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Effect of Diabetes mellitus in patients with acute exacerbation of the chronic obstructive pulmonary disease

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Abstract:

Background: Acute exacerbation chronic obstructive pulmonary disease (AECOPD) is the leading morbidity and mortality cause worldwide. Many studies showed the association of hyperglycaemia with poor results from a wide range of acute illnesses.

Aim and Objectives: To investigate the association between concentrations of blood glucose & clinical outcomes in AECOPD patients admitted to the hospital.

Material and Methods: This is a hospital-based retrospective analysis carried out on AECOPD patients admitted during the period of January 2021 to March 2022. Detailed history, clinical examination, blood investigations were performed. Random blood glucose levels at the admission were noted, and the subjects were separated into groups of four on the basis of blood glucose levels (≤ 140 mg/dl, 141- 170 mg/dl, 171-200 mg/dl, >200 mg/dl). The clinical outcome was compared among these four groups.

Results: In this study majority were male patients (86%) with age ranging from 66-75 years (46%). About 85% of patients were smokers, and 15% were non-smokers. 68% of the study group population was hyperglycaemic (RBS >140 mg/dl). Among different quartiles, the mean length of stay in hospital was statistically considerable (p=<0.05), signifying an increased length of stay in hospital trend as the admission RBS levels increase. There was no statistically significant relationship amongst the RBS quartiles of ≤140 mg/dl and RBS quartiles of 141-170mg/dl (p=0.997). There was a statistically considerable correlation amongst the RBS quartiles ≤140 mg/dl and RBS quartiles ≥201 mg/dl(p=000), and this study's crude rate of mortality was 5%. The population under quartile of RBS ≥201mg/dl had the highest percentage. All the people who died were over the age of 56 years. The mean HbA1c among dead (9.43 ± 2.25) and alive (6.78±1.70) showed significant relation (p=<0.05).

Conclusion: Higher the admission RBS, longer was the mean length of stay in hospital and mortality in the AECOPD diagnosed patients. Maintaining the blood glucose levels < 170 mg/dl than the strict glycaemic control, i.e.<140 mg/dl, could benefit these patients' outcome. This study indicates that for clinically treating the AECOPD patient population, targeted surveillance, as well as DM management, are critical.

Key-words: AECOPD, diabetes mellitus, RBS, hyperglycaemia, length of hospital stays, mortality

Introduction:

Acute exacerbation chronic obstructive pulmonary disease (AECOPD) is a global health concern with high economic as well as social costs and is marked by persistent limitation of airflow.[1, 2]Chronic alveolar and bronchial inflammation during exposure to noxious gases or particles, predominantly those found in tobacco smoke, is linked to AECOPD development.[2]With these added pulmonary abnormalities, Acute exacerbation chronic obstructive pulmonary disease (AECOPD) has a systemic aspect that involves considerable extra-pulmonary effects such as dysfunction of skeletal muscle, osteoporosis, depression and loss of weight.[3]Understanding the pathogenetic mechanisms behind these systemic impacts is very poor, although these are likely to be multifactorial and interrelated, which also involves physical inactivity, oxidative stress, tissue hypoxia and systemic inflammation.[3] Extra-pulmonary AECOPD manifestations might inversely result in impaired functional status, aggravated dyspnea, reduced health-related quality of life, and raised risks of deaths in these subjects.[4]

Around the globe, acute exacerbation chronic obstructive pulmonary disease (AECOPD) is a leading chronic mortality and morbidity cause throughout the world. It has a wide-ranging negative influence on both patients as well as the healthcare system. As a result, it has become a global public health issue of rising significance. [5] Currently, AECOPD is the world's fourth-leading mortality cause. [4]By 2030, AECOPD is expected to be the third leading death cause. [6]Many such studies showed that low-grade chronic inflammation is a part of insulin resistance syndrome and is linked to diabetes mellitus (DM) development.[7,8]

As a result, one of the common denominators between DM and AECOPD is certainly chronic systemic inflammation. According to epidemiological findings, DM is more prevalent in patients diagnosed with AECOPD, and it possibly influences their prognosis. [8,9] Hyperglycemia linked to critical illness (also known as stress diabetes or stress hyperglycemia) is an outcome of several aspects, comprising increased catecholamines, growth hormone, cortisol, glucagon, glycogenolysis and gluconeogenesis.[11]Insulin resistance, which has been observed in over 80% of critically ill subjects, may also be a contributing factor.[12]Previously, hyperglycemia was assumed to be an adaptive response necessary for survival, and it was not regularly monitored in ICU (intensive care units).[13,14]Though, recent proofs suggesting an association of uncontrolled hyperglycemia with poor outcomes has incited efforts to prevent as well as correct hyperglycemia in critically ill subjects on a routine basis. However, on the other hand, a number of research have found a correlation between reduced lung function and DM. [14-16] The connections between 2 complex diseases are undoubtedly complicated, and further investigation is needed for improving our understanding regarding these. With this scenario, the present study was designed with the primary aim to understand the correlation of hyperglycemia to the outcome of patients with AECOPD in an attempt to take a step forward for the improvement of the outcome of these patients in the future.

Subjects and Methods:

The present study is hospital-based prospective research carried out on admitted patients diagnosed with AECOPD under the Respiratory Medicine Department in Malla Reddy Institute of Medical Sciences, Suraram, Hyderabad during the time period of January 2021 to March2022. Subjects were excluded if they had bronchial asthma, pneumonia, pulmonary tuberculosis, interstitial lung disease, bronchiectasis, AECOPD subjects with myocardial infarction, or reduced ejection fraction/requiring surgery/CVA/ Chronic Kidney Disease.

Data collection:

The information about the demographics, comorbidities, consent of the subjects, necessary particulars of the patients, a detailed history was taken. Detailed clinical examination was *viz.* Random blood sugar immediately at the admission time & other baseline studies are essential for ruling out other comorbid circumstances like ECG, renal function test, chest X-ray, HbA1c,2D Echo, CBC (complete blood count), ABG (arterial blood gas), spirometry and sputum examination test was conducted. Each patient's length of stay in the hospital (in days) was noted. The subjects in the hospital were followed up over time till death ensued or until they were discharged. For the purpose of this analysis, a composite adverse outcome was described as death or length of stay lengthier compared to the median length of stay. In this study, hyperglycemia was assumed as random glucose in the blood of ≥140 mg/dl. The information was recorded into standardized tables for comparison, with the study's population separated into quartiles or groups based on levels of blood glucose and age. These quartiles are:1) Random glucose in blood equal to less than 140 mg/dl (excluding hypoglycemia assumed as <60mg/dl),2) Random glucose in blood141 to 170mg/dl,3) Random glucose in blood 171 to 200 mg/dl, and4) Random glucose in blood equal to more than 200 mg/dl.

Statistical analysis:

For each quartile of random blood glucose, the mean length of stay in the hospital was determined. The number of deaths was compared between the hyperglycemic and normoglycemic population, and the post-hoc test was used to examine the disparity between the mean lengths of stay in the hospital. The study results were interpreted with the p-value. Statistical significance was classified by p0.05.

Results:

A total of hundred AECOPD diagnosed subjects admitted between January 2021 to March 2022 study period were included. The majority of study patients, *i.e.*, 46%, were 66-75 years of age group followed by 38% belonged to the age group of 56-65 years(Figure1) with male predominance(86%) compared to female (14%)(Figure 2). Out of the 100 patients, 84 (98.8%) and 1 (1.2%) male and female patients were smokers, respectively(Figure 3). In our study, for random levels of blood glucose >140mg/dl was assumed as hyperglycemic. Of the hundred subjects, hyperglycemia was observed in 68% (n=68) patients, and normoglycemia was observed in 32% (n=32) patients (Table1) (Figure 4).

Two subjects in the 46-55 years of age group were males, 5 (13.2%) in the 55-65 years of age group were female, and 33(86.8%) were male. 9 (19.6%) patients were female, and 37(80.4%) were male subjects in the age group 66-75. All the 10 patients in the age group of 76-85 years were male, and all the 4 subjects in the age group of>85 years were female.(Figure5) Though no considerable(p=0.43)relationship was seen between sex and age in hyperglycemia among patients(Table 2) .When comparing the mean length of stay in hospital among RBS quartiles, it was discovered that the mean length of stay increased with an increase in levels of RBS. In general, there was a substantial difference in the mean length of stay in hospital between different quartiles(p<0.001)(Figure 6).The post-hoc test was used to compare the mean length of stay in hospital between the different RBS quartiles, which showed no statistically considerable association among the RBSquartiles≤140 mg/dl as well as 141-170mg/dl. (p=0.997). However, there is a statistically considerable(p=0.00) association between RBS quartiles ≤140 mg/dl with ≥201 mg/dl with, and there is the statistical significance (p=0.02) between 141-170 with ≥201with (Table 3).

A total of 8 patients showed mortality. Among 8 patients, 7 patients' RBS was more than 201 mg/dl during the time of admission, and 1 patient was 171-200mg/dl. As there was an increased random level of blood glucose, the mortality percentage also increased. The population under quartile of RBC $\geq$ 201mg/dl had the highest percentage. (Table 4)There were 100% deaths in the population with hyperglycemia& no death in the population having normoglycemia. The rate of mortality was seen in the group with the age of more than 56 years. The mean HbA1c among dead and alive showed a statistically significant relation(p=<0.05). (Table 5)In patients diagnosed with AECOPD, 38%and 62% of the patient's sputum are gram-positive and gram-negative(Figure7). Out of 38 sputum gram stain positive patients, sputum culture and sensitivity reports revealed showed sensitivity for *Klebsiella pneumonia*(31.6%), *Streptococcus pneumonia (*23.70%), *E. coli (*10.5%), oral commensals (13.2%), *Staphylococcus aureus*(10.5%), and *Acinetobacter Sp. (*10.5%) (Table 6)(Figure8).

Discussion:

Globally, COPD is one of the leading mortality and morbidity cause. AECOPD-related strategies to minimize the length of stay in hospital and mortality are being tested. Previous research has found that fixed variables such as male sex, older age [17,18], arterial pH [17], comorbidity, and higher-income [18], predict in-hospital deaths from AECOPD. In a wider range of acute illnesses, hyperglycemia at the time of presentation is related to a poor prognosis. In AECOPD, the correlation between the levels of blood glucose & clinical outcomes has been not established fully. As a result, the current study was carried out to see whether there was a correlation between levels of blood glucose at the admission time and clinical results in AECOPD patients admitted in Respiratory Intensive care unit and Respiratory wards of Malla Reddy Institute of Medical Sciences .In our study, male predominance (86%) was observed among study subjects compared to female subjects. This was similar to the prevalence study carried out by Menezes AM et al. In our study, the population's mean age was 68.55 ± 7.54 years and was comparable with an assessment done in a prospective study [19]conducted in the year 1997 in the province of Barcelona, Spain, at an acute care teaching referral centre, where the population's mean age understudy was 72.2 ± 9.25 years. In the present study, 85% of study subjects smoked & 15% did not non-smoke. The smoking population had acquired more than 20 pack-years. This indicates the well-known fact that in smokers, there is high AECOPD incidence than the non-smokers, which is confirmed by & systematic review & meta-analysis of studies conducted in twenty-eight countries between 1990 and 2004 [20]as well as through study findings from Japan.[21]

The assumption of hyperglycemia was at >140 mg/dl random levels of blood glucose in the present study. About 32% had normoglycemia, and 68% had hyperglycemia. Among hyperglycemic, 35 subjects (51.47%) suffered from diabetics & 33 subjects (48.52%) were non-diabetics signifying that the presence of acute hyperglycaemia is often seen in stress situations, both non-diabetic and diabetic subjects. In this research, all subjects were separated into 4 quartiles on the basis of RBS at admission time, *i.e.,*≤140 mg/dl, 141-170mg/dl, 171-200 mg/dl, &≥200 mg/dl & mean length of stay in hospital was calculated and compared amongst quartiles with the help of ANOVA, which indicated statistically significant co-relation ($p < 0.05$), suggesting that there is a trend towards the longer length of stay in hospital as the admission levels of RBS rises. These findings were comparable to Baker EH et al. study findings where in the patients had been separated into quartiles, *i.e.,*<6 mmol/l (108mg/dl),6 to 6.9mmol/l(<126mg/dl), 7 to 8.9 mmol/l(126-162mg/dl) &>9 mmol/l(>162mg/dl) on the basis of highest levels of glucose in blood measured either during or at the time of admission[22]& too in agreement with other study findings stated by Parappil[23]& Burt.[24]A potential explanation is that both nondiabetic and diabetic patients experience acute hyperglycemia in stressful conditions. [25,26]If the lungs are considered, hyperglycemia is assumed to damage them by destroying capillaries and inducing non-enzymatic collagen glycosylation.[27]Hyperglycemia tends to induce cellular stress through a number of mechanisms, which can be harmful to the lungs.[28]These processes will result in weakened immunity and increased vulnerability to infections, resulting in negative consequences. Our findings contradict those of Kasirye and Islam, who found no association between levels of glucose in blood & length of stay or unfavourable consequences in their studies.[29,30]To sum up, these findings showed that hyperglycemia has an inconsistent impact on outcomes in subjects hospitalized with AECOPD aggravations. This could be described, in part, by protocols of glucose measurements utilized in various research, which comprised mean daily values, admission values, mean continuous values and peak values, as well as management approaches and medication selection.

There was no statistical significance among the RBS quartiles 140 mg/dl & 141-170 mg/dl when the mean length of stay in hospital was compared among different quartiles using the post-hoc test. (p=0.997). However, there was a statistically considerable association among the RBSquartiles≤140 mg/dl with≥201 mg/dl with p-value 0.00. Furthermore, we found statistical significance between 141-170 and ≥201 with a p-value of 0.002. Based on the findings of our research, RBS > 170 mg/dl is harmful to patients with AECOPD. This, however, has yet to be proven conclusively. Baker discovered that RBS effects greater than 7 mmol/l (126 mg/dl) were harmful to patients with AECOPD in his research.[22]Gao L discovered in a prospective study that severe glucose control procedures are related to unfavourable clinical results in subjects admitted with AECOPD.[31]The patients in the intensive glucose control group were given insulin as needed to keep their FBG (fasting blood glucose) between 4.4 & 6.1 mmol/l (80-110 mg/dl) & their postprandial blood glucose below 8 mmol/l (144 mg/dl) in this study. The intensive glucose control group had a higher incidence of hypokalemia and hypoglycemia. This indirectly supported our conclusion that if levels of blood glucose are kept below 170 mg/dl, than strict glycaemic control (140 mg/dl) might aid in achieving an improved result. In non-randomized, prospective, single-arm intensive glycaemic control research carried out by Archeron subjects with AECOPD showed that intensive glucose control could be achieved within the acute medical ward with similar efficacy and safety to that accomplished with subjects admitted to ICU (intensive care unit). Controlling blood glucose levels might be helpful to patients suffering from AECOPD.[32]Our study observed a total death of 8 patients among 100 patients (8%). Out of these, six patients were in GOLD stage IV, as shown by their medical history. Amongst 8 subjects, 7 patients' RBS at the time of admission was > 201 mg/dl,&1patient was 171-200 mg/dl. With the increased random level of blood glucose, the mortality percentage increased. The population with the low quartile of RBS of 201mg/dl had the highest percentage. All of the deaths occurred in subjects over the age of 56 years. The mean HbA1c among dead (9.43 ± 2.25) and alive (6.78±1.70) showed significant relation (p=<0.00). These results are similar to the studies reported by Baker et al. and Parappi, where they found that higher blood glucose levels were linked to unfavourable consequences. [22,23]

In our study, out of 100 patients diagnosed with AECOPD, 38% and 62% of patient's sputum shown gram-positive and gram-negative. Out of 38 sputum gram stain positive patients, sputum culture and sensitivity reports revealed showed sensitivity for *Klebsiella pneumonia*(31.6%), *Streptococcus pneumonia (*23.70%), *E. coli (*10.5%), oral commensals (13.2%), *Staphylococcus aureus*(10.5%), and *Acinetobacter Sp. (*10.5%).These findings are in concurrence with results reported by Madhavi et al. [33]Whereas, in studies reported by Chawla et al. and Patel AK, who had found *Pseudomonas aeruginosa* and *Streptococcus pneumoniae* as the most common organisms found in hyperglycemic and AECOPD, respectively. [34,35] The difference may be because the bacterial isolates are dependent on the bacteria prevalence in the environment of hospital, community, exacerbation severity and antibiotic prophylaxis.

Conclusion:

DM is prevalent comorbidity in patients diagnosed with AECOPD. Increasing the concentrations of glucose in the blood are related to unfavourable clinical consequences in AECOPD patients. Our study findings delineated that higher admission RBS, lengthier was the mean length of hospital stay and mortality in the AECOPD patients. Maintaining the blood glucose levels < 170 mg/dl, than the strict glycaemic control, i.e. <140 mg/dl, could benefit the outcome of these patients. Hence, this research indicates that for clinically treating the AECOPD patient population, targeted monitoring, as well as DM management, is crucial. However, extensive prospective studies need to conducted to confirm further the association between DM and AECOPD as blood glucose control is a potentially modifiable factor.

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Acknowledgement:

Table 1: Demographic details of the patients

Age-wise distribution			
Age	**No. of patients**	**Percent (%)**	
46-55	2	2.00	
56-65	38	38.00	
66-75	46	46.00	
76-85	10	10.00	
>85	4	4.00	
Total	100	100.00	
Gender			
Female	14	14.00	
Male	86	86.00	
Total	100	100.00	
Smoking among study population			
Signs	**Male**	**Female**	**Total**
Smokers	84	1	85
	98.80%	1.20%	100.00%
Non-Smokers	2	13	15
	13.30%	86.70%	100.00%
Total	86	14	100
	86.00%	14.00%	100.00%
Hyperglycemia among study population			
RBS (mg/dl)	**No. of patients**	**Percent (%)**	
≤140	32	32.00	
>140	68	68.00	
Total	100	100.00	

Table 2.Association between sex and age in hyperglycemia among patients

Age (years)	**Gender**			
	Female	**Male**	**Total**	**p-value**
46-55	0	2	2	0.43
	0.00%	100.00%	100.00%	
55-65	5	33	38	
	13.20%	86.80%	100.00%	
66-75	9	37	46	
	19.60%	80.40%	100.00%	
76-85	0	10	10	

	0.00%	100.00%	100.00%	
>85	0	4	4	
	0.00%	100.00%	100.00%	
Total	14	86	100	
	14.00%	86.00%	100.00%	

Table 3. Comparison of mean length of hospital stay among quartiles by using ANOVA and between the quartiles by using Tukey's post hoc test

Comparison of mean length of hospital stay among quartiles by using ANOVA					
RBS Quartiles	**Mean**	**Std. Deviation**	**F value**	**P-value**	**Inference**
≤140	6.09	1.87	9.066	0.000	HS
141-170	6.24	1.03			
171-200	7.58	2.73			
200	8.84	2.82			
Total	7.28	2.56			
Comparison of mean length of hospital stay between the quartiles y using Tukey's post hoc test					
RBS Quartiles		**p-value**	**Inference**		
<140	141-170	0.997	NS		
	171-200	0.122	NS		
	≥201	0.000	HS		
141-170	171-200	0.303	NS		
	≥201	0.002	HS		
171-200	≥201	0.235	NS		

NS-Non significant; HS-Highly significant

Table 4. Comparison of mortality according to Quartile levels

Age(years)	**RBS (mg/dl)**				
	140	**141-170**	**171-200**	**200**	**Total**
46-55	0	0	0	0	0
56-65	0	0	0	2	2
66-75	0	0	0	3	3
76-85	0	0	1	2	3
>85	0	0	0	0	0
Total	0	0	1	7	8

Table 5. Showing mortality among normoglycemic and hyperglycaemic patients and mean HbA1c among dead and alive

Mortality among normoglycemic and hyperglycaemic patients			
Age (yrs)	**RBS (mg/dl)**		
	140	**141-170**	**Total**
46-55	0	0	0
56-65	0	2	2
66-75	0	3	3
76-85	0	3	3
>85	0	0	0
Total	0	8	8

Mean HbA1c among dead and alive patients				
Outcomes	**Mean**	**T value**	**P-value**	**Inference**
Alive	6.781522	-5.68	0.00	HS
Dead	9.437500			

HS-Highly significant

Table 6. Sputum gram stain, culture and sensitivity in study group

Sputum gram stain	**No. of patients**	**%**
Positive	38	38.00
Negative	62	62.00
Total	100	100.00
Sputum culture	**No. of patients**	**%**
E. coli	4	10.50
Klebsiella pneumonia	12	31.60
Oral commensals	5	13.20
Staphylococcus aureus	4	10.50
Streptococcus pneumonia	9	23.70
Acinetobacter *Sp.*	4	10.50
Total	38	100.00

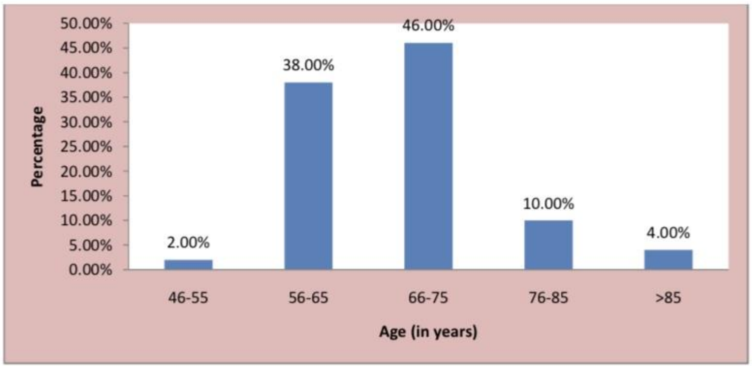

FIGURE 1: shows age wise distribution of patients

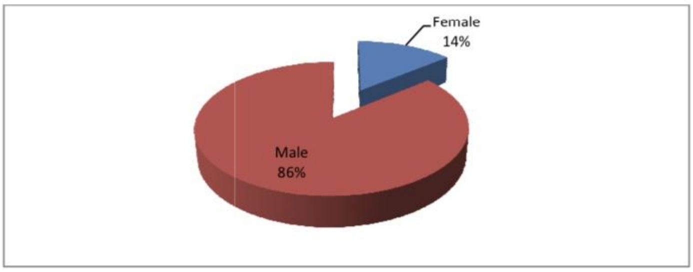

FIGURE 2: shows gender wise distribution

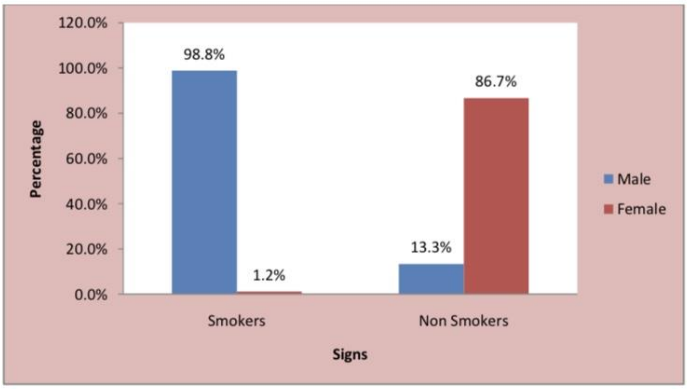

FIGURE 3: shows smoking among study population

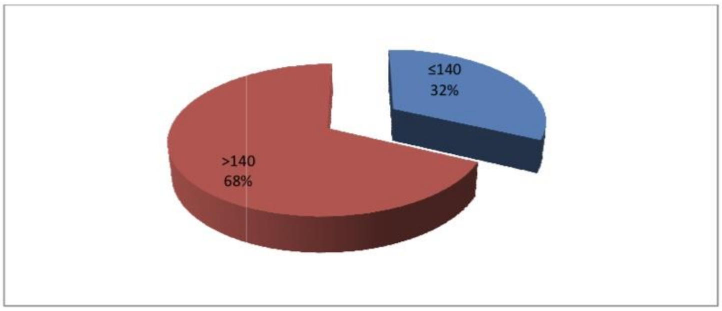

FIGURE 4: shows hyperglycemia among study population
(32% normoglycemic and 68% hyperglycemic)

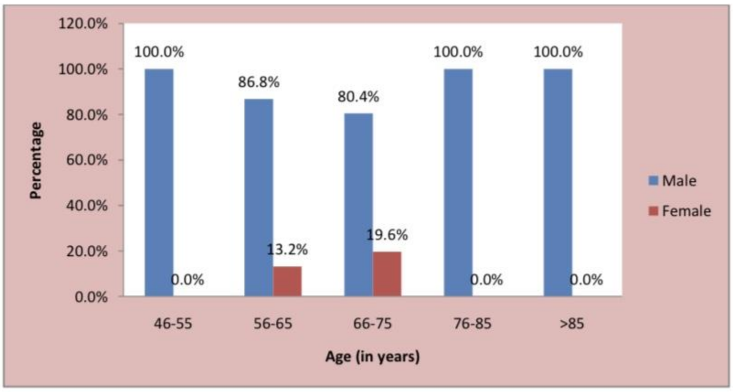

FIGURE 5: showing association between age and sex in hyperglycemia

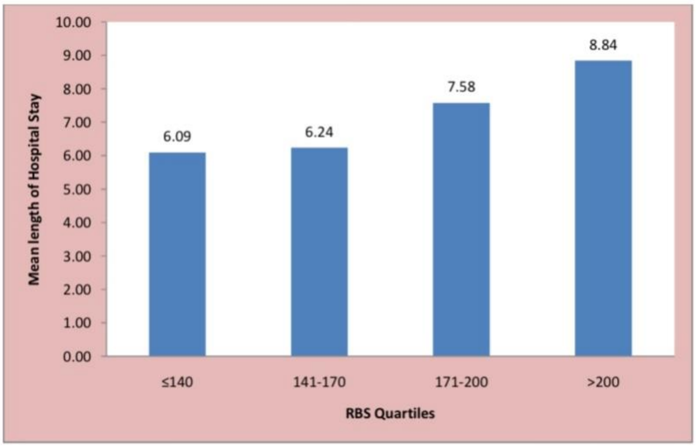

FIGURE 6: showing comparison of mean length of hospital stay among quartiles by using ANOVA

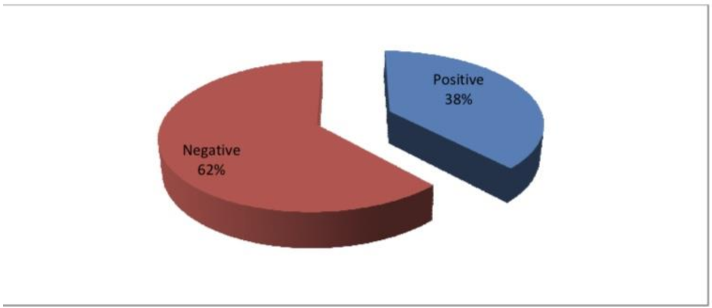

FIGURE 7: sputum gram staining in study groups

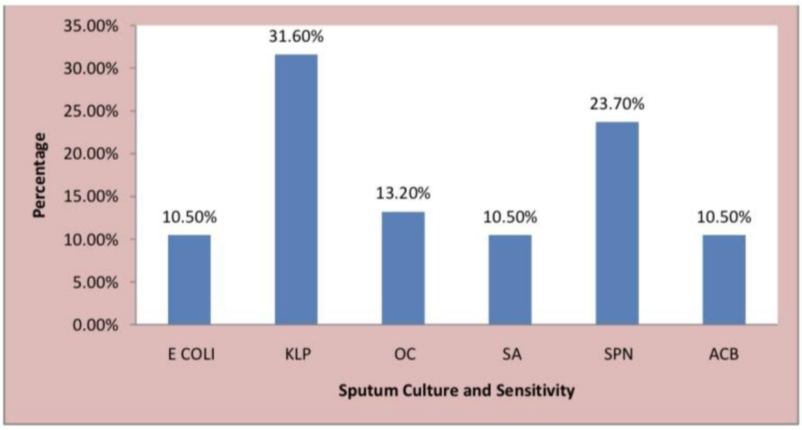

FIGURE 8: sputum culture and sensitivity results