DISSERTATION ON SERUM BNP

LEVELS IN

COMMUNITY ACQUIRED PNEUMONIA AND ITS COMPARISION

WITH CRB-65 AS A PROGNOSTIC MARKER

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CERTIFICATE

This is to certify that the dissertation entitled " **SERUM BNP LEVELS IN PNEUMONIA AND ITS COMPARISION WITH CRB-65 AS A PROGNOSTIC MARKER**" is a bonafide work done by **DR S SURESH KUMAR**, post graduate student, Institute of Internal Medicine, Madras Medical College, Chennai-3 in partial fulfillment of the University Rules and Regulations for the award of MD Branch – I Internal Medicine, under our guidance and supervision, during the academic period from may 2010 to april 2013.

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DECLARATION

I solemnly declare that the dissertation entitled" **SERUM BNP LEVELS IN PNEUMONIA AND ITS COMPARISION WITH CRB-65 AS A PROGNOSTIC MARKER** " is done by me at Madras Medical College, Chennai-3 during May2010 – April 2013 under the guidance and supervision of Prof.S.Tito M.D, to be submitted to The Tamilnadu Dr M.G.R Medical University towards the partial fulfillment of requirements for the award of M.D DEGREE IN GENERAL MEDICINE BRANCH-I.

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CONTENTS

INTRODUCTION

INTRODUCTION

Community-acquired pneumonia (CAP) ,a relatively easily treatable condition is still among the top 10 killer diseases competing with the likes of non – communicable diseases which are not fully curable. The scenario is particularly worse in the developing countries. Inspite of the antibiotic revolution , the mortality rates may be as large as 30-50% in the 10% of the patients who may need intensive care . The morbidity associated with the disease is also enormous contributing much to the economical burden of the community.

The secret of successfully managing the disease in a clinically and economically fruitful manner begins with identifying the patients who may need a higher level of care among a bigger group of patients who may be treated as out patients. This is particularly important because of the extreme difference in the costs incurred in treating both these groups of patients.

The clinical prognostic indices like pneumonia severity index(PSI) and CRB-65 have stood the test of time and are still being used in developing countries. But these are cumbersome and the observations may be examiner dependent. There arose a need for a reliable and quick laboratory based index which could help in triaging the patient.

Various inflammatory markers like CRP , Procalcitonin have been analysed as potential candidates for triage because of the concept that the clinical severity of pneumonia is proportional to the inflammatory response.

But there were other factors ,which also determine the severity of the disease. One important factor that could determine the severity is the extent of myocardial involvement . Hence the cardiac biomarkers were used in assessing the severity of pneumonia. The most useful of them are the natriuretic peptides and the most measurable of these peptides were BNP and NT- Pro BNP .

The initial studies focused BNP as a marker of cardiac wall stress and hence a measure of the extent of myocardial involvement in the disease. But subsequently with the studies and experiments that showed that inflammatory cytokines and possibly hypoxia could also stimulate BNP release , there arose an interesting concept that BNP may be a surrogate marker of most of the

factors that individually contribute to mortality and morbidity in pneumonia. The presence of renal failure in pneumonia could further elevate BNP levels. Though the cause for elevation of BNP in pneumonia is an interesting area of research , the severity of BNP rise is the concern in pneumonia because it may be a measure of multiple poor prognostic factors like the severity of inflammation, hemodynamic imbalance and the presence of renal injury. Hence BNP may be a good marker for triaging the patients with pneumonia. The recent studies have stood by this idea, but studies in the Indian context are lacking

Hence we aimed to analyse the prognostic implications of BNP levels in patients with community acquired pneumonia in a small group of patients by comparing it with a standard prognostic marker like CRB-65 .

AIMS AND OBJECTIVES

AIM OF THE STUDY

1. To estimate serum BNP levels in patients diagnosed with community acquired pneumonia

2. To analyze whether elevated BNP levels correlate with a higher mortality rate and a clinically severe disease as measured by the morbidity and outcomes.

3. To compare serum BNP levels with CRB-65 score in predicting the clinical severity and mortality in pneumonia.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

Pneumonia is an infection of the pulmonary parenchyma[1]. Pneumonia is classified into community-acquired pneumonia (CAP) in which the patient gets infected with the pathogen outside the hospital and is usually diagnosed in less than 48 hours of admission and health care–associated pneumonia (HCAP) in which the person is supposed to have acquired the infection in the hospital and hence is diagnosed more than 48 hrs after admission.

Pneumonia that occurs as a result of occurrence of infection because of proximity to or presence in a healthcare setup called hospital acquired pneumonia is further classified into two types. The first variety is hospital-acquired pneumonia (HAP) ,mostly acquired in a non ICU setting. The second, ventilator-associated pneumonia (VAP) is acquired when the person is put on ventilator support. This is important because of the difference in etiological agents, treatment and hence the final outcome.[2]

Pneumonitis is inflammation induced by non-infectious cause, such as radiation or chemical injury[3]. The following literature will focus entirely on community acquired pneumonia.

PATHOGENESIS:

Pneumonia results from microbial proliferation in the respiratory zones of the airway more specifically the alveoli [4]. The organisms usually reach the lungs through the oropharynx or blood . As important as the microbe in the pathogenesis of pneumonia is the inflammatory response of the host to the organism. Inhalational pneumonia is most often due to microorganisms that

(1) have high potential to survive in the body

(2) have a smaller size

(3) are immune to host defences[3]

.The severity of pneumonia depends on the the quantity and quality of the bacteria in the inoculums and the capability of the host defence to deal with them[2]. An intense inflammatory process ensues after propagation of organisms in the lower respiratory tract as determined by the aforementioned factors.

The inflammatory process is mediated by proinflammatory cytokines such as TNF and a series of interleukins (Interleukins-1,2, 6, and 8) [7]and is balanced by anti-inflammatory mediators. Cytokines are responsible for the clinical and laboratory manifestations of bacterial pneumonia.

PATHOLOGY

Pneumonia can , pathologically and hence as a result clinically, be differentiated into typical and atypical pneumonias. Typical pneumonia is usually of bacterial origin and is characterised by neutrophilic infiltration of alveoli. Atypical pneumonias ,as caused by viruses , are usually associated with mononuclear and lymphocytic infiltration of the air spaces.[6]

Anatomically and radiologically, pneumonia can be classified as bronchopneumonia and lobar pneumonia. In bronchopneumonia , infection usually spreads from bronchi to the alveoli. It may hence involve more than one lobe and the findings are patchy. Lobar pneumonia involves most of the airspaces of a single lobe.

In the pre antibiotic era , pneumonia usually goes through a series of 4 stages:[6]

1. stage of congestion – heavy congested lobes filled with protein rich exudates ,bacteria and very few pus cells
2. stage of red hepatization - a firm lung containing neutrophils , rbcs and fibrin
3. stage of gray hepatisation- a dry lung filled still with purulent exudates
4. stage of resolution- only cellular debris are found.

ETIOLOGY

The etiological agent responsible for CAP cannot be identified in approximately 50% of cases. the likely microbial causes of CAP differ according tothe severity of disease at clinical presentation[5]. S. pneumoniae, M. pneumoniae, Chlamydophila pneumoniae, and viruses are likely to cause mild CAP whereas in patients with CAP severe enough to warrant hospitalization, S. pneumoniae is the most commonly identified etiologic agent followed by H. influenzae and M. pneumonia. Gram-negative enteric bacilli, S. aureus, Legionella spp., and respiratory viruses other than the influenza virus are uncommon, with an incidence of less than5%. Polymicrobial infections account for 10% to 20% of episodes

Risk factors for CAP include alcohol intake , bronchial asthma, immune deficiency states, Smoking, underlying structural airway or parenchymal lung diseases, and an age of 70 years versus 60–69 yrs.[3]

Other comorbidities associated with increased rates of CAP and subsequent mortality include cardiac failure, renal failure , liver cell failure , neoplasms , diabetes, mental retardation , memory loss , cerebrovascular diseases immunodeficiency states and malnutrition .

CLINICAL FEATURES

Pneumonia is characterized by the presence of fever, malaise , and respiratory symptoms such as cough (90%), sputum production (66%), breathlessness (66%), pleuritic pain (50%), and hemoptysis (15%)[2]. Hemoptysis is more often a feature of more severe necrotising forms of pneumonia[4] . Elderly patients may have different clinical presentations and are more likely to present with confusion, weakness, failure to thrive, delirium, abdominal pain, or generalized deterioration of their clinical status. Symptoms like headache, loose-stools, muscle pain, joint pains, occur in 10–30% of patients as non-pulmonary manifestations[3,8]. Physical findings include tachypnea , tachycardia ,clinical evidence of consolidation like midline trachea , increased vocal resonance , tubular breathing , crackles , aegophony , and whispering pectriloquy corresponding to the areas of consolidation.

CAP was historically classified as either typical or atypical. Typical pneumonia presented with acute onset of cough, purulent expectoration, breathlessness, pyrexia, prostration and was commonly associated with bacteria such as pneumococci, Hemophilus influenzae. On the other hand, atypical pneumonia was insidious in onset and was associated with dry cough, low grade fever, and mild dyspnea. It was caused by agents such as *M* pneumoniae and C pneumoniae. Choice of initial antibiotics was based on whether pneumonia was typical or atypical.

SEVERE COMMUNITY ASSOCIATED PNEUMONIA[3]

Of patients with CAP 8–10% require intensive care unit (ICU) management for respiratory and/or hemodynamic support. Pneumonia that requires care in an ICU is designated as severe CAP. End organ dysfunction is usually present and patients frequently require mechanical ventilation. The mortality rate of severe CAP ranges between 22% and 50%.

Common Causes of Severe Community-Acquired Pneumonia in descending order of frequency are

Streptococcus pneumoniae

Enteric gram-negative bacilli

Staphylococcus aureus

Legionella spp.

Mycoplasma pneumoniae

Respiratory viruses

Pseudomonas aeruginosa

RADIOLOGICAL FEATURES[2]

The presence of air bronchograms and a lobar or segmental pattern is more characteristic of typical than atypical causes of pneumonia. In contrast, a mixed pattern (alveolar and interstitial disease) is more frequentlyobserved with atypical pneumonias

LABORATORYEVALUATION;

Evaluation of patients with pneumonia includes tests to identify the specific pathogen causing the infection as well as laboratory tests to determine the severity of illness and to monitor for dysfunction in extrapulmonary organs.

Evaluation of patients with CAP who require hospitalization includes complete hemogram , renal function tests , serum sodium levels, blood sugar levels, liver function studies, and arterial blood gas analysis.

MICROBIOLOGICAL EVALUATION[3]

Identification of the infecting microorganism serves to verify the clinical diagnosis of infection and facilitates the use of specific therapy. Blood cultures are positive in only 10% of patients with CAP. Sputum gram stains are may guide the early antibiotic therapy in pneumonia giving a rough idea of the pathogens involved. But there is a high likelihood of contamination with oral and pharyngeal commensals.

The following is a guide to the battery of investigations to be done in a patient with CAP:

OUTPATIENTS;

None*

HOSPITALISED PATIENTS:

• Repeated blood cultures , atleast twice

• Gram stain and culture of a valid sputum sample

• Urinary antigen test for detection of *Legionella pneumophila* (in endemic areas or during outbreaks)

• Stain for acid-fast bacilli and culture of sputum (if tuberculosis is suggested by clinical history or radiologic findings)

• Fungal stain and culture of sputum, and fungal serologies (if infection by an endemic mycosis is suggested by the clinical history or radiologic findings)

• Sputum examination for *Pneumocystis jirovecii* (if suggested by clinical history or radiologic findings)

• Serologies for *M. pneumoniae, Chlamydia sp, Coxiella burnetii, Legionella* spp., and respiratory viruses (in endemic areas or during outbreaks)

• Culture and microscopic evaluation of pleural fluid (if significant fluid is present)

PATIENTS UNDER INTENSIVE CARE[9]

• Sputum Gram stain and culture sensitivity, endotracheal aspirate, or bronchoscopically obtained specimens using a protected specimen brush or BAL if patient in a position to expectorate.

• Other procedures as for other hospitalized patients

INVASIVE PROCEDURES

Because of the higher rates of non- specificity of expectorated sputum, an invasive procedure may be needed to obtain suitable material for microscopy and cultures. This may be important in the management of patients with life-threatening CAP in whom diagnostic materials cannot otherwise be obtained

rapidly, patients with progressive pneumonia despite seemingly appropriate antimicrobial therapy, immunocompromised patients.

Bronchoscopic Samples:

When compared with sputum cultures, routinely processed bronchoscopic specimens demonstrate improved sensitivity and equal specificity for the culture of pathogenic fungi and mycobacteria. However, such materials have unacceptably poor specificity for routine bacterial cultures owing to oropharyngeal contamination. In contrast, semiquantitative or quantitative cultures of materials obtained bronchoscopically with a protected sheath brush or through bronchoalveolar lavage (BAL) and by direct lung aspiration have been successfully used for aerobic and anaerobic bacterial cultures. A threshold of 103 CFU/mL has been recommended to distinguish colonization from infection in protected sheath brush cultures and 10^4 CFU/ml in BAL fluid.

Transthoracic lung aspiration obtains specimens suitable for microbiologic and cytologic examination directly from lung parenchyma. It is a more successful method for diagnosing malignant pulmonary lesions than infectious diseases.

COMPLICATIONS:

Common complications that can occur during the course of disease or later are

Para-pneumonic effusions

Empyema

Lung abscess

Acute respiratory distress syndrome

Secondary infections like meningitis, arthritis, endocarditis, pericarditis, and peritonitis.

Nonpulmonary organ dysfunctions like renal failure, hepatic failure, disseminated intravascular coagulation, hemodynamic instability, and coma .

DIAGNOSIS

Pneumonia is a clinical diagnosis with symptoms of dyspnea, cough with or without expectoration, fever or hypothermia, chest pain, and chills, with clinical examination suggestive of consolidation in most patients with presence of characteristic parenchymal infiltrate on chest radiograph[9].

ASSESSMENT OF SEVERITY:

Once the diagnosis of pneumonia has been made, the clinician must decide whether the patient can be managed in the outpatient setting or hospitalised.. Pneumonia is the fourth most frequent cause of hospitalizations[2]. It also remains a leading cause of mortality particularly in developing countries. In spite of the application of numerous and efficient antimicrobial drugs, the lethal outcome of community-acquired pneumonia (CAP) treated ambulatorily ranges from 0.6 to 1.5%. In patients who require hospitalization, mortality rate ranges from 5 to 13%. However, in case of development of complications and in artificially ventilated patients, the mortality rate rises up to 50%. Hence physicians started realising the need for a accurate and quick predictor of poor outcomes and complications that might aid the physician on deciding change in antibiotics and the level and intensity of care [10]. Also more than half of those patients with pneumonia may be treated on an out-patient basis , with oral drugs thus saving lot of manpower and resources.

A precise, objective model of pneumonia prognosis could help doctors estimate the risk for a particular patient, as well as help them reach the decision regarding hospitalization[11] The need for these prognostic scoring tools is motivated by extreme differences in costs of treating patients with CAP in the

hospital , ICU and as an outpatient[37]. Ninety percent of the estimated cost for care of pneumonia is related to inpatient expenses and the cost of hospitalizing an individual patient exceeds the cost of outpatient care by a factor of 15.

OLDER PROGNOSTIC INDICES:

The initial prognostic tools were based on history, clinical examination and basic investigations. In 1993, the American Thoracic Society identified risk factors that increased the risk of mortality or a downhill course for patients with CAP[14]. They recommended inpatient therapy if one or more of these factors were present.

Factors in the history
Age greater than 65 years
Suspicion of aspiration
Cardiac failure
Bronchitis or emphysema
Diabetes mellitus
Alcohol abuse
Chronic renal failure
Liver cell dysfuction

Previous splenectomy
Hospitalization during the prior 12 months
Altered mental status
Physical findings
Temperature greater than 38.3°C
Tachypnea greater than 30 breaths/p min
Systolic BP less than 90 mm Hg
Associated extra-pulmonary infections
Laboratory abnormalities
Whitebloodcellcount<4or>30x10^9
Hematocrit <30%
PaO_2<60mmHg or $PaCO_2$>50mmHg on room air
Blood urea nitrogen = 20 mg/dL or creatinine = 1.2 mg/dL
IMAGING;
Multilobar or rapidly progressive radiographic infiltrates

.

But this method was highly unstructured and oversimplified .

PNEUMONIA SEVERITY INDEX:

Fine and colleagues developed a two step prognostic model which came to be known as pneumonia severity index (PSI)[13]. Here they identified patients with no risk factors and assigned them to class 1 . Then they further stratified the patients to class 2 to class 5 depending upon the presence or absence of risk factors like higher age, history of coexisting conditions like cerebro vascular diseases, liver diseases, renal failure,congestive cardiac failure,neoplasms, signs on physical examination like delirium, tachypnea , systolic BP , temperature, pulse rate and laboratory factors like arterial pH, BUN , serum Na^+, blood sugar, PCV , SpO2 and the presence of pleural effusion[3,14]. They assigned points for each of these variables as follows;

Demographic factor	
Age	
Male	Age in years
Female	Age in years –10
Hospital residents	+10

Comorbidities[12,20]	
Malignancies	+30
Liver failure	+20
Cardiac failure	+10
Cerebrovascular disease	+10
Renal failure	+10
Clinical findings	
Confusion	+20
Tachypnea > 30/min	+20
Systolic blood pressure <90 mm Hg	+20
Hypo or hyperthermia <35°C or 40°C	+15
Tachycardia > 125/min	+10
Laboratory and radiographic findings	
Acidosis pH <7.35	+30
BUN > 30 mg/dL	+20
Serum Na^+ <130 mmol/L	+20
Blood sugar >250 mg/dL	+10
PCV <30%	+10

Partial pressure of arterial oxygen <60 mm Hg	+10
Pleural effusion	+10

A risk score is obtained by summing the patient's age in years (age -10 for females) and the points for each applicable patient characteristic. Patients with a score < 50 can be treated as outpatients , whereas those with scores > 90 need to be hospitalised. Proper management of patients with scores of 70–90 requires careful application of clinical judgment.

Patients who have a PSI score of belonging to class I or II with a score of less than 70 have less than 1% chance of dying due to pneumonia in 30 days. They can be managed as outpatients with oral antibiotics. Patients with a PSI score of 71 to 90 which assigns them to class III have a 1 month mortality rate of around 2.8% . they shall be admitted to hospitals and given a short course of oral or IV antibiotics with monitoring. Hospital care is appropriate for patients with scores of 91 to 130 (class IV), who have a 30-day risk of death of 8.2% to 9.3%, and for patients with a score of more than 130 (class V), who have a 30-day risk of death of 27.0% to 31.1%. However, its calculation is burdensome and prone to individual errors.[16]

The British Thoracic Society came up with their own prognostic algorithm which was simple and named it the CURB-65 score based on the variables on presentation that were taken into account.[15]

(1) Confused state of mind(C)

(2) Urea levels in blood higher than 7 mmol/L (U)

(3) Respiratory rate of 30/min or more(R)

(4) hypotension with low systolic BP (<90 mm Hg) or diastolic BP(<60 mm Hg (B)

(5) Age 65 years or greater(65)

Their algorithm assigns one point for each of these individual variables depending upon their presence or absence. The cumulative score is calculated by making a sum of the points assigned against the individual variables to a maximum score of 5.

Scores 0 or 1 (group 1), 2 (group 2), and 3 to 5 (group 3) carry a 30 day mortality rate of 1.6%, 9.1%, and 23%, respectively. Outpatient treatment is recommended for pts assigned to group 1 , group 2 patients require a short duration of inpatient care and monitoring, and intense monitoring is

recommended for group 3 . Pts with scores of 4 or 5 shall be managed in an ICU setting.

The IDSA and the ATS have published ICU admission criteria for patients with CAP. According to these criteria , ICU admission is warranted for patients who fulfill three minor criteria or one major criterion among the following criteria. Management of severe CAP per these guidelines has been associated with decreased mortality.[17]

MINOR CRITERIA

Tachypnea > 30 breaths/min

PaO2/FIO2 ratio < 250

X –ray showing involvement of more than one lobe

Delirium

Renal failure (BUN level > 20 mg/dL)

Reduced WBC count < 4000 cells/dL

Reduced platelet count < 100,000 cells/dL)

Fall in core body temperature to < 36^0c

Fall in BP requiring rapid volume replenishment

MAJOR CRITERIA

Need for supportive ventilation

Septic shock with need for pressor agents

INFLAMMATORY BIOMARKERS IN PNEUMONIA;

The clinical and biochemical prognostic markers discussed above are cumbersome and most of them are useful in assessing mortality and morbidity in short term only. Pneumonia is basically a disease in which there is a strong associated inflammatory response which also determines the clinical severity of the disease and hence the final outcome. Hence the idea of using inflammatory biomarkers came on and they were put to test against the clinical and other biochemical parameters. In recent years biomarkers have come up in a big way in western countries and they have been used for finding the etiological agent , assessing the severity and prognosis and making important decisions regarding the treatment.[18]

Leucocyte count was initially used as a the inflammatory marker to predict the prognosis. Further studies have used various relatively more advanced markers like C-reactive Protein, Procalcitonin , Arginin-vasopressin(C-terminal-proAVP -Copeptin), Natriuretic peptides , Adrenomedullin , Interleukin-6 & 10, Liposaccharide binding protein and serum cortisol levels for assessing the extent of inflammatory response, severity of the disease and hence the prognosis.

COMMON INFLAMMATORY BIOMARKERS:

CRP is the fore runner of the inflammatory biomarkers that were subsequently developed to assess the severity of pneumonia. Any inflammation can lead to increase in CRP as many cytokines promote its hepatic synthesis.. It is found in the serum very quickly , as early as 2 hrs , after the trigger. Measuring CRP level is a screen for infectious and inflammatory diseases.for this purpose it is better than WBC count and ESR. Rapid, marked increases in CRP occur with inflammation, infection, trauma and tissue necrosis, malignancies, and autoimmune disorders. But the problem with CRP is its poor specificity . The median serum concentration of CRP is 0.8 mg/l in normal human beings. CRP rises up to 50,000-fold in acute inflammatory states such as that found in pneumonia.

Procalcitonin(PCT) is a peptide precursor of the hormone calcitonin, the latter being involved with calcium homeostasis. It is synthesized in the parafollicular cells of the thyroid. It is also produced like a cytokine by liver, and monocytes. PCT is relatively specific for inflammation induced by bacterial infections as the viral infections and other tissue stressors do not stimulate the release of PCT. This is particularly helpful in deciding whether or not to use antibiotic therapy in a given case of pneumonia.

CARDIAC BIOMARKERS:

Adrenomedullin (ADM) and Procalcitonin(PCT) belong to the same gene family, which may explain their sensitivity and specificity to diagnose systemic bacterial infections. ADM possesses immunomodulatory and bactericidal properties, and is one of the strongest endogenous vasodilators.

Arginin-vasopressin (AVP) is usually measured via its prohormone fragment C-terminal-proAVP (Copeptin) whose serum levels are significantly elevated in septic shock.[24]

NATRIURETIC PEPTIDES;

Natreiuretic peptide family contains 4 members who share a common 17-peptide ring structure. These are the atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP) , C-type natriuretic peptide (CNP) and dendroaspis natriuretic peptide (DNP)[19]. Atrial natriuretic peptide(ANP) and Brain type natriuretic peptide(BNP) have been found to be useful in predicting the prognosis in patients with pneumonia.[21]

These are secreted by cardiac myocytes in response to volume or pressure overload of the ventricles and atria that impose excess stress on their walls .

ATRIAL NATRIURETIC PEPTIDE (ANP)[22]

ANP is also called Cardionatrine, Cardiodilatine(CDD) or atriopeptin[23]. It is released by atrial myocytes in response to increased blood volume in atria. Other ANP secretagogues are sympathetic stimulation , hypernatremia, angiotensin-II and endothelin. Its fuctions are mediated by its action on its three receptors, NPR-A , NPR-B and NPR-C. ANP exerts its main actions in the kidneys by afferent arteriolar dilatation, efferent arteriolar constriction, mesangial relaxation , decreasing sodium reabsorption in the DCT and cortical collecting duct of the nephron , inhibiting renin secretion, reducing aldosterone secretion by the adrenal cortex. All these actions ultimately contributing to natriuresis and volume reduction. ANP has been studied in two different forms in assessing the severity of pneumonia.The N-terminal PRO ANP (NT Pro ANP) and the mid regional Pro ANP(MR Pro ANP). The MR Pro ANP is found to be more useful than the former in pneumonia.[24]

BRAIN TYPE NATRIURETIC PEPTIDE (BNP):

B-type natriuretic peptide, secreted by the cardiac ventricles whenever their walls are exposed to excessive stretch. It is a polypeptide hormone containing thirty two aminoacids.The human BNP gene is located in the first chromosome and with the gene product being proBNP[21]. BNP got its name from porcine brain from which it was first extracted in 1988. Atrial myoctes have the highest ability to produce BNP but ventricle wins the duel because of its

relatively higher muscle mass . Recent studies have shown that some BNP is secreted by fibroblasts also but their relative contribution is not known. The ability to produce BNP is induced in less than 60 mins in response to either pressure or volume overload of the heart. Calcium ions play a role in the control of release of BNP.. BNP is secreted in combination NT-proBNP which is its cleavage remnant.. NT – pro BNP is biologically inactive. BNP acts on the same set of receptors like ANP , NPR-A and NPR-B and activates them. But it has ten times lower affinity than ANP on these receptors[26]. But BNP stays in blood for longer period of time , infact around twice as long as that OF ANP making it ideal measurement and analysis.NT-Pro BNP has a similar advantage as compared to ANP.

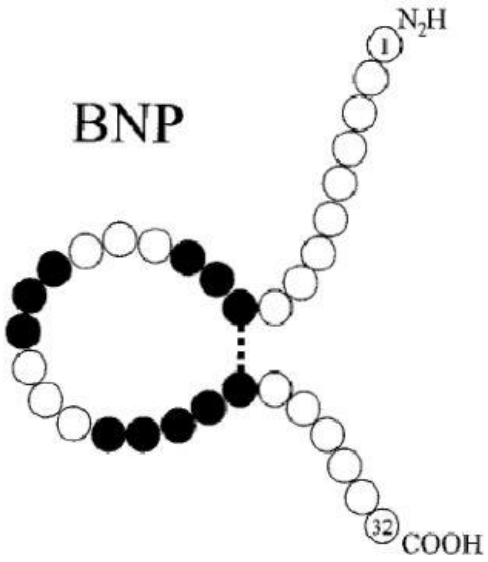

FIGURE A. MOLECULAR STRUCTURE OF BNP

BNP is cleared from the circulation by receptor-mediated endocytosis via the C-type natriuretic peptide receptor, as well as by enzymatic degradation via zinc-containing endopeptidases located on the vascular endothelial cells and in the renal tubules . As such BNP is mainly excreated through the kidneys leading to higher levels in cases of renal disease with or without failure.

BIOLOGICAL FUNCTIONS OF BNP:

The physiological effects of BNP are brought about by causing increased intracellular cyclic GMP production[27.] Both the natriuretic peptides act mainly to counter the excess hemodynamic challenge imposed by the renin-angiotensin system. The main action of BNP is on the kidneys and the vasculature as follows:

Cardiovascular and Renal Actions of BNP

- Sodium excretion
- Free water clearence
- Increasing GFR & filtration fraction
- Counteract renin release
- Reduction in blood levels of angiotensin II
- Reducing blood levels of aldosterone
- Vasodilation in systemic vessels
- Fall in systemic BP

- Venous hypotension
- Reduced pulmonary capillary wedge pressure

In addition the recent studies have focussed on the trophic effects of BNP on the heart. BNP is supposed to have protective effect against the detrimental fibrosis and remodelling that occurs in progressive heart failure.

METHOD OF ESTIMATION OF BNP:

BNP levels were initially assessed by competitive radioimmunoassays . this required extraction and purification of the plasma sample.Second-generation assays used monoclonal antibodies and radioisotope labels. Third-generation assays used immunofluorescent methods . These provided results in as little as 15 minutes[28].

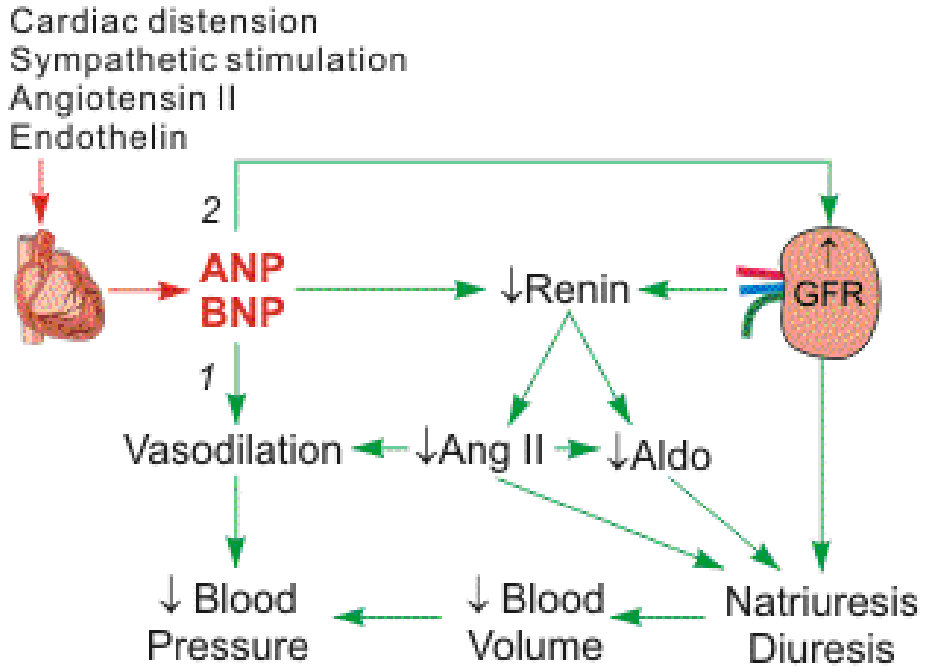

FIGURE B. PHYSIOLOGICAL ACTIONS OF BNP

BIOCHEMICAL IMPORTANCE OF BNP:

BNP was initially used as a biomarker in patients with acute dyspnea to differentiate cardiac causes from non-cardiac causes of dyspnea with values higher than 500 pg/ml almost diagnostic of a cardiac cause of dyspnea.[29] Subsequently it was found to have prognostic significance in such patients . This is due to the basic concept that BNP is a marker of cardiac stress and hence patients with higher BNP are supposed to have severe cardiac stress and hence poor prognosis. BNP accurately reflects current ventricular status, as its half-life is 20 minutes, as opposed to 1–2 hours for NT-ProBNP. So BNP was also used to monitor treatment response as well in congestive cardiac failure[30].

Closely related to these observations the further prognostic implications of BNP were described:

- BNP was also useful in assessing other conditions like CAD with normal LV fuction.[31]
- BNP was found to have important role in prognostication of millions of diabetics.[32]
- BNP was used to assess the prognosis of heart surgery patients by determining the post operative complications and outcomes.[33]
- Utility of BNP has also been explored in various emergency settings like preeclampsia, ICU and shock and ESRD.[34,35,36]

Subsequently other non-hemodynamic stimuli for the release of BNP were found like inflammatory cytokines and hypoxia and so the prognostic spectrum of BNP was expanded to other diseases that are mediated by acute inflammation and/or have associated hypoxia like COPD, sepsis and pneumonia.

BNP IN PNEUMONIA :

Ever since the advent of cardiac biomarkers for assessing the severity of pneumonia , there have been a few studies which have sought to analyse the prognostic importance of BNP in pneumonia by comparing it with clinical indices, biochemical parameters, inflammatory markers and other cardiac biomarkers. These studies have opened new avenues for further research and improved our understanding of the mechanism of BNP elevation in pneumonia and other conditions.

BNP was found to be elevated in patients with pneumonia and it independently mirrored the severity of pneumonia as made out by other

parameters. It was found to have more sensitivity and specificity when combined with other parameters in predicting the clinical course of illness. Elevated BNP was found to be an independent risk factor for mortality , prolonged hospital stay , need for ICU monitoring ,delayed clinical and radiological resolution .

Initially myocardial stress that a patient with pneumonia suffers was thought to be the main mechanism behind the elevated levels of BNP. But recent studies that have assessed the elevation of BNP in sepsis and the correlation of BNP with other inflammatory markers like CRP have evoked the possibility of inflammatory cytokines like IL-6, IL-1, and TNF-α being important secretagogues for BNP in pneumonia. Further experimental studies have confirmed this finding and have suggested that this is the most important reason for elevation of BNP in pneumonia.

Hypoxia was also expected to be an important factor in this setting but the subsequent studies failed to show any significant correlation.

Currently as it stands reason for elevation of BNP in pneumonia may be one of the following:

- Myocardial stress induced by pneumonia itself
- Severe inflammation
- Hypoxia
- Presence of other organ dysfunction like renal failure or cardiac failure

All these may complicate the course of pneumonia individually and is hypothesised that the cumulative effect of these factors is reflected in the levels of elevation of BNP depending upon their presence or absence. So BNP may be a one step test that says so much more than many factors combined.

The current guidelines promote the use of BNP in the risk stratification of congestive cardiac failure . Clinico- biochemical parameters are still being used in case of pneumonia. BNP may appear a costly alternative but it is nevertheless simple, quick and effective and may play an important role in the future in assessing the prognosis of pneumonia.

MATERIALS AND METHODS

MATERIALS AND METHODS:

The study was conducted in the Rajiv Gandhi Government General Hospital, Chennai during the period between May 1, 2012 and October 31,2012. The entire study was done on patients who were admitted under the care of Institute of Internal Medicine, Madras Medical College & Rajiv Gandhi Government General Hospital.

The laboratory work and other investigations were done with the help of other departments which include:

Institute of Biochemistry, MMC&RGGGH

Institute of Pathology , MMC&RGGGH

Barnard Institute of Radiology, MMC&RGGGH

Institute of Microbiology, MMC&RGGGH

Department of Cardiology, MMC & RGGGH

Fourty two consecutive patients with community acquired pneumonia were selected from our outpatient clinic and emergency ward as follows.

Community acquired Pneumonia was diagnosed in a patient when he or she presents with

1. One or more of the symptoms of pneumonia like fever, cough, dyspnea , hemoptysis or chest pain with
2. Clinical examination showing features of consolidation and
3. Radiological features of consolidation.

   and who does not meet the criteria for healthcare associated pneumonia.

INCLUSION CRITERIA;

1. All patients who fit into the description of community acquired pneumonia described above were included in the study.
2. Age greater than 18 years.

EXCLUSION CRITERIA:

1.Patients who had history , clinical and Echo-cardiographic evidence of heart disease

2.Patients with clinical , biochemical and radiological evidence of acute kidney injury or chronic kidney disease, with or without failure.

3. Patients with clinical and radiological evidence of COPD

4.Patients with previous history or radiological evidence of pulmonary tuberculosis.

An elaborate history was obtained from all the patients and their relatives regarding the presenting complaints, their elaboration , past medical history including diabetes mellites, systemic hypertension, ischemic heart disease, seizures, CVA , tuberculosis , bronchial asthma and COPD , retro viral disease , malignancies , prior surgeries and blood transfusion. Personal history, including alcohol intake, smoking , sexual habits and other adverse exposures ,was elicited.

All the patients underwent a thorough clinical examination from head to foot , including vital signs , SpO2, and detailed systemic examination , by two physicians to confirm the diagnosis and to pick up other relevant clinical findings.

They underwent all the necessary investigations like renal function tests, liver functions tests, complete blood count, blood –culture and sensitivity, sputum or tracheal aspirate – gram stain, culture and sensitivity, ECG, Chest X ray, USG abdomen , ECHO - cardiogram when there was a doubtful cardiac disease , CT-chest whenever the diagnosis is in doubt. The BNP levels on admission was

measured by using immune-fluorescence method. The choice of antibiotic usage and other treatments were left to the treating physician .

The patients were re-examined after 4 weeks in all the possible cases and the records were analysed in the other cases for resolution or persistence of symptoms , signs and radiological features. The duration of hospital stay was obtained from the records. In those who died during the follow up period , the records were analysed comprehensively and information gathered.

Statistical Analysis :

All the analysis were done using the statistical package - SPSS Software.

Consent

Written and informed consent were obtained from all the participants in feasible cases or their attenders .

Ethical Committee Approval

The study was approved by Institutional Ethics Committee of Madras Medical college .

OBSERVATION AND RESULTS

OBSERVATION AND RESULTS:

The study results were tabulated and a stepwise analysis performed beginning with the analysis of BNP levels in survivors and non- survivors. Since the BNP levels in the non-survivors were eccentric and confounding the analysis of BNP with other variables , the further comparisions in BNP used values from the survivors only.

The mean values in all the analysis were compared using the two- tailed unpaired t test and the level of significance assumed was 0.05.

The following variables were included in the analysis;

Age , sex, presence of co-morbidities, h/o prior antibiotic administration, alcoholism , smoking ,CRB-65 score , Total leucocyte count , BNP levels , cultured organism, duration of hospital stay, clinical and radiological resolution development of complications like pleural effusion , empyema , MODS, ARDS and mortality.

RESULTS

1. The mean BNP levels in male survivors was compared with that of female survivors.

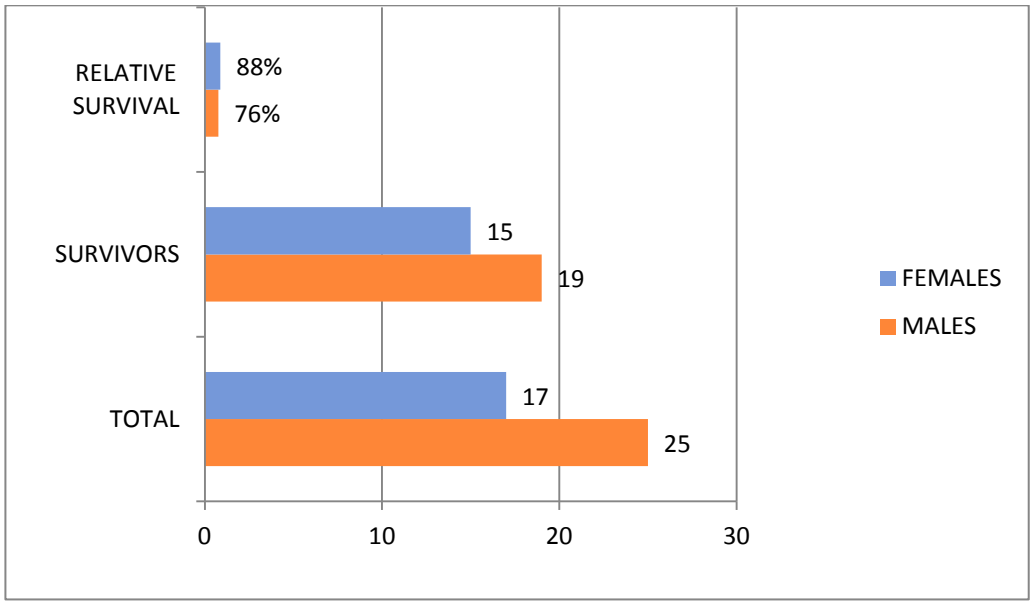

FIGURE.1.Number of males and females in the study and their relative survival percentage

There were 25 males and 17 females enrolled in the study.There were 19 male patients who survived the episode of pneumonia among the 25 males which amounts to 76%. 15 0f the 17 females(88%) survived .

The mean BNP level in male survivors was 160.32pg/ml with a standard deviation of 72.08 as against a mean BNP of 134.3pg/ml with a standard deviation of 44.77 in female survivors . The two tailed P value between the means was 0.23 which was insignificant with 95% confidence interval. Thus there was no significant sex influence on BNP.

SEX	MALE	FEMALE
SAMPLE SIZE	19	15
MEAN BNP(PG/ML)	160.3	134.3
STANDARD DEVIATION	72.08	44.77

TABLE 1. Comparision of mean BNP in male survivors with BNP levels in female survivors

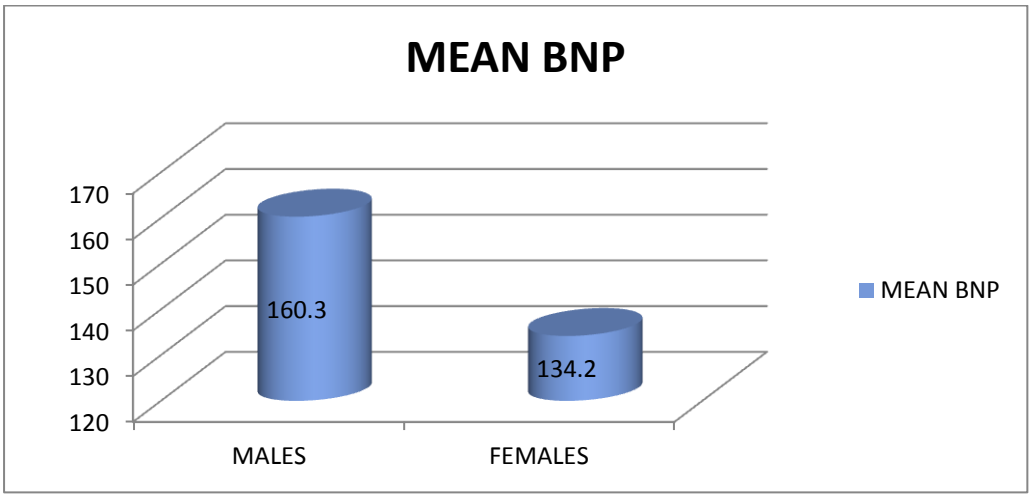

FIGURE 2.Mean BNP in males vs females

2. The mean BNP in age groups greater than 50 and less than or equal to 50 were compared. There were 17 patients in the age group 50 or less and 25 patients above 50 years.

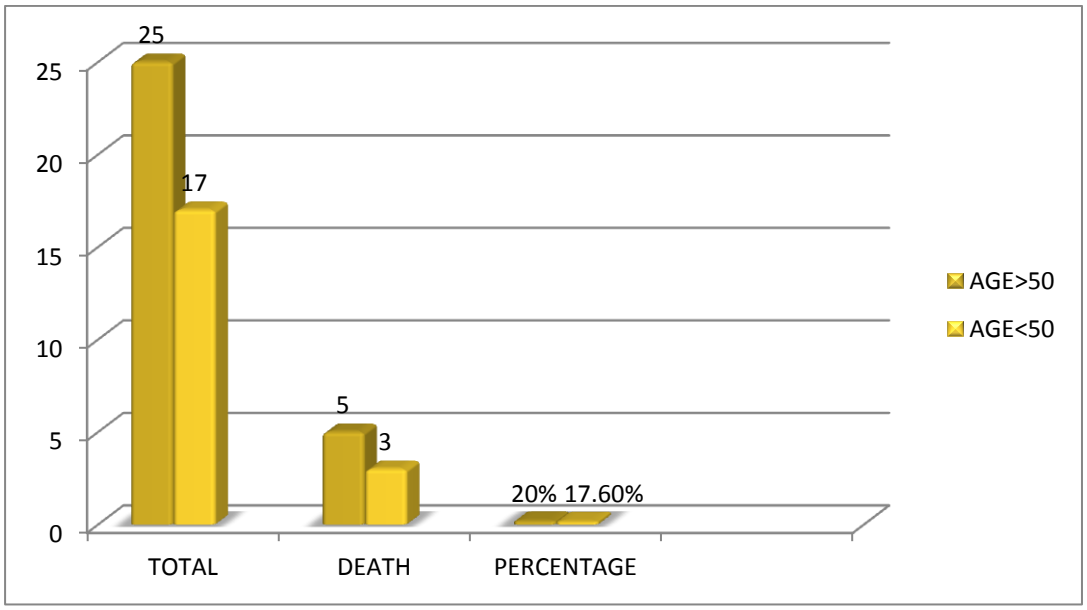

FIGURE.3.Comparision of relative mortality in age groups >50 and less than or equal to 50

AGE	>50	< OR =50
NUMBER	20	14
MEAN BNP	138.3	163.2

TABLE 2.Mean BNP in age groups >50 and <or =50 in those who survived

There were 5 deaths among those in age group more than 50 and 3 deaths in the other group, constituting 20% and 17% respectively.

The mean BNP levels in the survivors over the age of 50 was 138.3 pg/ml as against a mean of 163.2 pg/ml in those less than or equal to 50 years. Their standard deviations are 41.2 and 83.3 respectively. The two tailed P value for this variables was 0.27 which showed that age did not have any significant influence on the BNP levels.

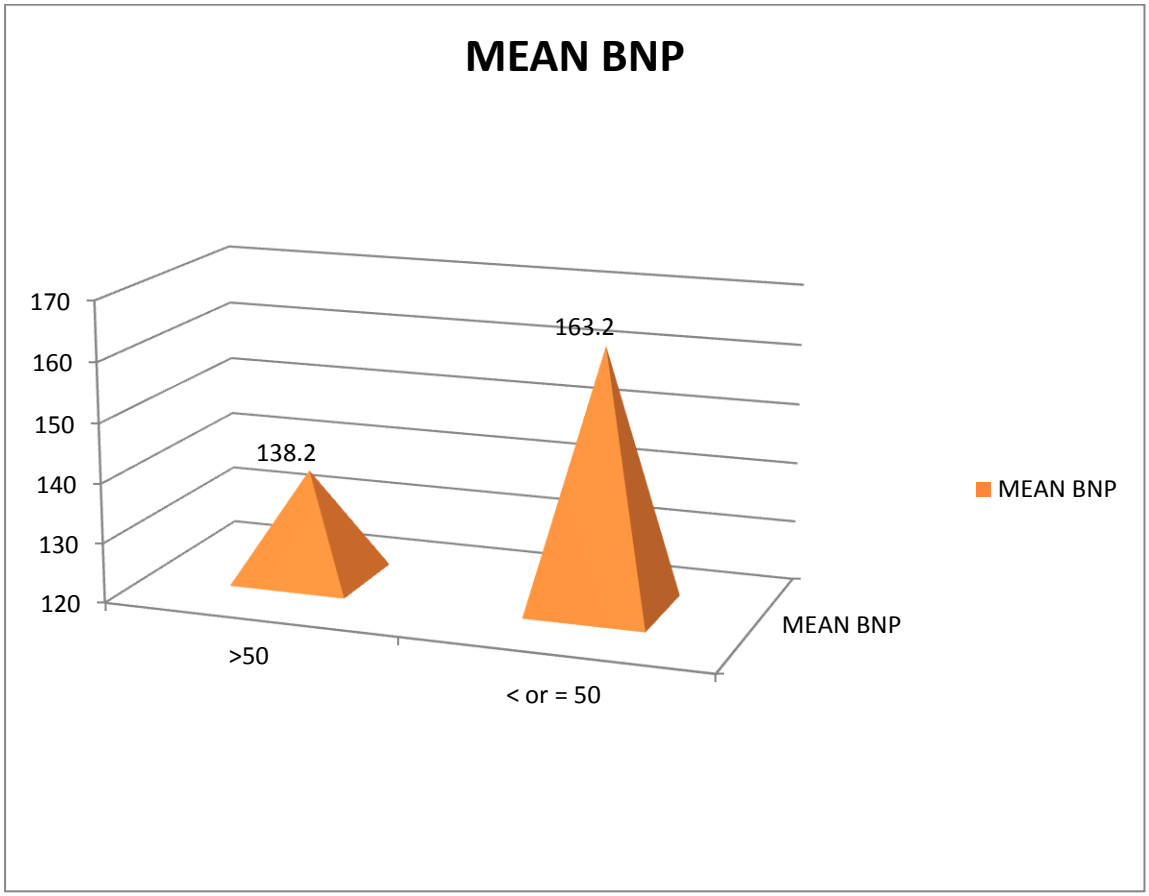

FIGURE 4. Mean BNP in age groups >50 and <or =50 in those who survived

3.The BNP levels in those who had co-morbidities that are not known to increase BNP were compared with the levels in those without any comorbidities. The conditions that were included are underlying malignancies diabetes mellites, systemic hypertension , previous CVA. There were 23 patients who had one morbidity or the other with diabetes being the commonest occurring in 15 patients. 8 patients had more than one comorbidity. The malignancies that were encountered were lung and gi malignancies.

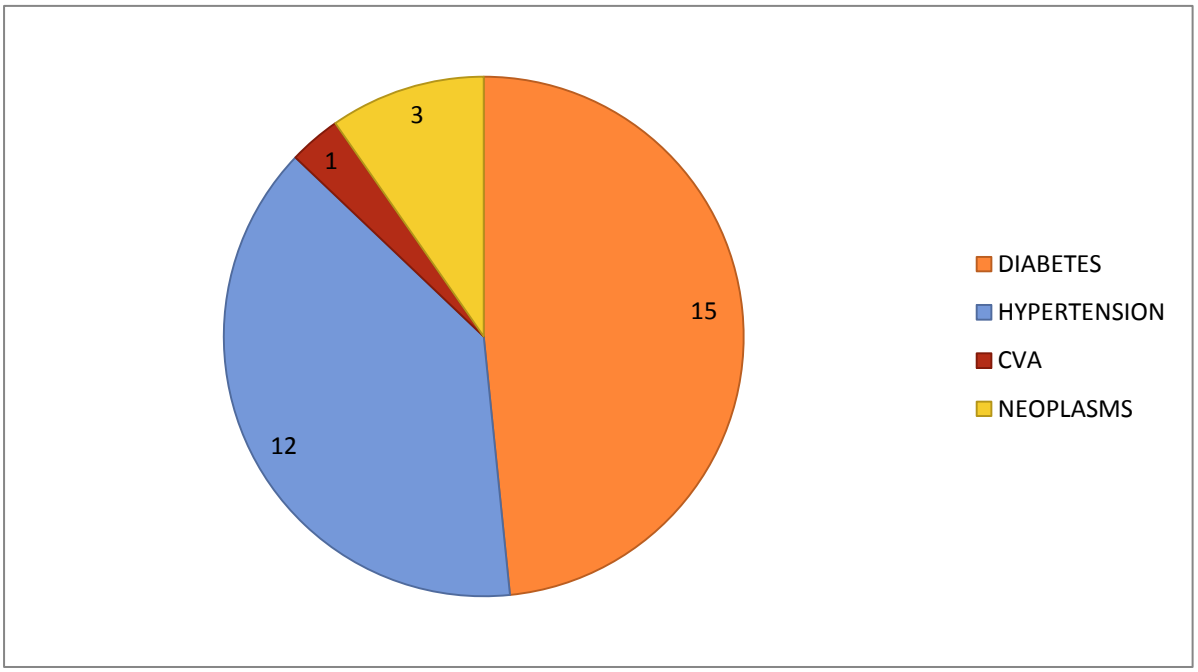

FIGURE 5.Distribution of comorbidities in the study population

There were 6/25 deaths in those with any one of the comorbidities compared to 2/19 deaths in those with no comorbidities.

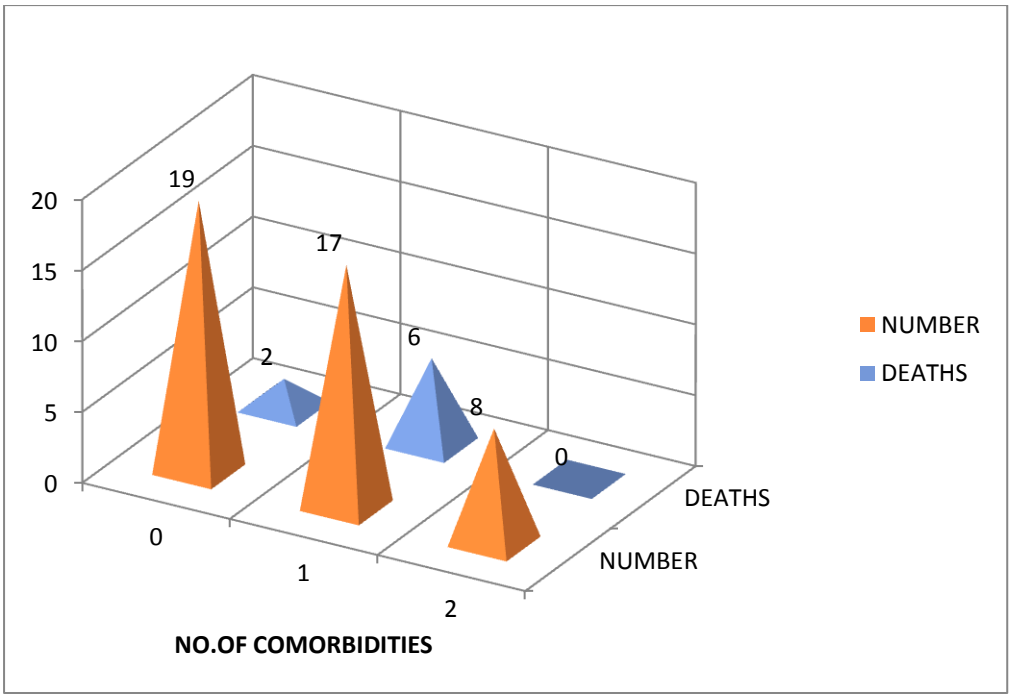

FIGURE.6 Correlation between no.of comorbidities and mortality

COMORBIDITIES	YES	NO
TOTAL PATIENTS	25	19
MEAN	148.7	149
S.D	54.8	70.4

TABLE.3. Correlation of comorbidities with mean BNP levels.

The mean BNP in patients with comorbidities was 148.7pg/ml against an almost similar value of 149.2pg/ml in patients with no comorbidities thus confirming that these diseases do not have any notable influence on the BNP levels. The P value was 0.9 and it was not needed in this case to decide the significance factor.

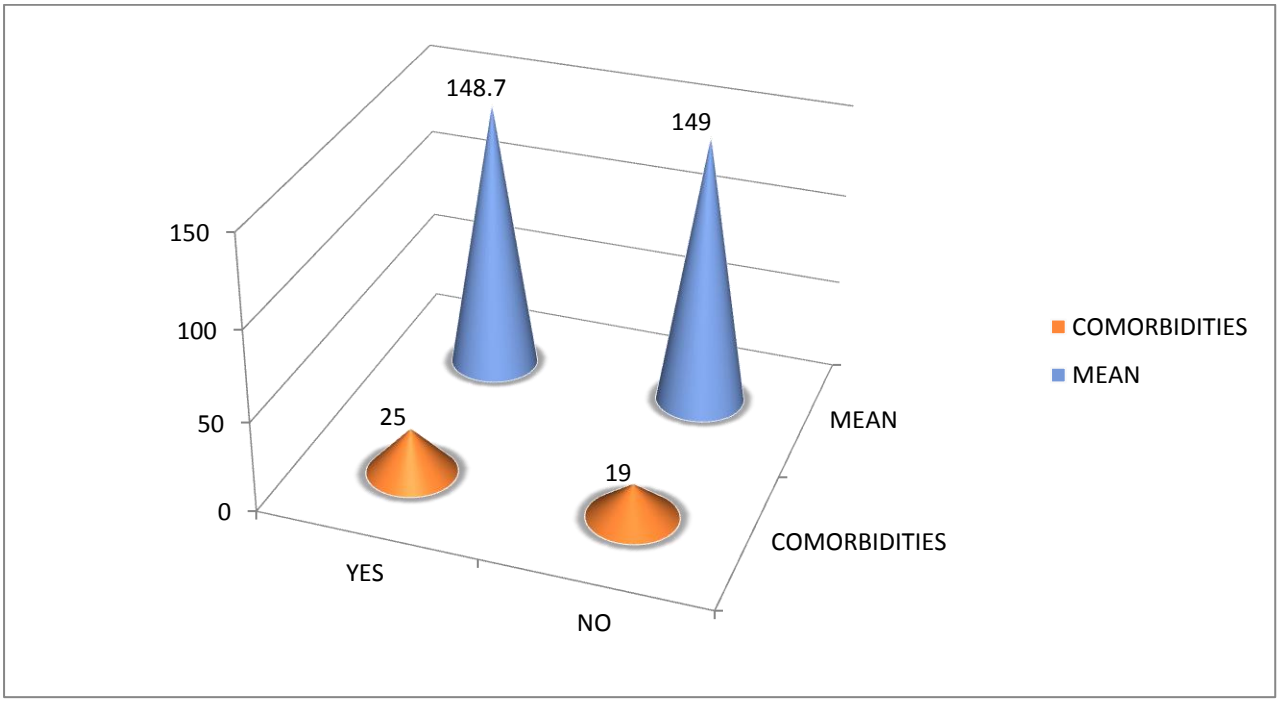

FIGURE7; Mean BNP in survivors with and without comorbidities

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4.The mean BNP in surviving smokers and non-smokers were compared. There were 13 smokers in the study of whom 9 survived with a mortality rate of 31%. The mortality rate among 29 non smokers was 13%

SMOKERS	YES	NO
NUMBER	9	25
MEAN	133.3	154.4
SD	74.2	57.8

TABLE 4.Mean BNP in smokers and non smokers among survivors

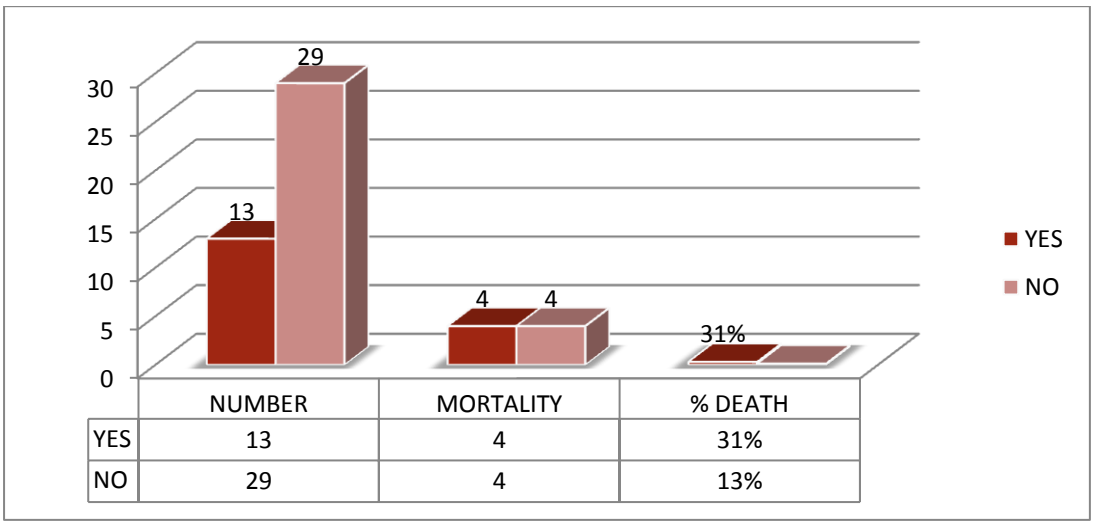

FIGURE 8. Mortality comparisions in smokers vs non-smokers

The mean BNP in surviving patients with history of smoking was 133.3 pg/ml with a standard deviation of 74.2. The mean BNP in non smoking survivors was 154.4pg/ml with a standard deviation of 57.82pg/ml. the P value on comparing the means was 0.39 which showed that there was no meaningful increase or decrease in BNP in patients who smoke. But the lower mean BNP was a surprising value.

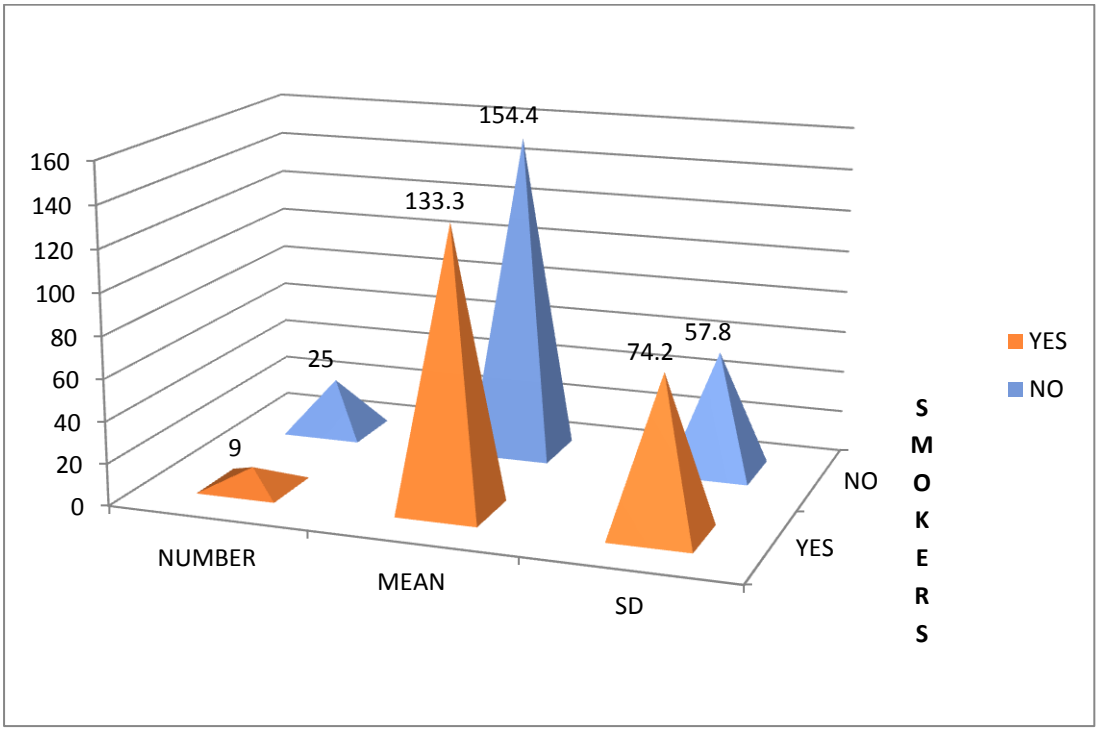

FIGURE 9.Mean BNP in smokers vs non- smokers in survivors.

5. The mean BNP in alcoholics who survived were compared to that of the non alcoholics who were alive. There were 15 alcoholics in the study with 14 of them being males. 14 of alcoholics survived the illness which was better than the survival rate of the 20 of the 27 non alcoholics who survived.

ALCOHOLIC	YES	NO
TOTAL NUMBER	15	27
SURVIVORS	14	2O
MEAN BNP	161.2	140.8

TABLE 5.Mean BNP in alcoholics and non-alcoholic survivors

The mean BNP in alcoholics who survived was 161.2pg/ml against a value of 140.8 pg/ml seen in non-alcoholics with a P value of 0.34 which showed that there was no significant influence of alcohol on the BNP level

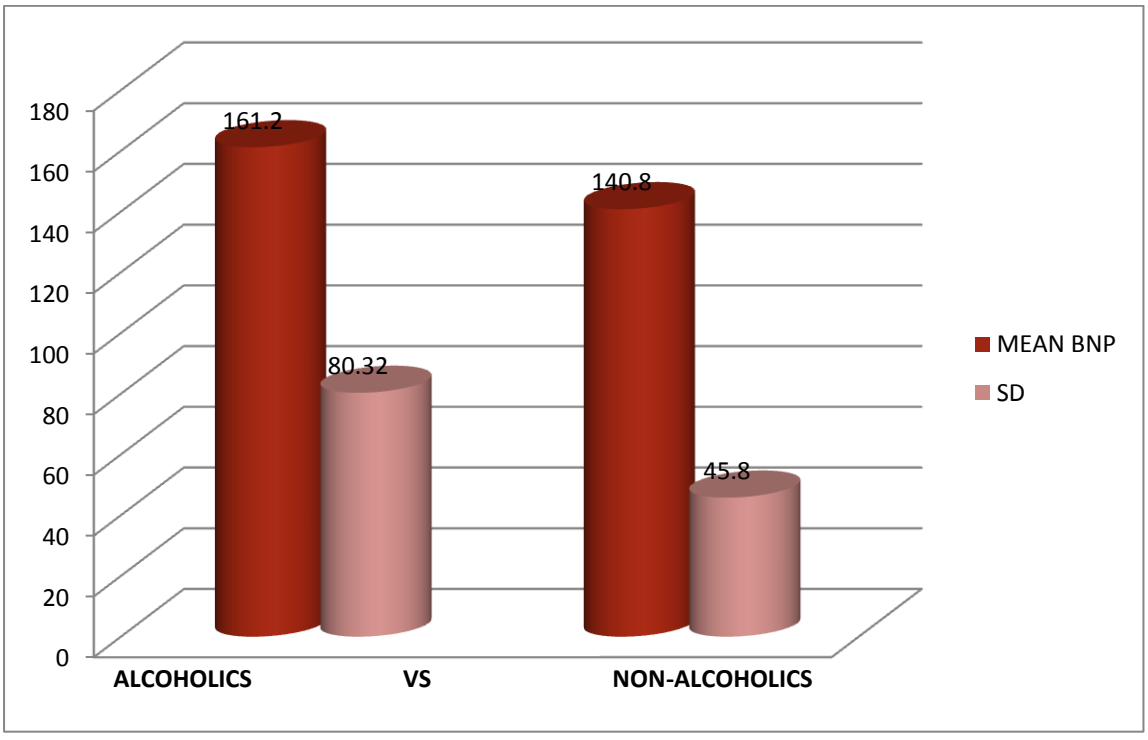

FIGURE 10.Mean BNP levels in alcoholics and non-alcoholic survivors

6. The mean BNP levels in survivors who were previously treated with antibiotics when they presented to the hospital were comparitively analysed with that of those who did not receive any antibiotics. 24 patients who presented to the emergency room had received some form of antibiotic therapy prior to coming to our institute. Infact all the 8 patients who died during the follow up period had received some prior anti-biotics. This observation can be explained by the level of care for which the patients in poor shape are being referred after initial antibiotic therapy.

PRIOR-ANTIBIOTICS	**YES**	**N0**
NUMBER	16	18
MEAN	162.9	136.4
S.D	55.06	66.81

TABLE 6.Mean BNP levels in survivors who received prior antibiotics vs those who were untreated.

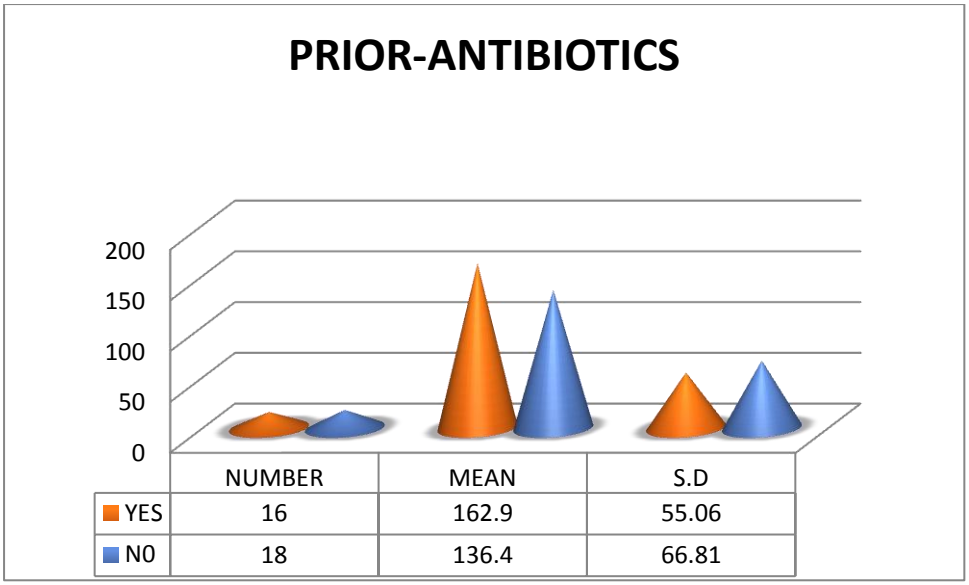

FIGURE 11.Mean BNP levels in survivors who received prior antibiotics vs those who were untreated.

7. The survival rate of patients who had an SpO2 of more than 90 0n presentation was analysed and the mean BNP level in survivors with an SpO2 of more than 90 was compared with that of persons with SpO2 less than 90 to find out if there was any relation between hypoxia and BNP release.

26 patients had an Sp02 of more than 90 and all of them survived. But there was 50% mortality in those persons who had an SpO2 of less than or equal to 90 at presentation.

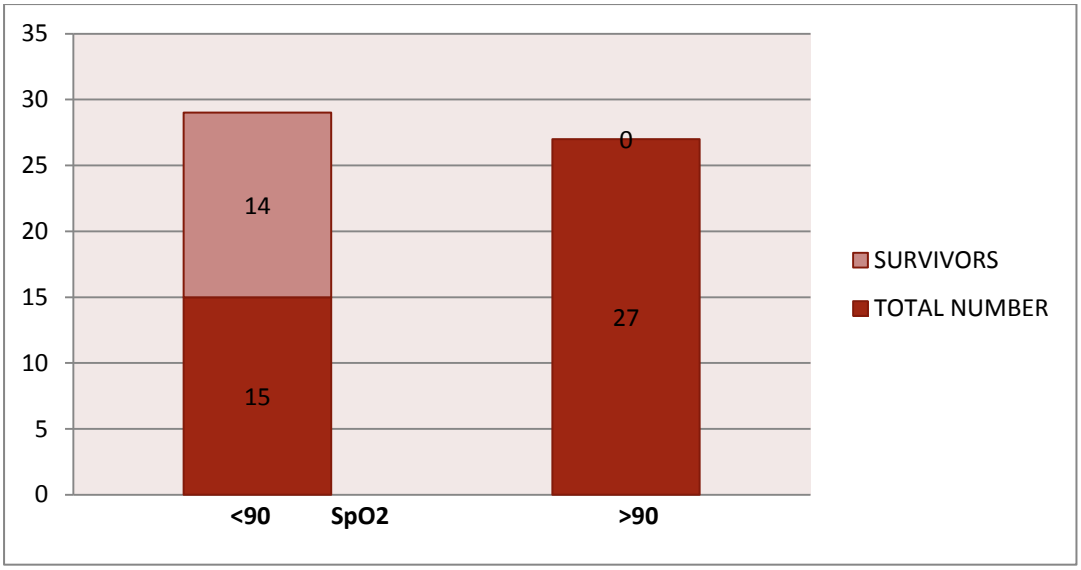

FIGURE 12.Correlation between SpO2 and mortality

The mean BNP level in survivors with SpO2 was 174.7 pg/ml with a standard deviation of 48.6 against a mean value of 140.9 pg/ml with a standard deviation of 64.4 in those with SpO2 of less than or equal to 90.

SpO2	>90	< OR = 90
NUMBER	**26**	**8**
MEAN BNP	**140.9**	**174.7**

TABLE 7.Mean BNP levels in survivors with SpO2 greater than 90 vs less than or equal to 90

The P value was 0.18 which showed that the difference was not that significant So the possibility of hypoxia being a stimulator of BNP received a jolt.

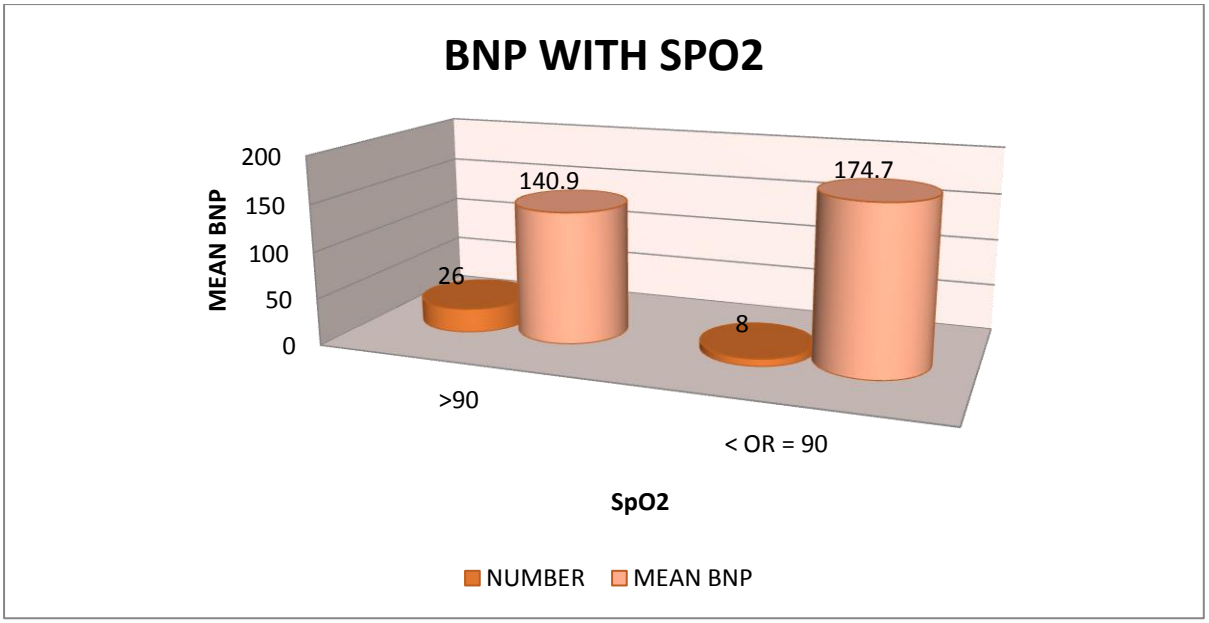

FIGURE 13., Mean BNP levels in survivors with SpO2 greater than 90 vs less than or equal to 90

8.The relative commonness of the nature of organism isolated was studied and any difference in the mean BNP levels of the two common group of organisms was analysed.

Of the 42 patients in the study, 17 patients harboured gram positive cocci with strep. Pneumoniae and Staph.aureus being the commonest. 10 patients were infected with gram negative bacilli like Pseudomonas or Klebsiella and 1 patient was found to have both these groups of bacteria. In 14 patients no organisms were isolated by routine gram stain and culture methods.

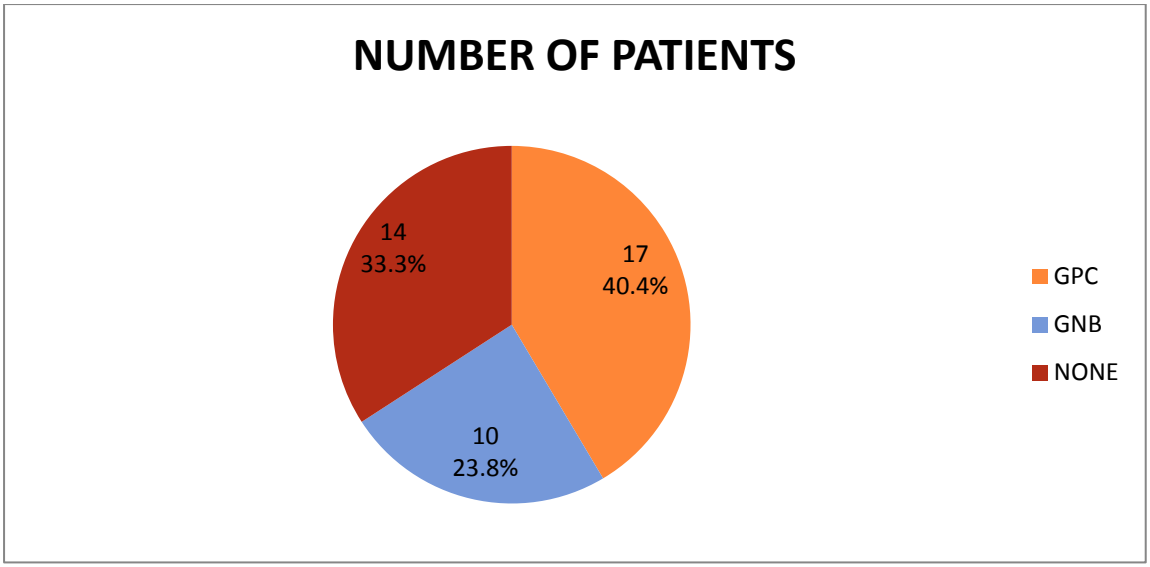

FIGURE 14.Relative frequencies of the causative group of organisms in pneumonia

The mean BNP in patients whose culture showed gram positive cocci was 127.6pg/ml .The mean BNP in patients with gram negative bacilli was 173.9pg/ml. the P value of the difference between the means was 0.102 . Though the difference was insignificant , there seems to be a greater tendency for the gram negative bacilli.

ORGANISM	GPC	GNB
NUMBER	14	10
MEAN	127.6	173.9

TABLE. 8.Mean BNP in survivors infected with gram positive cocci vs gram negative bacilli.

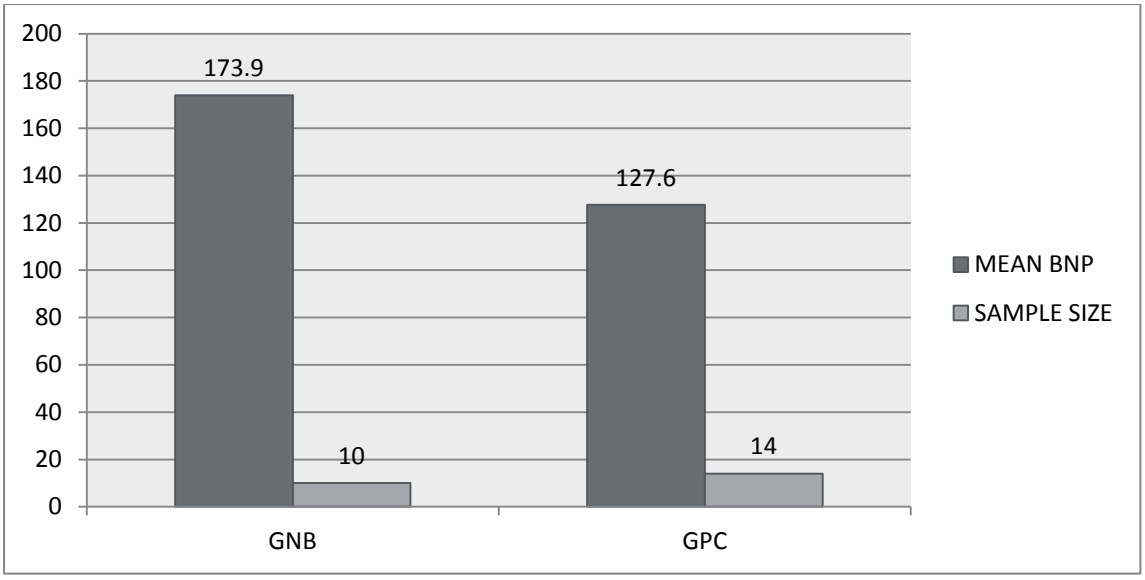

FIGURE 15. Mean BNP in survivors infected with gram positive cocci vs gram negative bacilli

9.The correlation between BNP levels and leucocyte count was studied to find out if there was any relation between the inflammatory response and the levels of BNP.The mean BNP in survivors with leucocyte count of more than 15,000 was compared with that of those patients with a leucocyte count of more than 15,000.The leucocyte count was highly variable in the study varying from as low as 2100 cell/mm^3 to as high as 28,200 cell/mm^3 and either extremes of values can be explained by pneumonia itself

LEUCOCYTE COUNT	**>15,000 /mm^3**	**<15,000/mm^3**
SURVIVORS	9	25
MEAN BNP	200.4	130.2

TABLE 9. Mean BNP in survivors with or without leucocytosis (>15,000)

The mean BNP in the 25 patients who survived with a leucocyte count of greater than 15,000 was 130.24pg/ml against a mean BNP of 200.4pg/ml in the 9 survivors with leucocyte count less than 15,000. The probability of this difference occurring by chance was 0.002 by two tailed paired t test. This shows that the release of BNP correlated well with the rise in leucocyte count. This emphasises the close relationship between BNP levels and inflammation.

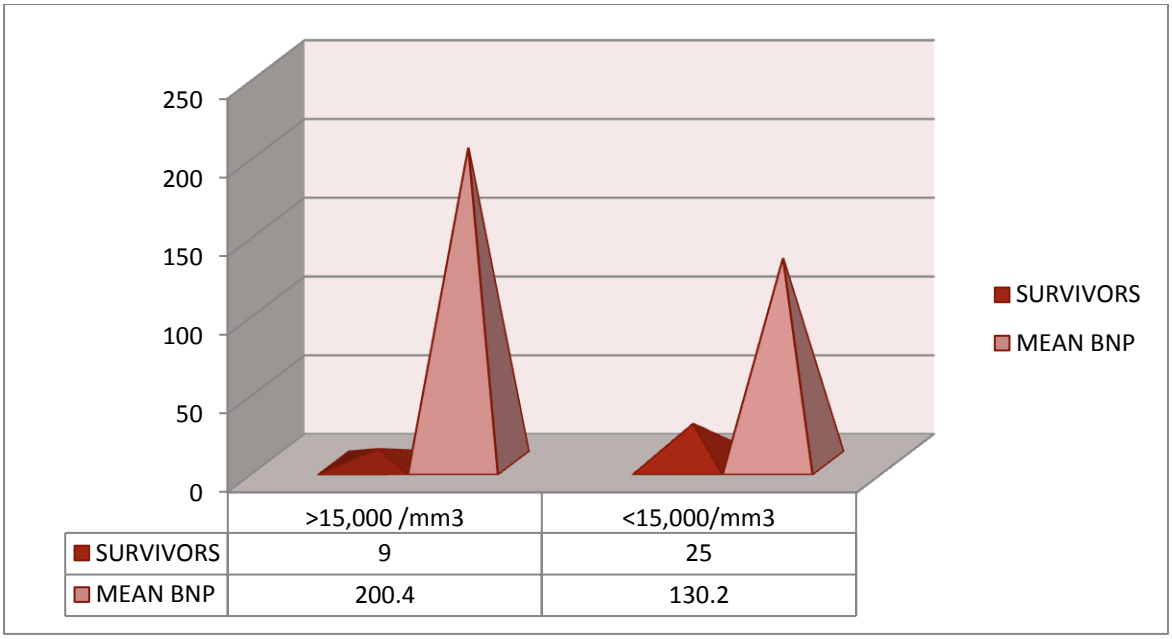

FIGURE 16.Mean BNP in survivors with or without leucocytosis (>15,000)

10.Having studied the correlation of BNP levels with the inflammatory response , the correlation between the BNP levels and clinical severity as assessed by CRB-65 score was analysed. The mean BNP in survivors with a CRB-65 score of 0 and 1 was compared with that of those with a score of 2 and 3.

CRB-65 SCORE	0 OR 1	2 or 3
NUMBER	19	15
MEAN BNP(pg/ml)	119.3	186.2

TABLE10.Mean BNP levels in persons with CRB scores 0 or 1 vs 2 or 3 among the survivors.

The mean BNP levels in survivors with CRB-65 score of 0 or 1 was 119.3 against a mean of 186.2pg/ml in survivors with a score of 2 or 3.

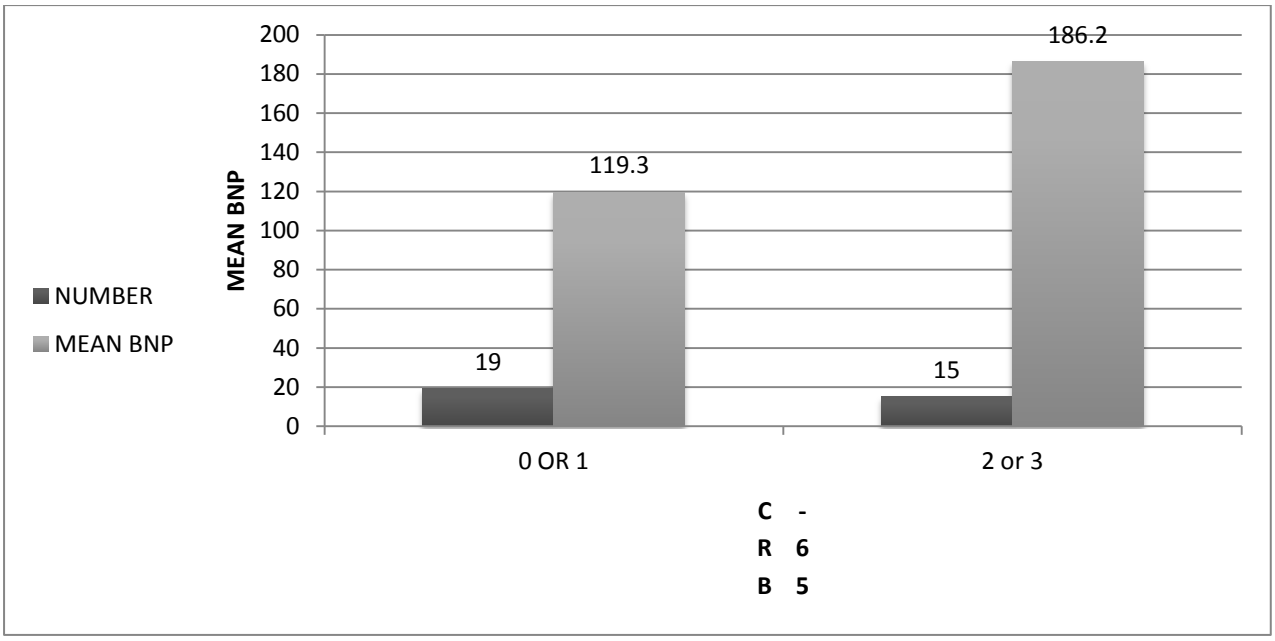

FIGURE17.Comparision of mean BNP levels in persons with CRB scores 0 or 1 vs 2 or 3 among the survivors

The P value for this set of means was 0.009 which showed that there was significantly higher levels of BNP in patients with a higher CRB-65 score thus ascertaining the fact that BNP levels varied directly with the clinical severity of pneumonia.

11. Having studied the variation of BNP levels with varied parameters in pneumonia, we analysed the BNP levels with the outcomes at after 4 weeks of follow up. First the correlation of BNP levels with clinical resolution of all the symptoms of pneumonia and its sequlae was studied in the survivors.

CLINICAL RESOLUTION	**YES**	**NO**
NO.OF.PATIENTS	27	7
MEAN BNP(pg/ml)	133.48	208.1

TABLE 11.Comparision of BNP in patients with and without clinical resolution among survivors

27 of the 34 survivors had clinical resolution of all the symptoms after 4 weeks.The mean of their initial BNP was 133.48pg/ml. 7 patients had some persisting symptoms in the form of either persisting cough , malaise or fatigue that prevented them from pursuing their occupation. The mean BNP level in them was 208.1 pg/ml. The P value for the difference between the means was 0.003 . Thus there was significant correlation between BNP levels at presentation and the rate and extent of clinical resolution.

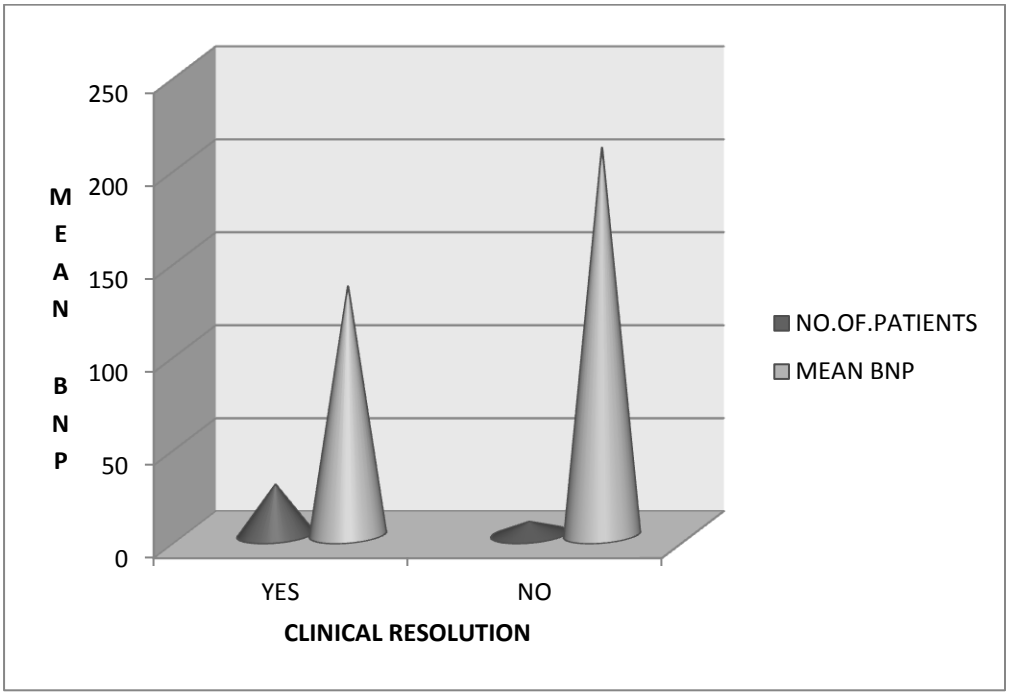

FIGURE 18. Comparision of BNP in patients with and without clinical resolution in survivors

12. The mean BNP levels were compared in patients who had complete radiological resolution and the patients who had persistent opacities at the end of 4 weeks to determine whether the BNP levels on presentation correlated with the rate of radiological resolution.

RADIOLOGICAL RESOLUTION	COMPLETE	INCOMPLETE
NO.OF SURVIVORS	13	21
MEAN BNP(pg/ml)	113.7	170.52

TABLE 12. Comparision of BNP in patients with and without radiological resolution in survivors

Among the 34 survivors, 13 patients(38%) had complete radiological resolution. The mean BNP in this group of patients was 113.7pg/ml. The mean BNP in the remaining 21 survivors without complete radiological resolution was 170.52pg/ml. The possibility that this difference has occurred by chance was found to be 0.0075 as determined by the two tailed value. This shows that there was a good correlation between BNP levels and the rate of radiological resolution.

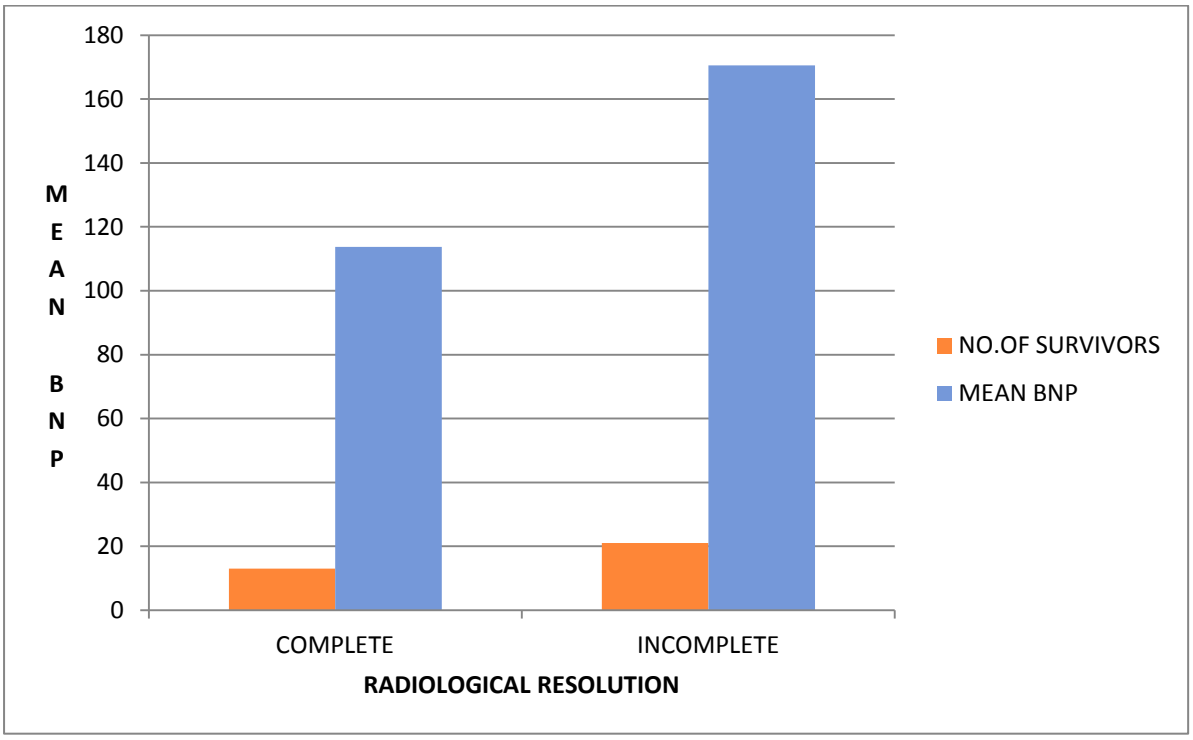

FIGURE 19. Comparision of BNP in patients with and without radiological resolution in survivors.

13. The mean BNP levels in the survivors who had a hospital stay of more than 10 days was compared with that of the survivors who had a stay of less than or equal to 10 days. This was done to analyse whether BNP levels on admission can predict the length of hospital stay.

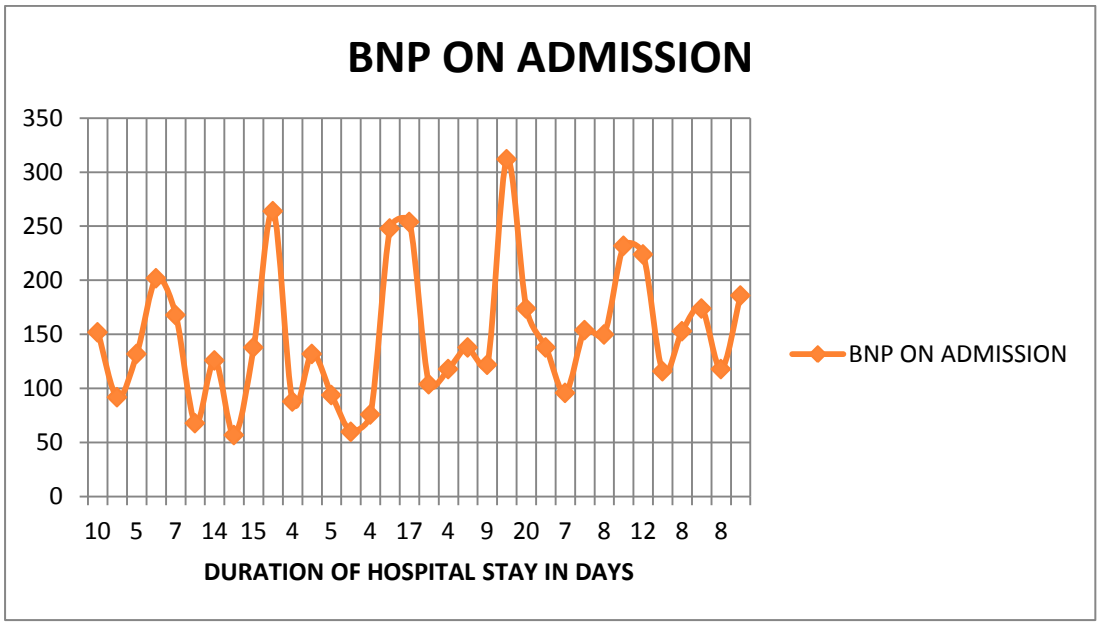

FIGURE 20.The distribution of BNP values in consecutive patients as a function of the duration of hospital stay.

13 of the 34 survivors had a stay of more than 10 days in the hospital with the maximum being 20 days.The mean admission BNP in this group was 196.2pg/ml against a mean BNP of 119.2pg/ml in the 21 patients who stayed for less than or equal to 10 days. The P value for the difference between the means

was 0.0001 which shows that a higher BNP level on admission predits a longer stay in hospital and a lengthier course of antibiotics.

DURATION OF STAY IN HOSPITAL	> 10 DAYS	< 0R=10 DAYS
NO. OF PATIENTS	13	21
MEAN BNP(pg/ml)	196.6	119.2

TABLE 13. Mean BNP in patients with a hospital stay of >10 days and < or = 10 days among survivors.

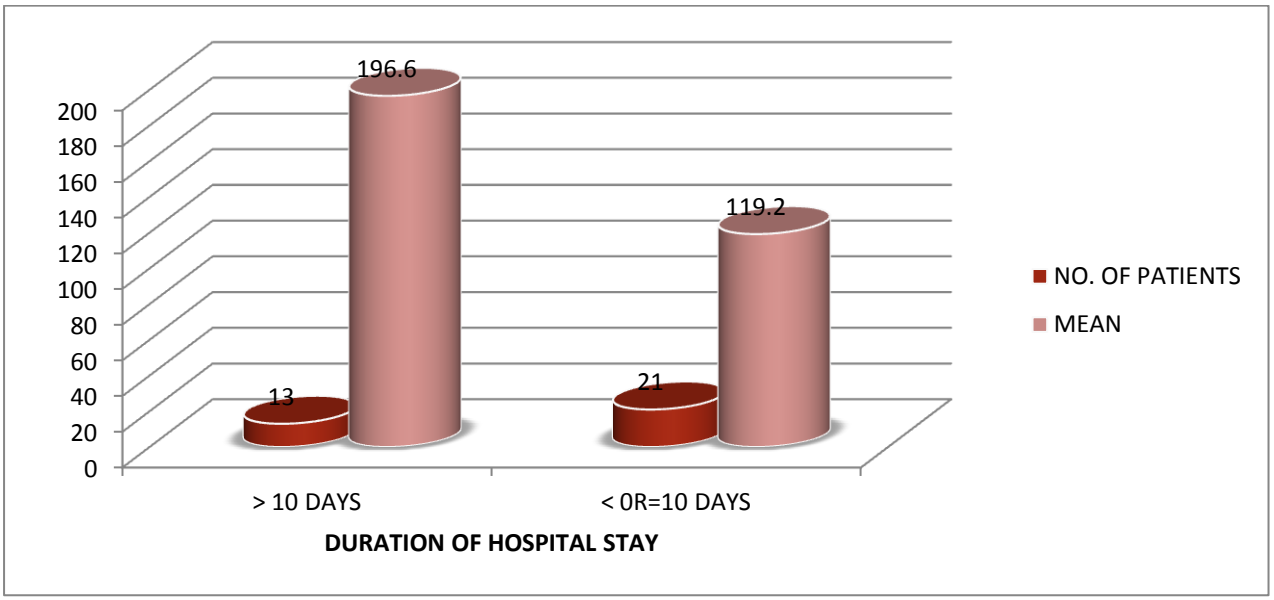

FIGURE 21. Mean BNP in patients with a hospital stay of >10 days and < or = 10 days among survivors.

14. The ability of BNP to predict mortality was assessed by reviewing the BNP levels in the survivors and non-survivors. Among the 42 persons in the study group 8 patients died during the follow up period with most of them dying in 3

days or less. Only one patient died after 17 days. Most of the patients who died had some form of multi-organ dysfunction.

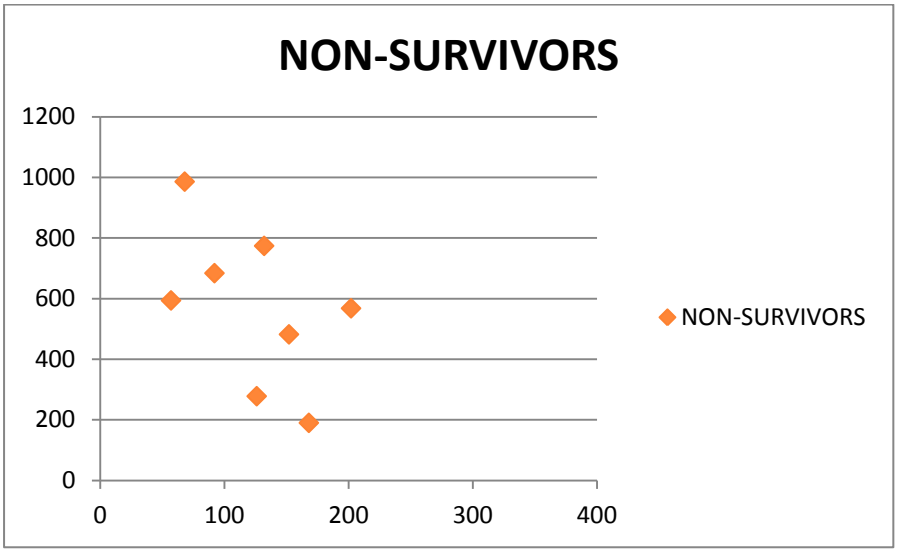

TABLE 14.A.Distribution of BNP values among survivors.

DEATH	**YES**	**NO**
NO.OF.PATIENTS	8	34
MEAN BNP(pg/ml)	569.5	148.82

TABLE 14.BMean BNP levels in survivors vs non-survivors

The mean BNP among the those who died was 569.5pg/ml with one patient showing values as high as 986pg/ml. one patient also died inspite of having a BNP value of 190pg/ml. The mean BNP in survivors was 148.28pg/ml with the highest value being 312 pg/ml. The P value of these two means was less than 0.0001 which shows that the difference in BNP levels was extremely significant. This shows that very higher levels of BNP on admission are associated with higher rates of mortality.

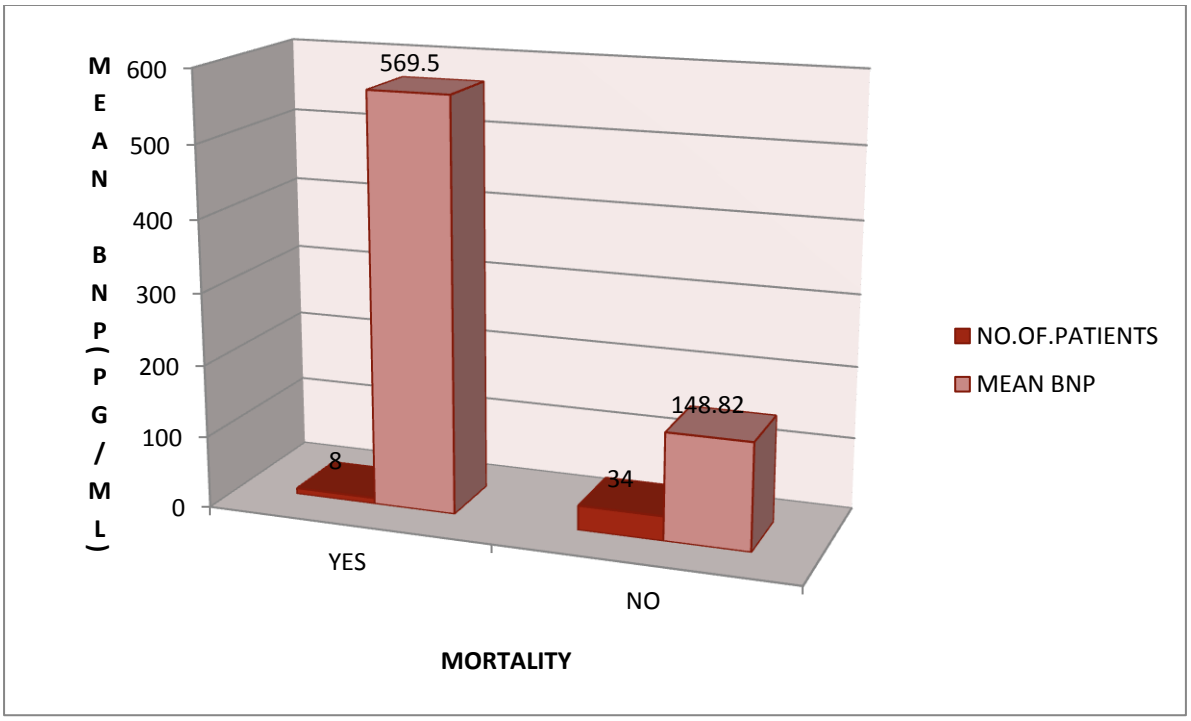

FIGURE .22. Mean BNP levels in survivors vs non-survivors.

15.The ability of BNP to predict the development of MODS was analysed by comparing the mean BNP in patients and survivors who who developed MODS with that of those who did not develop MODS.

There were 15 patients among the 42 who developed some sort of multiorgan dysfunction with the combination of renal and liver injury being the most commonest. Most of them were transient . The mean BNP in them was 346.5pg/ml as against a mean of 163.6pg/ml in the 27 who did not develop MODS . This was quite significant but because of the confounding effect of the extreme values in those who died we compared the BNP levels in those who developed MODS and survived.

DEVELOPMENT OF MODS	YES	NO
NO.OF PATIENTS	9	25
MEAN BNP(pg/ml)	190.9	133.7

TABLE 15.Mean BNP levels in those who developed MODS vs those who did not

The mean BNP in 25 survivors who recovered without developing MODS was 133.7pg/ml against a mean BNP of 190.9 pg/ml in those who survived after developing MODS**.** The P value for the difference between the means was 0.01 which shows that there was significant correlation between admission BNP levels and the development of MODS.

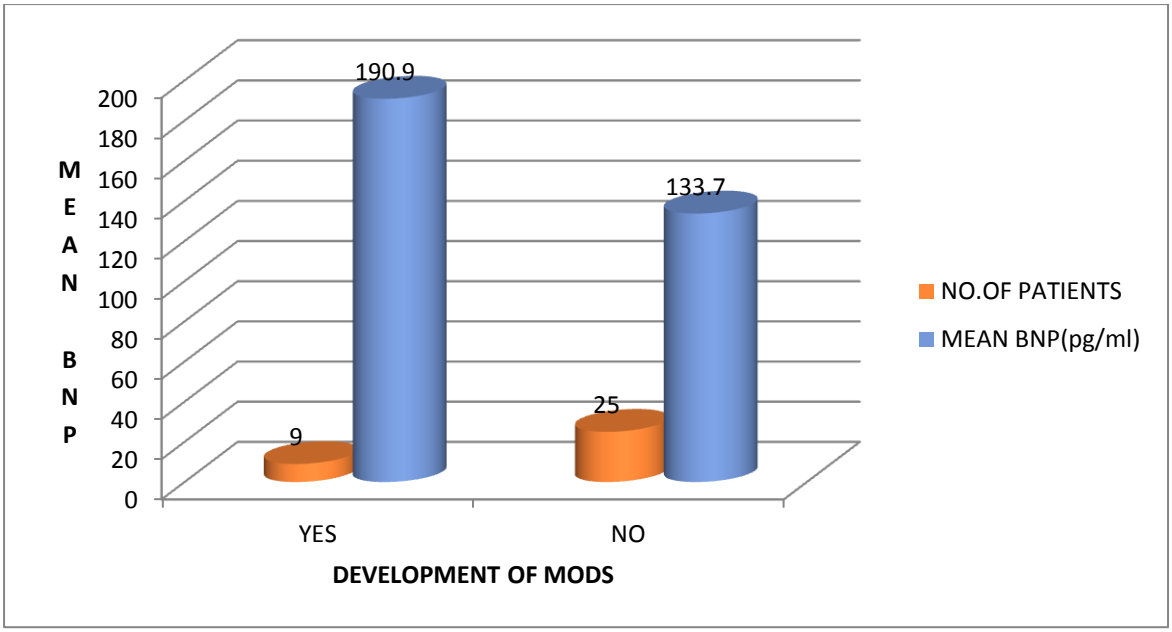

FIGURE 23.Mean BNP levels in those who developed MODS vs those who did not among the survivors.

16. Having comprehensively studied the relationship between different parameters , the ability of BNP to predict adverse outcomes was compared with that of other clinical and laboratory prognostic indices.

First we studied the ability of severity of leucocytosis to predict mortality . The mean leucocyte count in the 8 persons who died was 14,825.3 cells /mm^3 which was modified to 15,583.3 cells /mm^3 to avoid the confounding effect of the two extremely low values which were around 2500 cells/mm^3. The mean WBC count in the 34 survivors was 12,800.8 cells/mm^3.

SURVIVED	NO	YES
NUMBER	6	34
MEAN WBC COUNT (cells/mm^3)	15,583.3	12,800.8

TABLE.16. Mean leucocyte count in survivors vs non-survivors (eliminating extremely low values)

The difference between the means could have occurred by chance as suggested by a P value of 0.25. Hence the severity of leucocytosis did not correlate well with ultimate mortality**.**

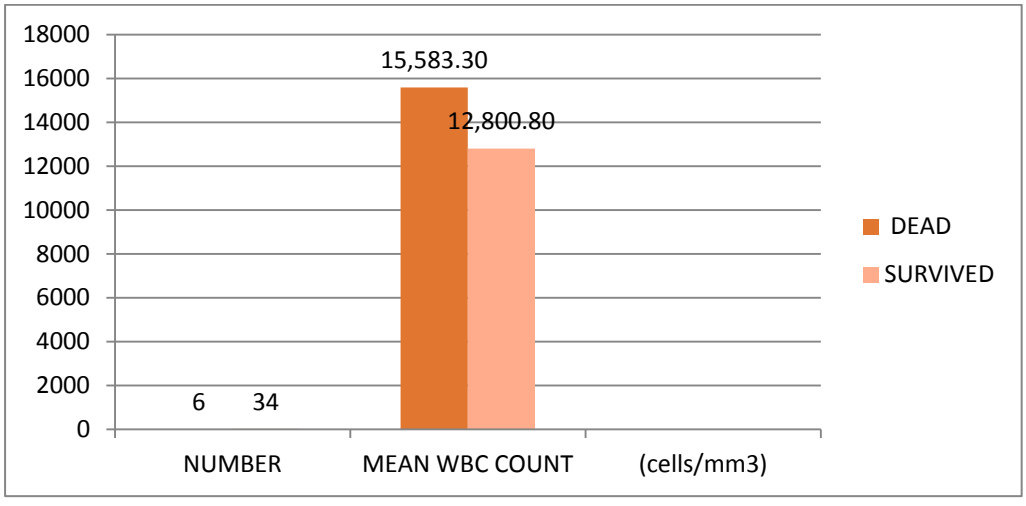

FIGURE 24. Mean leucocyte count in survivors vs non-survivors (eliminating extremely low values)

17. We analysed the ability of CRB-65 to predict mortality .The mean CRB-65 score in the 34 survivors was 1.38 against a score of 2.62 in non- survivors. The P value for the difference of means was 0.0005 which shows that a higher CRB-65 score of 2 or 3 on presentation was associated with a higher mortality.

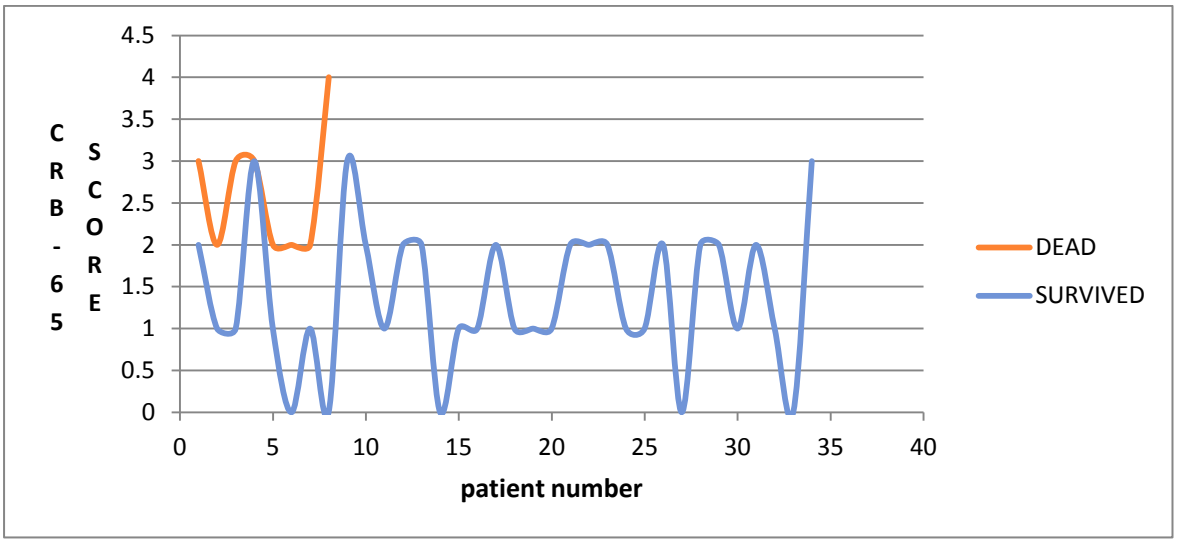

FIGURE.25.Distribution of CRB-65 values in the study group.

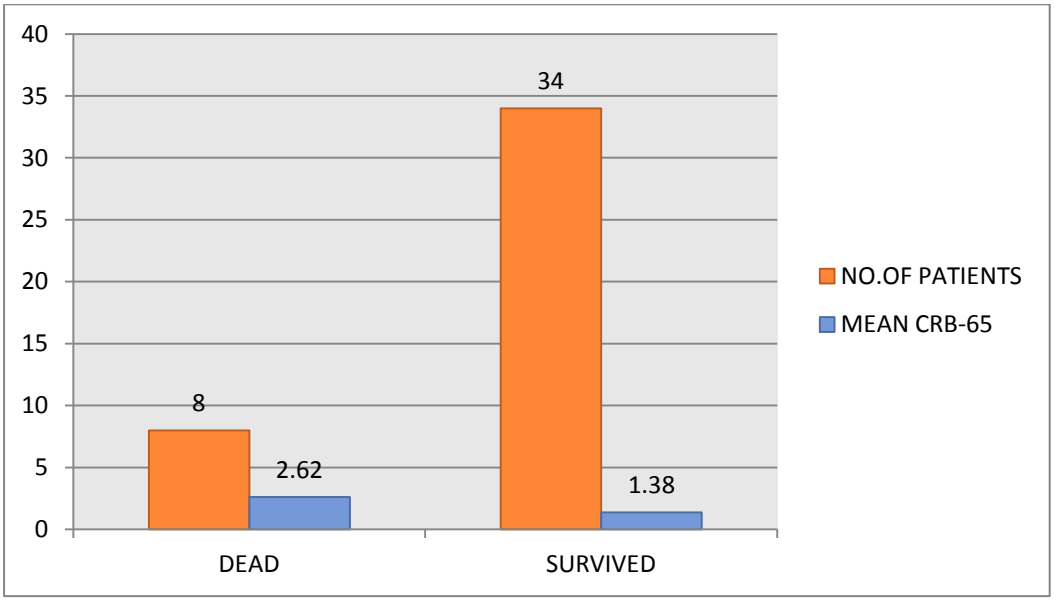

FIGURE.26. Comparision of mean CRB-65 score in survivors and non-survivors

18. Having realised that CRB- 65 score and BNP are comparable in predicting mortality we analysed if CRB-65 levels correlated with other morbidity parameters like the development of MODS and the duration of hospital stay.

First the ability of CRB-65 score to predict the occurrence of MODS was analysed. The mean CRB -65 score in those who developed MODS was 1.67 against a mean of 1.28 in the 34 patients who recovered without developing MODS. The difference between the means had a P value of 0.24 which showed that the variation was not significant.

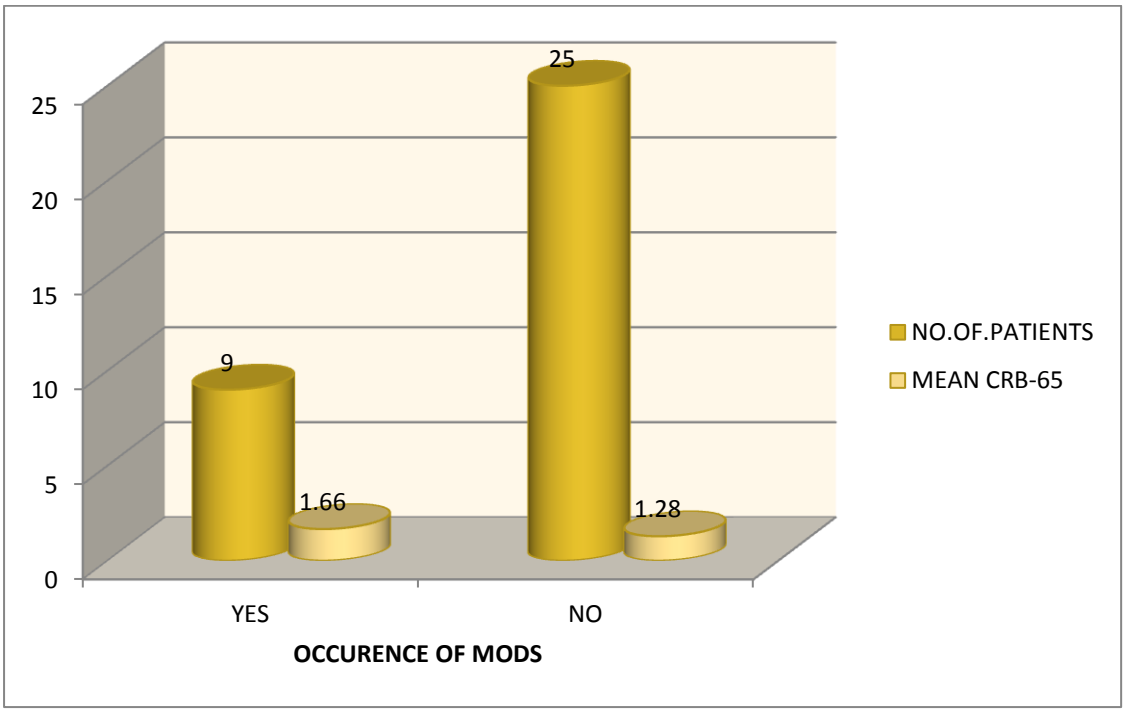

FIGURE 27. Comparision between mean CRB-65 levels and the occurrence of MODS

The ability of CRB-65 score to predict the duration of hospital stay was studied. The mean CRB-65 score in those patients who had a hospital stay of more than 10 days was found to be 2 against a score of 1 in those who hsd a hospital stay of less than or equal to 10 days. The P value of 0.0003 showed that the difference between the means was extremely significant. This shows that CRB-65 score was comparable to BNP in predicting the length of hospital stay .

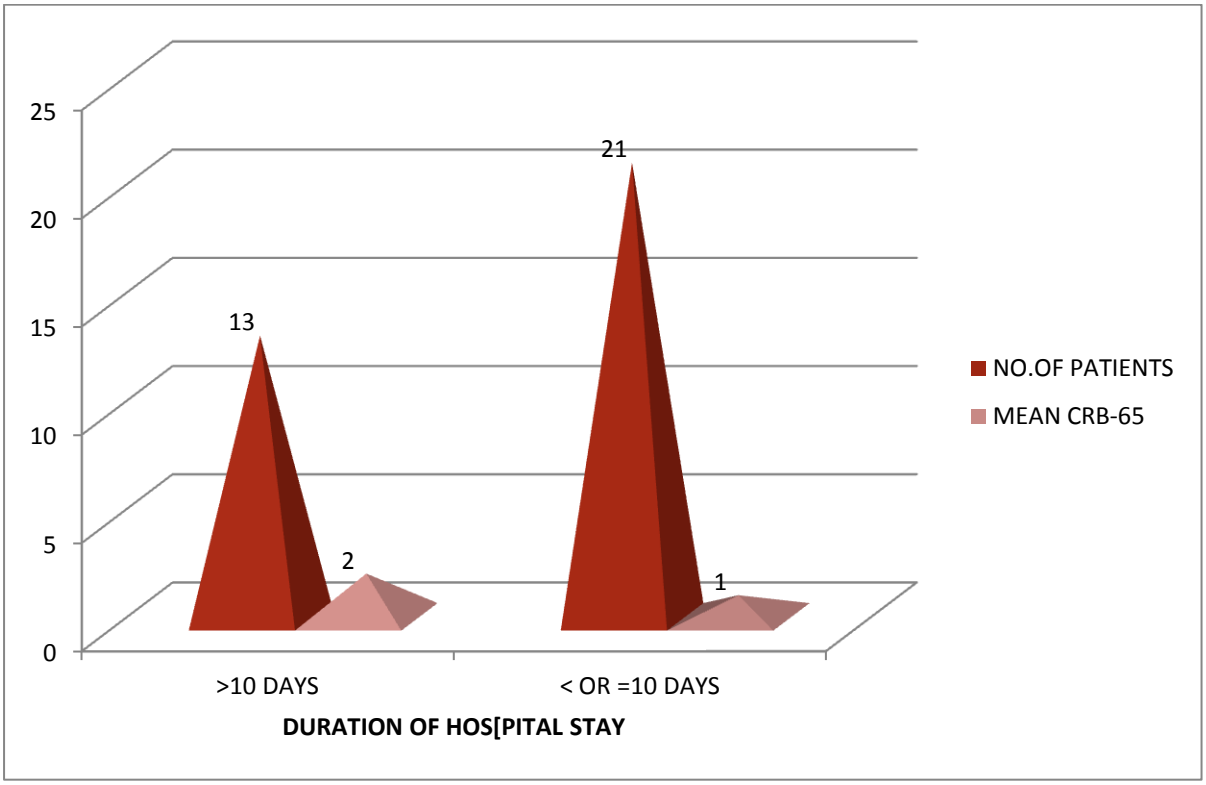

FIGURE 28. Comparision of CRB-65 scores with the length of hospital stay.

DISCUSSION

DISCUSSION

Brain type natriuretic peptide (BNP) which has consistently been found elevated in patients with congestive cardiac failure and is used for assessing the prognosis of the same for quite a while now has been tested in a variety of conditions including pneumonia due to the new found knowledge about the various stimuli promoting its release. The results in the study were analysed keeping this in mind and some significant conclusions were derived regarding every aspect of BNP.

The prime aim of the study was to assess the ability of BNP to predict poor outcomes including death in a patient with pneumonia. The study showed that the mean BNP value in non-survivors was (569.5 pg/ml) significantly higher than that (148.2 pg/ml) in survivors with a P value of 0.0001 . Values of more than 200 pg/ml was usually associated with clinically severe disease and values more than 400pg/ml are associated with a higher rate of mortality. This was very much in line with the results of the study published by **Christ-Crain M et al** in the journal of internal medicine in 2008 ;

One other parameter that correlated well with the mortality was the CRB- 65 score on admission with scores 2 and 3 predicting a poorer outcome as compared to scores 0 or 1. The P value for the level of significance was 0.0005. This closely mirrored the results of the study published by Bauer et al in the journal of internal medicine in 2006. The net coclusion is that BNP values are as good or slightly better in predicting mortality than CRB-65 score. Further there was very good correlation between the BNP values and the CRB-65 in the study group with a P value of 0.009.this shows that BNP levels vary directly in relation to the clinical severity of pneumonia as predicted by CRB- 65.

BNP was also found in some studies to be significantly associated with a higher morbidity in pneumonia. Our study showed that BNP levels in those who had some sequlae in the form of either ARDS , MODS or empyema was significantly higher than those who recovered without any complications. This confirmed the fact that a higher level of BNP predicts the likelihood of having a complicated course of pneumonia.

The study in particular analysed the ability of BNP and CRB-65 score to predict the development of MODS. The mean BNP in survivors who did not develop MODS was 133.7pg/ml against a mean BNP of 190.9 pg/ml in those who survived after developing MODS**.** The P value for the difference between the means was 0.01 which showed that there was significant correlation between admission BNP levels and the development of MODS. On the other hand the P

value in case of CRB-65 scores in the two groups was 0.24 suggesting that a higher CRB – 65 score did not significantly predict the occurrence of MODS.

But CRB – 65 score was comparable to BNP in predicting the length of hospital stay , with patients having a BNP value of more than 200pg/ml or a CRB-65 score of more than 1 both having an increased risk of a prolonged healthcare stay with a P value of 0.0001 and 0.0003 respectively.

Though there was good correlation between the clinical indices , BNP ,mortality and morbidity , the same was not the case with leucocyte count. There was good correlation between the BNP levels and the severity of leucocytosis (>15,000/mm3) as confirmed by a P value of 0.002. This affirms the proposed theory that inflammation also has role in the release of BNP in pneumonia.

But a higher leucocyte count failed to predict any significant rise in mortality as the P value was 0.24.

BNP levels on presentation also correlated well with the rate of radiological and clinical resolution in patients recovering from an episode of pneumonia with a P value of 0.0075 and 0.003 respectively.

There has been much speculations in recent studies that hypoxia may be one of the factors triggering the release of BNP. The mean BNP level in survivors with SpO2 was 174.7 pg/ml with a standard deviation of 48.6 against a mean value of 140.9 pg/ml with a standard deviation of 64.4 in those with SpO2 of less than

or equal to 90. **The P value was 0.18** which showed that the difference was not that significant. So , it is possible that hypoxia may be an additive factor with respect to BNP production and can by itself cannot cause a significant elevation in BNP.

The confounding effect of prior antibiotic therapy on BNP levels in the study was not significant as the difference in the mean BNP in the groups which received antibiotic therapy before coming to our hospital was not so different from that in the group which did not receive any antibiotic therapy.

We also studied the variation in the BNP values caused by the two common group of organisms implicated in causing pneumonia. The mean BNP values in the patients who were infected with gram negative bacilli (173.9 pg/ml) was a bit higher than the BNP values in those infected with gram positive cocci (127.6pg/ml). But the difference was not significance as shown by a P value of 0.102.

There was no gross difference in the elevation of BNP in alcoholics and non-alcoholics . The same was the case with smokers and non-smokers.

After having excluded patients with comorbidities known to influence BNP levels ,the mean BNP levels in patients with other comorbidities was analysed with hope of finding something interesting. But disappointingly there was no variation in the mean BNP levels with the other co-morbidities.

Margaret M Redfield et al in her study published in the J Am Coll Cardiol. 2002 proposed that BNP levels increases with age and the mean value is higher in females[38]. But our study differed in both these aspects with our study showing higher mean BNP in those in the age group less than 50 and in males , probably bigger samples are needed to test the results.

So it is clear that higher BNP levels correlated significantly with higher rates of mortality and morbidity in patients with community acquired pneumonia.BNP may be better than or as good as CRB-65 in this aspect . The extent of elevation of BNP is of more clinical significance than the cause of elevation because there may be multiple factors contributing to the elevation of BNP in pneumonia each of which has a prognostic significance of its own.

CONCLUSION

The inferences that this study brought about were

1. Assessing the BNP levels on admission is a rapid and reliable means triaging pneumonia patients into various levels of care.
2. A high BNP level on admission is an independent risk factor for high mortality and morbidity in patients with pneumonia.
3. BNP levels correlated with the clinical severity of the disease.
4. BNP levels may be as effective or better than CRB-65 score in predicting the disease course.

BNP may at present appear as a rather expensive alternative in our country but nevertheless it a more reliable method. Given the quantum of resources that may be wasted in cases of inappropriately triaged pneumonia , it is worth a go inspite of the cost.

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ANNEXURES

ANNEXURE 1.

ABBREVIATIONS USED IN THE TEXT

ANP- Atrial Natriuretic Peptide

ADM- Adreno Medullin

ATS-American Thoracic Society.

ARDS-Acute Respiratory Distress Syndrome.

AVP- Arginine Vasopressin

BAL-Broncho Alveolar Lavage

BUN-Blood Urea Nitrogen

BNP-Brain Natriuretic Peptide

CAP- Community Acquired Pneumonia

CFU-Colony Forming Units

CRB-Confusion, Respiratory rate , Blood pressure

CRP-C- Reactive Protein

HAP-Hospital Acquired Pneumonia

HCAP- Health Care Associated Pneumonia

ICU- Intensive Care Unit.

IDSA-Infectious Disease Surveilance Agency

MODS- Multi Organ Dysfunction Syndrome.

PCT- Pro CalciTonin

TNF-Tumour Necrosis Factor

VAP- Ventilator Associated Pneumonia

ANNEXURE 2

BNP IN PNEUMONIA AS A PROGNOSTIC MARKER AND ITS COMPARISION WITH CRB- 65 SCORE

PROFORMA

Name: Age: Sex:

Address: Occupation:

Symptoms:

- Dyspnea ; YES/NO MRC grade-
- Cough; YES/NO
- Expectoration; YES/NO
- Fever; YES / NO
- Chest pain; YES/NO
- Hemoptysis; YES/NO
- Oliguria; YES/NO
- Altered sensorium;YES/NO

Past history:

- Diabetes mellitus: YES/NO
    - Duration:

- Treatment: OHA/Insulin
- Compliance of treatment:
- Associated complications(if any)

- Hypertension;

  Duration ;

  Drugs used;

- Coronary artery disease; YES/NO
- Prior H/O CVA;YES/NO
- Other co morbid illnesses; (specify)

Treatment history:

- H/O prior treatment to the present illness ; YES/NO

Personal history:

- Smoker YES/NO
- Alcoholism; YES/NO

GENERAL EXAMINATION:

PULSE:

BLOOD PRESSURE:

GENERAL EXAMINATION:

SYSTEMIC EXAMINATION:

CVS: RS: ABDOMEN: CNS:

INVESTIGATIONS:

Hemogram			**RFT**		
TC		cells/mm^3	Glucose (F)		mg/dl
DC			Glucose (PP)		mg/dl
ESR		mm/hr	Urea		mg/dl

Hb		g/dl	Creatinine		mg/dl
PCV		%	Na+		mEq/l
Platelets		lakhs/mm^3	K+		mEq/l
RBCs		million/mm^3			

LIVER FUNCTION TESTS:

SPUTUM GRAM STAIN;

SPUTUM C/S;

BLOOD C/S;

ULTRASONOGRAM OF ABDOMEN:

ECG:

X RAY CHEST;

CT-CHEST;

ECHO CARDIOGRAM:

CRB-65 SCORE:

SERUM BNP LEVELS ON ADMISSION:

BNP IN PNEUMONIA AS A PROGNOSTIC MARKER AND ITS COMPARISION

WITH CRB- 65 SCORE

PARAMETERS AT THE END OF 4 WEEKS AFTER ADMISSION

Symptoms:

- Dyspnea ; YES/NO MRC grade-
- Cough; YES/NO
- Expectoration; YES/NO
- Fever ; YES / NO
- Chest pain; YES/NO
- Hemoptysis; YES/NO
- Malaise / fatigue higher than the pre illness level ; YES / NO
- Able to carry out daily work as previously; YES / NO
- Any other complaints;
- Duration of inpatient stay:

EXAMINATION;

PULSE RATE:

BLOOD PRESSURE:

RESPIRATORY RATE:

HEAD TO FOOT EXAMINATION:

RS EXAMINATION;

OTHER SYSTEM EXAMINATION;

ANNEXURE 3;MASTER CHARTS (1)

PT'S NAME	AGE	SEX	DYSPNEA	HEMOPTYSIS
KRISHNAN	67	M	YES	NO
SETHU	40	M	YES	NO
MOHANA SUDARAM	78	M	YES	NO
RAJAMMAL	62	F	YES	NO
LOGANATHAN	52	M	YES	NO
ELUMALAI	53	M	NO	NO
GOWRI	60	F	YES	NO
DHANALAKSHMI	45	F	YES	NO
ELUMALAI	65	M	YES	NO
SETTU	39	M	YES	NO
BALAN	66	M	NO	NO
MEENA	38	F	YES	NO
THIRUPATHY	47	M	YES	NO
ANNAMMAL	50	F	YES	NO
SATHISH	30	M	YES	YES
PUNNIYAKODI	60	M	YES	NO
SURESH BABU	32	M	YES	NO
SUSEELA	72	F	YES	NO
RAJ	75	M	YES	YES
MALA	38	F	YES	NO
THOMAS	64	M	YES	NO
CHINNAKULANDAI	68	F	NO	YES
PARANTHAMAN	40	M	YES	YES
KRISHNAMOORTHY	58	M	YES	NO
VINOD KANNAN	25	M	YES	YES
JAYA	56	F	YES	NO
RAJAMANICKAM	60	M	YES	NO
VASUDEVAN	69	M	NO	YES
ANJALAKSHMI	48	F	YES	NO
PARAMESWARAN	60	M	YES	NO
SIVAGNANAM	56	F	NO	YES
JAGAN	29	M	YES	YES
KALAIYARASI	23	F	YES	NO
RAYAN	49	M	YES	NO
KAMATCHI	60	F	YES	NO
SELLAMUTHU	35	M	YES	NO
NARAYANAN	62	M	YES	NO
VANNATHATCHI	60	F	YES	NO
RUKMANI	65	F	YES	NO
PARAMESHWARI	50	F	YES	NO
CHITRA	52	F	NO	YES
AYYAPAN	67	M	YES	NO

CHART 2

PT'S NAME	ASSOCIATED COMORBIDITIES				
	DIABETES	HYPERTENSION	CVA	NEOPLASMS	TOTAL COMORBIDITIES
KRISHNAN	NO	YES	NO	NO	1
SETHU	YES	NO	NO	NO	1
MOHANA SUDARAM	NO	YES	NO	NO	1
RAJAMMAL	NO	NO	NO	NO	0
LOGANATHAN	YES	YES	NO	NO	2
ELUMALAI	NO	NO	NO	NO	0
GOWRI	YES	NO	NO	NO	1
DHANALAKSHMI	NO	NO	NO	NO	0
ELUMALAI	YES	YES	NO	NO	2
SETTU	NO	NO	NO	NO	0
BALAN	YES	YES	NO	NO	2
MEENA	NO	NO	NO	NO	0
THIRUPATHY	NO	NO	NO	NO	0
ANNAMMAL	NO	NO	NO	NO	0
SATHISH	NO	NO	NO	NO	0
PUNNIYAKODI	NO	NO	NO	NO	0
SURESH BABU	NO	NO	NO	NO	0
SUSEELA	YES	NO	NO	NO	1
RAJ	NO	NO	NO	NO	0
MALA	NO	NO	NO	NO	0
THOMAS	NO	NO	NO	NO	0
CHINNAKULANDAI	YES	YES	NO	NO	2
PARANTHAMAN	YES	NO	NO	NO	1
KRISHNAMOORTHY	NO	NO	NO	YES	1
VINOD KANNAN	NO	NO	NO	NO	0
JAYA	YES	YES	NO	NO	2
RAJAMANICKAM	YES	NO	NO	NO	1
VASUDEVAN	NO	NO	NO	NO	0
ANJALAKSHMI	NO	NO	NO	YES	1
PARAMESWARAN	NO	NO	NO	NO	0
SIVAGNANAM	YES	YES	NO	NO	2
JAGAN	YES	NO	NO	NO	1
KALAIYARASI	NO	NO	NO	NO	0
RAYAN	YES	NO	NO	NO	1
KAMATCHI	YES	NO	NO	NO	1
SELLAMUTHU	NO	NO	NO	NO	0
NARAYANAN	NO	YES	NO	NO	1
VANNATHATCHI	NO	YES	NO	NO	1
RUKMANI	NO	NO	NO	YES	1
PARAMESHWARI	NO	NO	NO	NO	0
CHITRA	YES	YES	NO	NO	2
AYYAPAN	NO	YES	YES	NO	2

CHART 3

PT'S NAME	SMOKER	ALCOHOLIC	ANTIBIOTIC PRE-TREATMENT	CONFUSION
KRISHNAN	YES	YES	NO	NO
SETHU	NO	YES	NO	NO
MOHANA				
SUDARAM	NO	NO	NO	NO
RAJAMMAL	NO	NO	NO	YES
LOGANATHAN	NO	NO	NO	NO
ELUMALAI	YES	YES	NO	NO
GOWRI	NO	NO	NO	NO
DHANALAKSHMI	NO	NO	NO	NO
ELUMALAI	YES	YES	NO	YES
SETTU	NO	YES	NO	NO
BALAN	YES	NO	NO	NO
MEENA	NO	NO	NO	NO
THIRUPATHY	YES	YES	NO	NO
ANNAMMAL	NO	YES	NO	NO
SATHISH	YES	YES	NO	NO
PUNNIYAKODI	NO	NO	NO	NO
SURESH BABU	NO	YES	NO	NO
SUSEELA	NO	NO	NO	NO
RAJ	YES	NO	YES	NO
MALA	NO	NO	YES	NO
THOMAS	YES	NO	YES	YES
CHINNAKULANDAI	NO	NO	YES	NO
PARANTHAMAN	YES	YES	YES	NO
KRISHNAMOORTHY	NO	NO	YES	NO
VINOD KANNAN	NO	YES	YES	NO
JAYA	NO	NO	YES	NO
RAJAMANICKAM	NO	YES	YES	YES
VASUDEVAN	NO	NO	YES	NO
ANJALAKSHMI	NO	NO	YES	YES
PARAMESWARAN	YES	YES	YES	YES
SIVAGNANAM	NO	NO	YES	NO
JAGAN	NO	YES	YES	NO
KALAIYARASI	NO	NO	YES	NO
RAYAN	YES	NO	YES	NO
KAMATCHI	NO	NO	YES	NO
SELLAMUTHU	NO	NO	YES	NO
NARAYANAN	YES	NO	YES	NO
VANNATHATCHI	NO	NO	YES	YES
RUKMANI	NO	NO	YES	YES
PARAMESHWARI	NO	NO	YES	NO
CHITRA	NO	NO	YES	NO
AYYAPAN	NO	YES	YES	YES

CHART 4

PT'S NAME	RESPIRATORY RATE /MIN	SYSTOLIC BP (mm Hg)	SpO2	WBC COUNT
KRISHNAN	34	120	92	14600
SETHU	28	80	94	3900
MOHANA				
SUDARAM	27	100	96	11200
RAJAMMAL	42	80	92	12600
LOGANATHAN	36	100	92	12100
ELUMALAI	26	140	98	10400
GOWRI	38	100	88	16400
DHANALAKSHMI	29	110	96	7600
ELUMALAI	36	100	95	20200
SETTU	41	80	86	28200
BALAN	26	120	97	7800
MEENA	46	80	88	10600
THIRUPATHY	32	86	94	9200
ANNAMMAL	28	100	96	5400
SATHISH	36	110	92	4300
PUNNIYAKODI	39	100	92	12400
SURESH BABU	36	80	94	22400
SUSEELA	28	130	96	11100
RAJ	26	110	94	16800
MALA	32	100	94	8600
THOMAS	38	70	86	18900
CHINNAKULANDAI	30	80	96	14800
PARANTHAMAN	38	80	92	21200
KRISHNAMOORTHY	40	80	85	14600
VINOD KANNAN	38	90	91	15600
JAYA	34	140	88	10400
RAJAMANICKAM	46	80	88	2800
VASUDEVAN	24	110	96	9700
ANJALAKSHMI	52	70	76	2100
PARAMESWARAN	32	150	92	13800
SIVAGNANAM	28	110	98	12400
JAGAN	38	60	92	17400
KALAIYARASI	42	80	84	9800
RAYAN	44	80	84	22300
KAMATCHI	34	140	94	11400
SELLAMUTHU	48	70	76	18400
NARAYANAN	44	80	82	19600
VANNATHATCHI	40	170	90	11300
RUKMANI	46	80	78	19900
PARAMESHWARI	40	100	89	13600
CHITRA	26	100	97	12500
AYYAPAN	34	110	90	15800

CHART 5

PT'S NAME	ESR	CRB-65	ADMISSION BNP (pg/ml)	ISOLATED ORGANISM
KRISHNAN	48	2	152	NONE
SETHU	38	1	92	GPC
MOHANA SUDARAM	36	1	132	NONE
RAJAMMAL	48	3	202	NONE
LOGANATHAN	46	1	168	NONE
ELUMALAI	22	0	68	GPC
GOWRI	76	1	126	NONE
DHANALAKSHMI	32	0	57	GPC
ELUMALAI	62	3	138	GPC
SETTU	78	2	264	GPC
BALAN	26	1	88	GPC
MEENA	50	2	132	GNB
THIRUPATHY	32	2	94	NONE
ANNAMMAL	24	0	60	GPC
SATHISH	30	1	76	NONE
PUNNIYAKODI	54	1	248	GNB
SURESH BABU	56	2	254	GPC
SUSEELA	34	1	104	GPC
RAJ	38	1	118	GNB
MALA	36	1	138	GPC
THOMAS	44	3	482	NONE
CHINNAKULANDAI	54	2	122	GNB
PARANTHAMAN	68	2	312	GNB
KRISHNAMOORTHY	60	2	684	GPC
VINOD KANNAN	56	2	174	GPC
JAYA	52	1	138	GPC
RAJAMANICKAM	96	3	774	NONE
VASUDEVAN	28	1	96	GPC
ANJALAKSHMI	64	3	568	NONE
PARAMESWARAN	46	2	154	GNB
SIVAGNANAM	44	0	150	GNB
JAGAN	42	2	232	GNB
KALAIYARASI	52	2	224	NONE
RAYAN	96	2	190	GPC
KAMATCHI	36	1	116	GPC
SELLAMUTHU	86	2	986	GNB,GPC
NARAYANAN	78	2	278	NONE
VANNATHATCHI	44	2	153	GNB
RUKMANI	68	4	594	GPC
PARAMESHWARI	30	1	174	NONE
CHITRA	28	0	118	GNB
AYYAPAN	58	3	186	NONE

PT'S NAME	PARAMETERS ON REVIEW AT 4 WEEKS		
	CLINICAL RESOLUTION	RADIOLOGICAL RESOLUTION	HOSPITAL STAY(DAYS)
KRISHNAN	YES	NO	10
SETHU	YES	YES	3
MOHANA SUDARAM	YES	NO	5
RAJAMMAL	YES	NO	14
LOGANATHAN	YES	YES	7
ELUMALAI	YES	YES	3
GOWRI	NO	NO	14
DHANALAKSHMI	YES	YES	3
ELUMALAI	NO	NO	15
SETTU	YES	YES	9
BALAN	YES	YES	4
MEENA	YES	NO	13
THIRUPATHY	YES	YES	5
ANNAMMAL	YES	YES	3
SATHISH	YES	YES	4
PUNNIYAKODI	NO	NO	16
SURESH BABU	NO	NO	17
SUSEELA	YES	YES	5
RAJ	YES	YES	4
MALA	YES	NO	6
THOMAS	NA	NA	3
CHINNAKULANDAI	YES	NO	9
PARANTHAMAN	NO	NO	11
KRISHNAMOORTHY	NA	NA	4
VINOD KANNAN	YES	NO	20
JAYA	YES	NO	8
RAJAMANICKAM	NA	NA	3
VASUDEVAN	YES	NO	7
ANJALAKSHMI	NA	NA	1
PARAMESWARAN	NO	NO	14
SIVAGNANAM	YES	NO	8
JAGAN	YES	NO	12
KALAIYARASI	NO	NO	12
RAYAN	NA	NA	+2
KAMATCHI	YES	YES	6
SELLAMUTHU	NA	NA	17
NARAYANAN	NA	NA	2
VANNATHATCHI	YES	NO	8
RUKMANI	NA	NA	2
PARAMESHWARI	YES	YES	12
CHITRA	YES	NO	8
AYYAPAN	YES	NO	12

CHART 7

PT'S NAME	COMPLICATIONS				
	EFFUSION	EMPYEMA	ARDS	MODS	DEATH
KRISHNAN	NO	NO	NO	NO	NO
SETHU	NO	NO	NO	NO	NO
MOHANA SUDARAM	NO	NO	NO	NO	NO
RAJAMMAL	NO	NO	YES	YES	NO
LOGANATHAN	NO	NO	YES	YES	NO
ELUMALAI	NO	NO	NO	NO	NO
GOWRI	NO	NO	YES	YES	NO
DHANALAKSHMI	NO	NO	NO	NO	NO
ELUMALAI	YES	YES	NO	YES	NO
SETTU	NO	NO	YES	NO	NO
BALAN	NO	NO	NO	NO	NO
MEENA	NO	NO	YES	NO	NO
THIRUPATHY	NO	NO	NO	NO	NO
ANNAMMAL	NO	NO	NO	NO	NO
SATHISH	NO	NO	NO	NO	NO
PUNNIYAKODI	YES	YES	NO	YES	NO
SURESH BABU	YES	YES	NO	NO	NO
SUSEELA	NO	NO	NO	NO	NO
RAJ	NO	NO	NO	NO	NO
MALA	YES	NO	NO	NO	NO
THOMAS	YES	NO	YES	NO	YES
CHINNAKULANDAI	NO	NO	NO	NO	NO
PARANTHAMAN	YES	NO	NO	YES	NO
KRISHNAMOORTHY	YES	NO	NO	YES	YES
VINOD KANNAN	NO	NO	YES	YES	NO
JAYA	YES	NO	NO	NO	NO
RAJAMANICKAM	NO	NO	YES	YES	YES
VASUDEVAN	NO	NO	NO	NO	NO
ANJALAKSHMI	NO	NO	YES	YES	YES
PARAMESWARAN	YES	YES	NO	NO	NO
SIVAGNANAM	YES	NO	NO	NO	NO
JAGAN	YES	YES	NO	YES	NO
KALAIYARASI	NO	NO	YES	NO	NO
RAYAN	NO	NO	YES	YES	YES
KAMATCHI	NO	NO	NO	NO	NO
SELLAMUTHU	YES	YES	NO	YES	YES
NARAYANAN	NO	NO	YES	YES	YES
VANNATHATCHI	NO	NO	NO	NO	NO
RUKMANI	YES	NO	YES	NO	YES
PARAMESHWARI	YES	NO	YES	NO	NO
CHITRA	NO	NO	NO	YES	NO
AYYAPAN	NO	NO	NO	NO	NO

ANNEXURE 4; ETHICAL COMMITTEE APPROVAL FORM

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI -3

Telephone No : 044 25305301
Fax : 044 25363970

CERTIFICATE OF APPROVAL

To
Dr. S. Suresh Kumar
PG in MD General Medicine
Madras Medical College, Chennai -3

Dear Dr. S. Suresh Kumar

The Institutional Ethics committee of Madras Medical College, reviewed and discussed your application for approval of the proposal entitled "Serum BNP levels in community acquired pneumonia and its comparison with curb-65 score as a prognostic marker" No.27042012.

The following members of Ethics Committee were present in the meeting held on 19.04.2012 conducted at Madras Medical College, Chennai -3.

1.	Dr. S.K. Rajan. M.D.,FRCP.,DSc	-- Chairperson
2.	Prof. Pregna B. Dolia MD Director , Institute of Biochemistry, MMC, Ch-3	-- Member Secretary
3.	Prof. B. Kalaiselvi MD Prof. of Pharmacology ,MMC, Ch-3	-- Member
4.	Prof. C. Rajendiran, MD Director , Inst. of Internal Medicine, MMC, Ch-3	-- Member
5.	Prof. Md. Ali. MD.DM Prof & HOD, Dept. of MGE, MMC, Ch-3	-- Member
6.	Prof.P.Karkuzhali MD Director i/c, Prof., Inst. of Pathology, MMC, Ch-3	-- Member
7.	Prof. S. Deivanayagam MS Prof of Surgery, MMC, Ch-3	-- Member
8.	Prof. A. Radhakrishnan MD Prof of Internal Medicine, MMC, Ch-3	-- Member
9.	Thiru. S. Govindsamy. BABL	-- Lawyer
10.	Tmt. Arnold Soulina MA MSW	-- Social Scientist

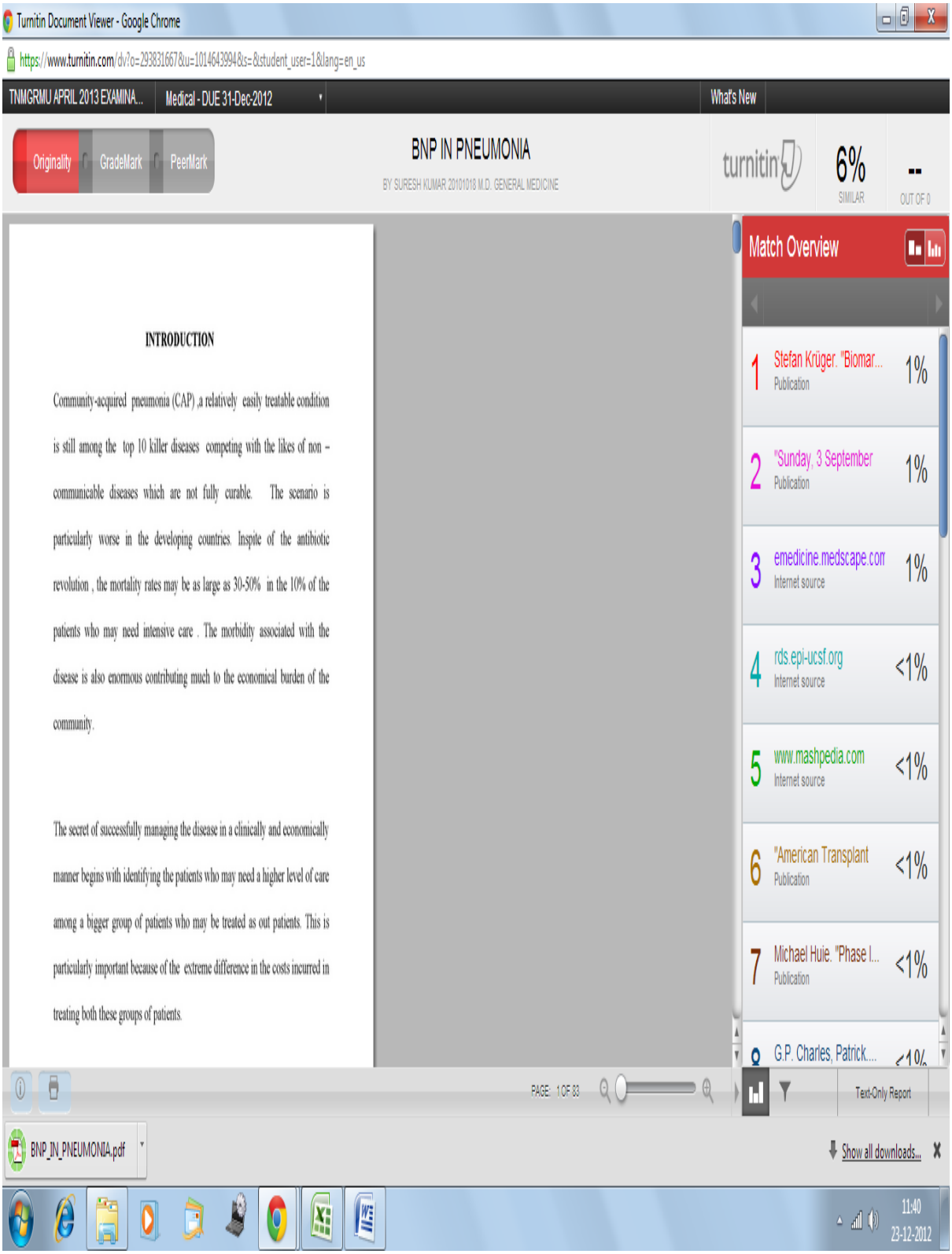
We approve the proposal to be conducted in its presented form.

Sd/ Chairman & Other Members

The Institutional Ethics Committee expects to be informed about the progress of the study, and SAE occurring in the course of the study, any changes in the protocol and patients information / informed consent and asks to be provided a copy of the final report.

Member Secretary, Ethics Committee

ANNEXURE 5; PHOTO COPY EVIDENCE OF ANTI-PLAGIARISM WEBSITE



ANNEXURE 6;DIGITAL RECEIPT OF ANTI-PLAGIARISM WEBSITE

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E-mail	drsuresh.svpr@gmail.com
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INTRODUCTION Community-acquired pneumonia (CAP) ,a relatively easily treatable condition is still among the top 10 killer diseases competing with the likes of non – communicable diseases which are not fully curable. The scenario is particularly worse in the developing countries. Inspite of the antibiotic revolution , the mortality rates may be as large as 30-50% in the 10% of the patients who may need intensive care . The morbidity associated with the disease is also enormous contributing much to the economical burden of the community. The secret of successfully managing the disease in a clinically and economically manner begins with identifying the patients who may need a higher level of...

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E-mail	drsuresh.svpr@gmail.com
Submission time	24-Dec-2012 05:06AM
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