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Sex Differences In Mortality Rate Among Chronic Obstructive Pulmonary Disease Patients With Covid - 19 In South Indian Population

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Abstract

Background*: Mortality rate among chronic obstructive pulmonary disease (COPD) is influenced by cardiovascular comorbidities and other lung diseases. Clinical scoring systems like BODE index analyze the severity in COPD which assesses four independent predictors, the body mass index (BMI), the degree of airflow obstruction assessed by the Forced Expiratory Volume in one second (FEV_1), the modified Medical Research Council (mMRC) dyspnoea scale, and the exercise capacity (6MWT) are helpful to estimate the mortality rate. Covid 19 pandemic, risked the lives of many vulnerable group like chronic lung disease patients. Impaired lung compliance which aggravated with Covid - 19 has been shown to increase the mortality rate along with other comorbidities in many. The present study focus to differentiate how mortality rate reflects in males and females with the severity of Covid-19 by predicting the BODE index.*

Design: *Cross sectional study*

Materials and methods: *The study was conducted in COPD patients who had contracted with Covid-19 and those who had not. COPD patients were further categorized based on the severity of the disease by GOLD criteria. Those patients, who were able to walk, met the inclusion criteria.*

Results*: Consecutive samples of 94 male and 92 female COPD patients with an age group of 55-65 years were included in the study, with and without infected by Covid -19. The difference in BODE index in all the groups were analyzed by unpaired 't' test and the difference of categorical variable in both groups were analyzed by Chisquare test.*

Conclusion*: There were more difficulties experienced in female population with comorbidities and significant*

changes noted in four year survival rate with a high mortality score among Covid group compared to non Covid. There were significant changes in most of the variables assessed like FEV1 % pred., FEV1/ FVC ratio predicted, 6MWT ($p \leq 0001$).

Key words: *BODE index, COPD, Covid-19, non covid, mortality rate, sex difference, comorbidities.*

INTRODUCTION

COPD is a heterogeneous clinical syndrome characterized by chronic airway obstruction with increased airway resistance and is frequently associated with cardiovascular diseases. Global burden of disease study updated about the risk factors for COPD in 2019 and it is the third leading cause of death in worldwide population according to World health organization (WHO). The recent reports of this reassures that, COPD results from tobacco smoking, air pollution, occupational exposure to dusts or chemicals. Common symptoms include cough, sometimes with phlegm, difficulty breathing, wheezing and tiredness. People with COPD are likely to have comorbidities like cardiovascular diseases (CVD), diabetes mellitus (DM), hypertension, osteoporosis, metabolic syndrome, sleep disorders, and lung cancer [1,2]. There are studies which emphasize that CVD, cigarettes smoking, DM and lung cancer are high risk factors for increased mortality rate [3-6]. Other predictors include previous hospitalizations for acute exacerbation, age, sex and cardiovascular mortality [7]. COPD is not curable but symptoms can improve if one avoids smoking, exposure to air pollution and also with medication.

To detect COPD, Pulmonary Function Tests (PFT) is useful in which FEV_1 is reproducible and is highly sensitive index of obstructive lung disorder according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) report 2018 [8]. Female population is more affected with chronic lung diseases than males, mostly due to the fact that males have greater lung capacity and flow volumes and rates when compared with the females of same height and age. Therefore, cigarette smoking will lead to more complications in females compared to male smokers [9-11]. Globally few studies were conducted in large population to see the sex differences in comorbidities and mortality risks which showed that females had higher prevalence of asthma, arthritis and COPD severity compared to age matched males. Males had higher prevalence of coronary artery diseases, heart attacks and gout though much other comorbidity like dislipidemia, hypertension was similar in both groups [11]. Studies are less in Indian population which explains the sex differences in these comorbidities among chronic lung disease patients. BODE index is mostly used parameter to predict the severity in COPD which assesses four independent predictors like BMI, the degree of airflow obstruction assessed by FEV_1, dyspnea scale, and the exercise capacity.

With the onset of Covid -19 pandemic, people with chronic lung diseases like COPD and asthma were more vulnerable to Covid-19 infection. The severity was more with age and acute exacerbations which lead to increased mortality rate irrespective of inhaled corticosteroids treatment [12]. Some studies explains that Covid-19 infected patients with COPD, had higher mortality rate based on the predictors like Body Mass Index (BMI) and ADO index (Age, Dyspnoea and Obstruction) [13]. But, there are very less data available to study how the mortality rate is predicted among chronic lung disease patients with Covid in males and females. The present study aims to investigate the severity in mortality rate among male and female COPD patients of different GOLD stages, with the interference of Covid- 19 along with other comorbidities with the help of BODE index score.

METHODS

A cross-sectional study was conducted at the Department of Pulmonary medicine and Physiology, in a tertiary care hospital in Kerala, India, on COPD patients. The study was conducted after lock down of Covid-19. All the participants were well informed about the study and written consent was obtained from them.

Inclusion criteria

Patients with COPD who were able to walk for 6MWT, included in the study. All were screened for Covid-19 through RTPCR/Antigen test diagnosed during the study period. There were a total of 186 consecutive patients participated in the study with age matched males and females. The Covid-19 study group was with mild to

severe symptoms with varied changes in SPO_2ranges from 80 - 95 % in room air and non Covid -19 COPD patients were taken as the control group.

Exclusion criteria

Patients with uncontrolled systemic arterial hypertension and uncontrolled pulmonary hypertension, pulmonary embolism, giddiness on standing, syncopal spellswere excluded from the study.

Ethics approval

The protocol was presented to the Institutional Ethics Committee (IEC), and approval was obtained (Ref No:10/IEC/20/AIMS-29).

The study participants were with COPD with and without Covid -19. From the study conducted by Becklake Met al. (9), the sample size is calculated as n = 80 in males and females. All the patients with Covid-19 syndrome had the symptoms 4-6 months back with mild to severe difficulties (people with mild symptoms of Covid-19 were symptomatic but did not have complications of severe hypoxia and major viral pneumonia; people with moderate cases had clinical signs of pneumonia but did not have signs of complications, such as SPO_2 90% in room air; people with severe symptoms had trouble breathing or severe shortness of breath). All patients were symptomatic for 8-12 weeks mostly with fatigue, dizziness, inappropriate palpitations, orthostatic intolerance, brain fog, nausea, anxiety and syncope. Moderately symptomatic patients were hospitalized during this period.All cases of Covid-19 were confirmed through real-time reverse-transcriptase polymerase chain reaction (RTPCR) assays on nasopharyngeal swabs. None of the patients were with active Covid-19 disease symptoms during this evaluation (asymptomatic for atleast 1 month) and all were vaccinated.

Classification of COPD - All the patients were categorized into COPD based on the GOLD criteria (stages I – IV) of spirometry (8), clinical history with questionnaire, comorbidities, 6MWT, high resolution computed tomography scan (HRCT) and routine blood investigations and on medication for 2-3 years after diagnosis. Pulmonary function tests (PFT) was done using Spirotrac - Software Reference Number: 68606 V1.16 Vitalograph. All patients with a baseline SpO2 ≥90% were taken up for the 6 MWT in a 100 m long passage near the out patient clinic.

Methods of data collection

A written informed consent which included a review of their medical records was obtained from every patient and the study was conducted in accordance with the Helsinki Declaration. Anthropometric assessments, Demographic and disease characteristics like symptom scores, hospitalization, exacerbation history, smoking history, etc., PFT, 6MWT were collected.

Calculation of BODE index

The BODE index score comprises body mass index(BMI), post-bronchodilator FEV1%predicted, grade of dyspnoea(measured by the modified Medical Research Council dyspnoea scale, mMRC) and the six-minute-walking distance [14 -17]. This index was developed to assess an individual's risk of death or hospitalization and based on that four year survival is estimated. The total points of BODE index score ranges from 0 to 10. The components of BODE index are explained as:

a) BMI - Body Mass Index, scores 0 or 1, because of the inflection point in the inverse relation between survival and body mass index at a value of 21. If the BMI is >21, score is 0 and if it is ≤ 2, score is 1.

b) **FEV_1** (postbronchodilator percent predicted): greater than 65% = 0 points; 50-64% = 1 point; 36-49% = 2 points; less than 35% = 3 points

c) mMRC dyspnoea scale - Scores on the modified Medical Research Council dyspnoea scale ranges from 0 to 4; 0 – "No breathlessness except with strenuous exercise"; 1 – "Troubled by shortness of breath when walking up a slight hill"; 2 – "Walks slower than people of the same age on the level because of breathlessness or has to stop for breath when walking at own pace on the level"; 3 – "Stops for breath after walking about 100yards or

after a few minutes on the level"; 4 – "Too breathless to leave the house or breathless when doing simple daily living". The BODE index point score is marked as 0,1,2 or 3 if the dyspnoea scale appears as 0-1, 2,3,4 respectively.

d) 6 Minute Walk Test is a sub-maximal exercise test, developed by American Thoracic Society, used to assess aerobic capacity and endurance. The distance covered over a time of 6 minutes is used as the outcome by which to compare changes in performance capacity. The baseline dyspnoea and overall fatigue was assessed by BORG scale [17]. The object of this test is to walk as far as possible for 6 minutes, back and forth in a hallway. Participants were allowed to stop in between if exhausted and quit at any point if exerting more. The meters covered in 6 minutes and resting time were noted. SPO_2, heart rate, arterial blood pressure were checked before and after the walk test.

The BODE index point score with 6MWT is assessed as 0 = ≥ 350, 1 = 250–349, 2 = 150–249 or 3 = ≤ 149

By adding the total BODE index points scored according to this calculation, the approximate 4-year survival rate is as follows:

0-2 points = 80%, 3-4 points = 67%, 5-6 points = 57%, 7-10 points = 18%

STATISTICAL ANALYSIS

The data entered in to Excel worksheet and analysis performed using SPSS 23. Descriptive and inferential statistical analysis was carried out. Results on quantitative measurements are presented on mean and SD. Normality of data was tested using Shapiro wilk test. Differences between means were tested with Student's t-test (unpaired t test). Significance was accepted at $p < 0.05$.The difference of categorical variable in both groups will be analyzed by Chi square test.

RESULTS

Characteristics of participants: A total of 186 COPD patients who met the inclusion criteria were analyzed in the study. The male participants were 94 and female participants were 92. The demographic variables were assessed and shown in Table 1.

The mean ages of the male and female groups were similar (55 to 65), and there was no difference between the groups in the age distributions. BMI, arterial blood pressure values and duration of the disease between males and females were insignificant. Women were more likely to be never smokers (2%), and men were more likely to be ex smokers (55%). FVC% predicted and FEV1% predicted in men and women did not differ much, but generally those values were less due to COPD. SPO_2 before and after 6MWT were slightly more in men and it was highly significant when compared to women. The meters covered during 6MWT were more in men compared to women.

Regarding COPD severity according to GOLD classification, females had a higher proportion of moderate to very severe COPD with Covid (16.66%), and men had a higher proportion of severe COPD without Covid (18.51%). Patient characteristics for the same are presented in Table 2.

The comparison of difficulties in both genders with Covid-19 is shown in Figure 1. Proportion of ex smokers is very high in males (55%) compared to females (2%). Hospitalisation and exacerbation rates related to Covid infection were more in female population whereas cardiovascular comorbidities were almost same in both genders.

It was observed that the mortality rate is more in female COPD patients with Covid -19 in GOLD stages II, III and IV. According to BODE index score, number of female patients with high mortality rate were double compared to male patients especially in GOLD stage II. Figures 2 & 3 gives more clarity why exacerbations were high in females with Covid hospitalization. More number of patients was in stage II compared to all other GOLD stages irrespective of sex.

BODE index score which shows 4 year survival rate exhibited more changes in GOLD stages II and III. Survival rate in both males and females of Covid infected groups were more significant compared to that of Non Covid groups in both the stages as shown in Table 3. Compared with the male group, the survival rate of the female

group was significantly lower.

DISCUSSION

The current study was to assess the changes in mortality rate among male and female patients of COPD with the Covid -19 complications and other comorbidities. The analysis was done and compared the severity in all the participants who were categorized according to GOLD stages of COPD. All of them were assessed for BODE index score which is a reliable predictor of COPD outcomes such as hospitalization and survival [14,18]. The BODE index score was calculated by adding the points of individual's BMI, post-bronchodilator FEV1%predicted, grade of dyspnoea(measured by the mMRC) and the six-minute-walking distance. The total score points estimated the patients' four year mortality rate.

The age matched males and females (55-65 years) showed not much significance in demographic variables such as BMI, arterial blood pressure and duration of COPD. Patients were selected with disease duration of 3-5 years. Smoking history of patients was an important factor to worsen COPD as well as Covid -19 difficulties. As many studies proved that past history of smoking itself is a threat for the rapid mortality rate in COPD patients. In this study, most of the ex smokers who were predominantly males had been quit smoking at least 10 -15 years back. Still this seems to increase their risk for mortality rate. It was observed in some western countries that female smokers are not less than male smokers and because of the increased COPD cases in females; the risk for mortality is almost equal in both genders [19]. Hospitalization and death from lung failure are reported to be more common in females with severe COPD than males in western countries. Smoking females have more chances for decline in lung function over time [20, 21]. Some studies found that X chromosome has susceptibility towards COPD and therefore there is risk for early onset of COPD in females. This suggested that oestrogen may contribute to decline in lung function while testosterone may be protective, and therefore suggesting a contribution of sex hormones for having more susceptibility of females to rapid FEV1 decline [22]. In the current study, we tried to find the differences in mortality rate among males and females in South Indian population. Post bronchodilator FEV1% predicted was significantly less in females. It was found that females have more breathing difficulties and more over, comorbidities aggravated their hospitalization as well as exacerbations with Covid -19.

The 6MWT is widely used to evaluate functional capacity in patients with COPD. The cohort study done by Frisk et al. included 389 patients aged 44-75 years, with clinically stable COPD in GOLD stages II-IV. The follow-up time was 3 years. They measured 6MWT, spirometry, fat and fat free mass index (FMI and FFMI), and assessed physical activity, smoking habits, comorbidities and exacerbations by questionnaires. The functional capacity over 3 years was significantly reduced for patients in GOLD stages III and IV. They found that Implementation of physical training programs seem to be important for maintaining functional capacity over time in COPD patients [23]. In our study, we found that the mean distance covered in 6MWT, by females was less (364 m) when compared with males (419 m). The resting time during walk test was more and duration of walking was less in females as they had more breathing difficulty. Similarly, the SPO_2 values were less in females before and after the walk test and it was highly significant. All these findings suggest that females were more dyspnoeic even when comorbidities were almost common in both genders.

When we considered the GOLD stages, the severity with COPD was slightly more in females especially with stages II and III irrespective of Covid -19 infection. In Covid groups of both gender, Covid - 19 related hospitalization and exacerbation were more in females which indicated higher mortality rate in them compared to males. Globally the rate of hospitalization and death was more in male population [24-26] whereas Indian female population was more with fatality rates [27,28]. When we analysed male and female COPD patients with Covid-19, more were categorized into GOLD stage II. These patients were assessed for the BODE index score and estimated a four year survival rate based on this. BODE index score indicates 80% survival rate if obtained between 0-2 points, 67% with 3-4 points, 57% with 5-6 points and only 18% with 7-10 points [18]. In GOLD stage II category, number of female patients was more with 80% and 57% survival rate compared to males. Likewise, in stages III and IV, number of females was slightly more with 57% survival rate which indicated

more fatality rate in females.
It was observed that more patients were in GOLD stages II and III. Prevalence of female population with Covid -19 was noted in all these stages which were indicative of higher mortality rate in females.

CONCLUSION

Our study focussed on the mortality rate among males and females which were determined by BODE index, Covid hospitalizations, exacerbations and other comorbidities. Considering all these factors, we estimated four year survival rate according to BODE index in all the GOLD stages for COPD patients. In conclusion, COPD with Covid -19 is associated with increased mortality in both genders which was suggested by other studies. But we found increased risk in females which was not specified much so far. The results show that females are more dyspnoeic and they have reduced life expectancy compared to males. We also have a significant data of women, which other COPD studies related to mortality rate might not have achieved. But more sample size in all GOLD stages with and without Covid -19, would have been ideal to support these findings. Less duration of study and no follow up of the patients were other limitation to prove these findings.

List of abbreviations

COPD– Chronic obstructive pulmonary diseases; BODE- BMI, obstruction, dyspnoea, exercise capacity; BMI- body mass index; FEV1 % - Forced expiratory volume in one second; SPSS- Statistical package for the social sciences; RTPCR - reverse-transcriptase polymerase chain reaction; mMRC- modified Medical Rsearch Council; 6MWT- six minute walk test; GOLD- Global initiative for chronic obstructive lung disease; WHO- World health organization; CVD- cardiovascular diseases; DM- diabetes mellitus; PFT- pulmonary function test; ADO- Age, dyspnoea, obstruction; HRCT- high resolution computed tomography scan; SPO2 – oxygen saturation.

Competing interests

The authors declare that they have no competing interests.

Author Contributions

DJC: Contributed in plan, protocol writing, implementation, data collection, interpretation of data and conclusion. **JMK**: Contributed in plan, protocol interpretation of data and conclusion. **RD**: Contributed in plan, interpretation of data and conclusion.

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Tables

Table 1 : Demographic variables of all patients (n= 109)

Demographic variables	Group	Mean±sd	P value (Un paired t test)
Age (in years)	Males (n=53)	62.17±0.2	0.2331
	Females (n=56)	61.29±5.33	
BMI (kg/m$^{2)}$	Males	23.56±4.315	0.067
	Females	24.60±1.889	
Duration of the disease (in years)	Males	3.83±.72	0.3171
	Females	3.705±0.64	

FEV1% predicted	Males	63.113±0.944	0.0001
	Females	59.448±6.408	
Ex smokers	Males	48±4.52	0.0001
	Females	2±0.58	
Systolic Blood Pressure (mmHg)	Males	129.97±6.971	0.831
	Females	129.61±11.347	
Diastolic Blood Pressure (mmHg)	Males	78.82±13.314	0.268
	Females	80.78±6.222	
Basal SPO_2 (before 6MWT)	Males	98.025±0.586	0.03
	Females	95.621±7.97	
6MWT (Meters covered)	Males	419.67±84.300	0.001
	Females	364.58±93.894	
SPO_2 (after 6MWT)	Males	96.88±1.50	0.0004
	Females	93.88±5.75	

* SPO_2 – Oxygen saturation, 6MWT – 6 minute walk test, sd – standard deviation

Table 2: Classification of male and female patients according to GOLD stages with and without Covid

GOLD stages as per severity of COPD	**Percentage of Males**		**Percentage of Females**	
	Covid (n=26)	Non Covid (n=27)	Covid (n=30)	Non Covid (n=26)
Stage I (FEV1 ≥ 80% predicted)	15.38	29.6	16.66	26.92
Stage II (50% ≤ FEV1 < 80% predicted)	61.5	51.85	60	57.69
Stage III (30% ≤ FEV1 < 50% predicted)	15.38	18.51	16.66	11.53
Stage IV (FEV1 ≤ 30% predicted)	7.69	0	6.66	3.84

Table 3: GOLD stages II and III showing significant changes with 4 year survival rate in male and female patients with and without Covid -19.

GOLD stages	4 year survival rate	Males Mean±sd	Females Mean±sd	P value (Un paired t test)
Stage II (Covid -19)	67 %	16.23± 4.55	10.54±2.57	0.0001
	57 %	10.21±3.55	20.52±6.424	0.0001
Stage II (Non Covid -19)	67 %	10.25±1.254	11.574±3.54	0.0114
	57 %	7.56±2.254	9.247±2.34	0.0002
Stage III (Covid -19)	67 %	4.25±1.34	6.42±2.217	0.0001
	57 %	4.35±1.52	2.69±0.584	0.0001
Stage III (Non Covid -19)	67 %	3.87±2.38	2.54±1.75	0.0136
	57 %	2.56±1.254	3.54±1.58	0.0005

Figure 1: Representation of male and female COPD patients with Covid difficulties and other comorbidities.

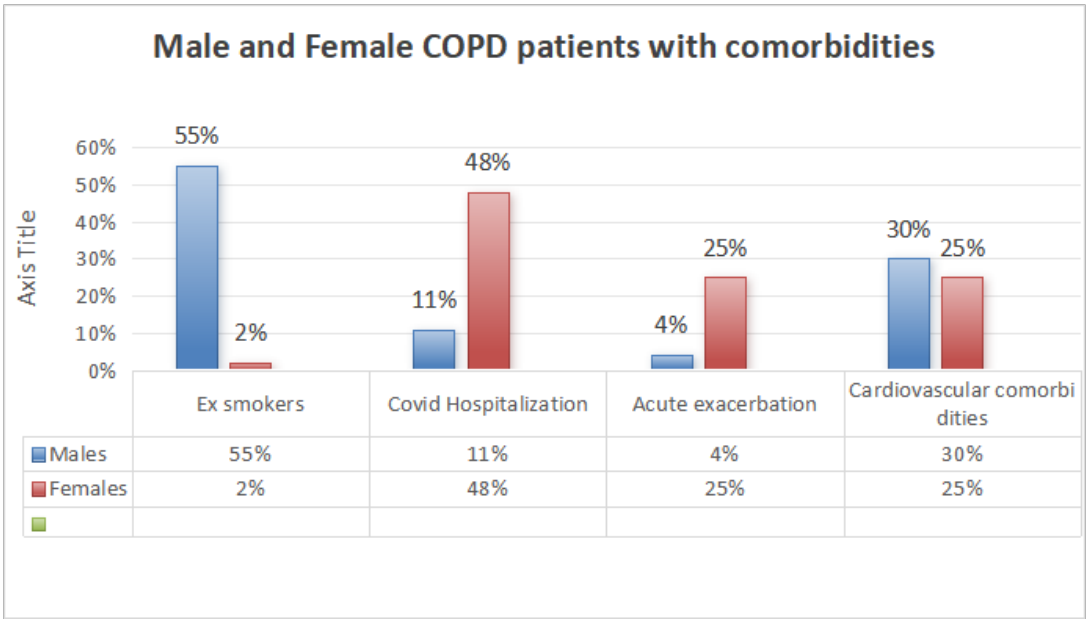
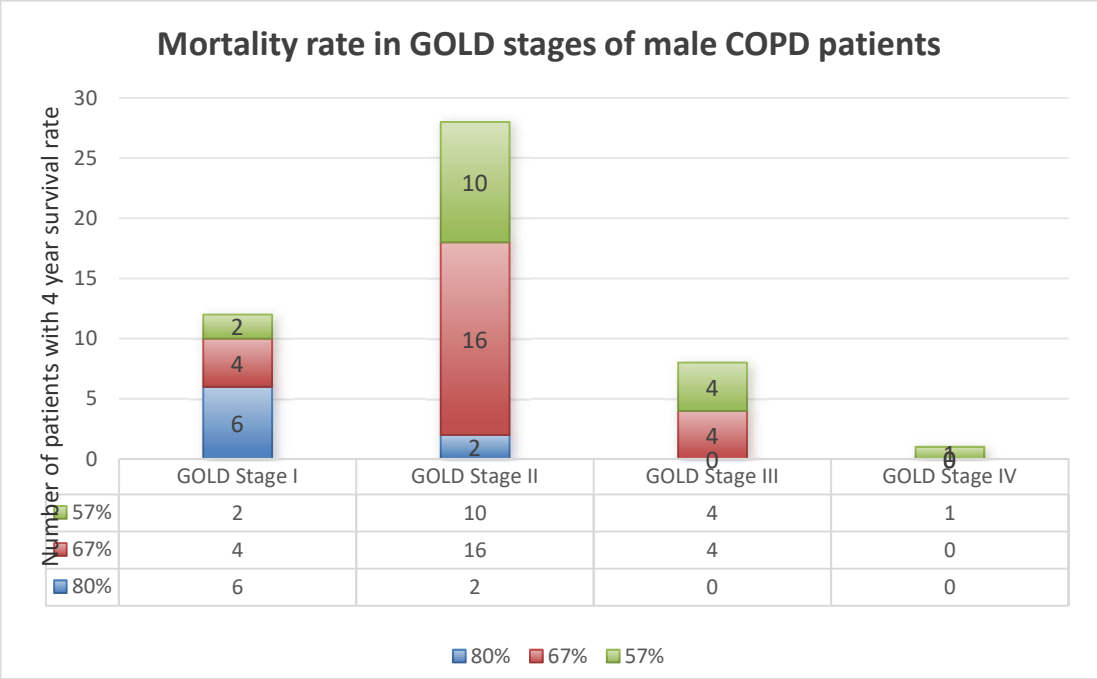
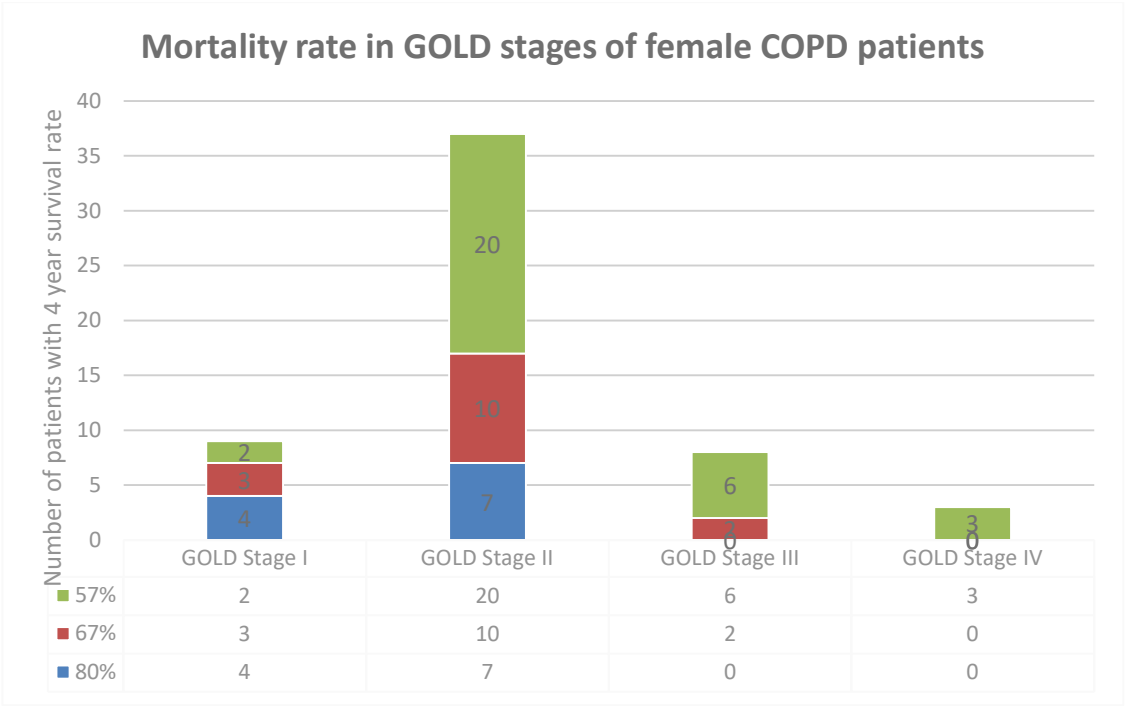


Figure 2: Mortality rate in male COPD patients with Covid -19, categorized according to GOLD stages by approximating four year survival rate based on BODE index point score



* Color grids shows the percentage of four year survival rate

Figure 3 : Mortality rate in female COPD patients with Covid -19, categorized according to GOLD stages by approximating four year survival rate based on BODE index point score



* Color grids shows the percentage of four year survival rate