y	N	N	N	25	96	9.6	NO GROWT	N	48	N	N	N	N	0	5	NO	NO	0	N	N	DISCHARGE	N
42	1019537	55	F	26.3	I	7	OUTDOOR F	N	N	N	Y	N	N	32	84	11.5	MORAXELLA	N	48	Y	N	Y	N	0	10	5	NO	7	Y	Y	DISCHARGE	N
43	1009322	63	M	21.8	I	8	UNKNOWN		Y	N	Y	N	N	28	88	10.5	NO GROWT	N	48	N	Y	N	N	0	10	NO	NO	0	Y	N	DISCHARGE	N
44	1009711	56	M	22.9	II	7	CURRENT SI	N	Y	Y	Y	N	N	29	86	12.8	COMMENSA	N	48	Y	Y	N	N	0	12	NO	NO	0	Y	N	DISCHARGE	N
45	1009600	72	M	19.7	I	7	INFECTION	N	N	Y	N	Y	N	32	84	12.5	STREP PNEU	N	48	N	N	Y	N	0	12	4	NO	7	Y	Y	DISCHARGE	Y
46	1009587	65	F	24.8	II	8	INDOOR PO	N	N	N	N	N	N	23	92	11.4	NO GROWT	N	48	N	N	N	N	0	7	NO	NO	0	N	N	DISCHARGE	N
47	1009364	59	M	25.3	I	5	CURRENT SI	N	Y	N	N	N	N	27	85	10.6	COMMENSA	N	48	N	Y	N	N	0	10	NO	NO	0	Y	N	DISCHARGE	N
48	1009322	52	M	24.7	I	6	UNKNOWN	N	Y	N	N	N	N	30	86	13.2	COMMENSA	N	48	Y	Y	N	N	0	12	NO	NO	0	Y	N	DISCHARGE	N
49	1009755	59	F	24.6	I	7	INDOOR PO	N	N	N	N	N	HYPOTHROI	26	88	11.9	COMMENSA	N	48	N	Y	N	N	0	10	NO	NO	0	Y	N	DISCHARGE	N
50	999033	64	M	23.5	III	8	OUTDOOR F	N	N	N	N	N	N	25	90	12.8	COMMENSA	N	48	N	Y	N	N	0	10	NO	NO	0	Y	N	DISCHARGE	N