Cardiovascular comorbidities and clinical outcomes in a cohort of adults with COPD in Jos, Nigeria: A prospective analytical study

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Abstract

Background: Chronic obstructive pulmonary disease (COPD) is a significant contributor to morbidity and mortality worldwide. Cardiovascular diseases (CVD) are a leading but under-recognized cause of morbidity and mortality among persons with COPD. This is concerning and highlights the need for more studies and awareness, particularly in resource-limited settings.

Methods: This prospective cohort study involved 82 eligible adults with spirometry-confirmed COPD enrolled consecutively at Jos University Teaching Hospital (JUTH). Each participant underwent a medical history review, physical examination and relevant investigations. Each was followed up for 450 days through monthly clinic visits and phone calls. Clinical outcomes (cardiopulmonary-related hospitalizations and deaths) were recorded. Data was analyzed using Epi-Info version 7.2 and Stata version 13.

Results: About 67.1% (55) had comorbid cardiovascular disease. The common CVD found were pulmonary hypertension (45.5%, 37), arrhythmias (40.0%, 33), systemic hypertension (38.2%, 31), and heart failure (30.9%, 25) among others. CVD comorbidity was significantly associated with COPD progression (p=0.047), higher 450-day hospitalization rate and duration (p=0.015 and 0.050); and mortality rate (p=0.029). Kaplan-Meier analysis showed a significant statistical difference in time to first hospitalization (p<0.085), duration of hospitalization (p=0.013), and time to mortality (p<0.085) over 450 days in participants with CVD compared to those without, Cox proportional hazard analysis further showed that those with CVD had a risk of 253% for hospitalization and 230% for mortality over 450 days.

Conclusion: Cardiovascular comorbidities are common in patients with COPD. They are important determinants of morbidity, hospitalization and mortality. Early diagnosis and management will significantly reduce morbidity and mortality in these patients.

Keywords: Chronic obstructive pulmonary disease (COPD), Cardiovascular disease, Comorbidities, Clinical outcomes, Hospitalization, Mortality.

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Introduction

Chronic obstructive pulmonary disease (COPD) is defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD 2024) as a heterogeneous lung condition characterized by chronic respiratory symptoms (dyspnoea, cough, expectoration and exacerbations) due to abnormalities of the airways (bronchitis, bronchiolitis) and alveoli (emphysema) that cause persistent, often progressive airflow obstruction. a progressive but treatable airflow limitation disorder associated with enhanced inflammation in the airways and lungs.[1] Globally, COPD is the fourth leading cause of death, and it is projected to become the third leading cause by 2030.[2] The prevalence of COPD has been steadily increasing and currently stands at 1% across all age groups, 10% for those above 40 years, and as much as 20% for those above 70 years.[1-6] This increase is more significant in sub-Saharan Africa, especially in Nigeria, where the disease is often underdiagnosed.[4-6] According to the BOLD study, the prevalence of COPD in Nigeria is estimated at 7.7% for adults above 40 years. This alarming trend is attributed to the growing epidemic of smoking and environmental air pollution and an aging global population.[1-6]

Despite being defined by abnormal spirometry, COPD is more than just a respiratory ailment. It has a significant impact beyond the lungs, leading to extra-pulmonary consequences and co-morbidities.[7-11] Research shows that co-morbidities are common in COPD patients, with about two-thirds of them having one or two co-morbidities, and one-third having at least three. Common co-morbidities associated with COPD include CVDs (such as arterial hypertension, coronary artery disease, and heart failure), respiratory infections, lung cancer, diabetes mellitus, and osteoporosis. These co-morbidities are major determinants of health status, health expenditure, and prognosis in patients with COPD, and are linked to increased morbidity and mortality.[7-11] Studies suggest that a significant proportion of mortality in COPD (around 70%) is attributable to co-morbidities, with CVDs alone accounting for about 50%.[18-20] Furthermore, CVDs are reported to occur with varying degrees of airflow limitation, which is the hallmark of COPD.[21-27] This association can be explained by shared risk factors and pathophysiologic interactions,

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such that either may precede the other and manifest at any point in a spectrum manner.[22,23,25] Forced expiratory volume in one second (FEV1) is also a significant contributor, alongside smoking, hypertension, and dyslipidemia, as a predictor of all-cause and cardiovascular mortality in the general population.[1,2,27-29] Thus, the likelihood of cardiovascular morbidity and mortality increases with worsening FEV1, with the rate of FEV1 loss independently predicting mortality.[21-27] In real-world situations, the evidence suggests that COPD and cardiovascular diseases commonly co-exist.[7-9,12,21,22,30-33] Failure to identify comorbid cardiovascular diseases in COPD by clinicians and provide appropriate management can have implications for the well-being of the patients. Improved understanding of the association can help predict and manage risk in patients with COPD and comorbid CVD, improving their quality of life and reducing morbidity and mortality.[13,29]

Finally, COPD complexity and mortality are increased by co-morbidities and have the potential to have a devastating impact on the individual and society.[7-13,30-34] This underlines the necessity for greater awareness among patients, clinicians and the public, as well as adequate planning on the part of health authorities. Studies looking into the burden of CVD and its impact on clinical outcomes in COPD are few in Africa. This study sought to provide information to fill part of this gap.

Method

Study site and population:

The study was conducted at Jos University Teaching Hospital's (JUTH) medical outpatient clinic in Plateau State, Nigeria. The study population are adult clients diagnosed with COPD and receiving care at the clinic.

Inclusion and exclusion criteria:

Enrolment criteria included adults with confirmed COPD by spirometry, excluding pregnant or postpartum persons, those with acute illnesses and severe psychiatric illnesses.

Study design:

This was a hospital-based cohort study carried out from March 2015 to June 2016.

Sample size estimation:

This was a convenient sampling of all eligible and consenting patients. Eighty-two participants were enrolled in the study.

Study procedure:

Pretest of data collection instrument

A structured interviewer-administered questionnaire was developed to collect relevant sociodemographic and clinical data. The questionnaire was pretested on ten patients two weeks before the commencement of the study. It was repeated a week later to determine the degree of reproducibility and concordance and this was found to be nearly 100% in all cases.

Data collection

Each participant was interviewed to obtain relevant demographic and clinical history. Anthropometric and cardiovascular examinations were performed according to standard recommendations and findings documented.[35] Serum lipid profile, fasting plasma glucose, serum creatinine, and uric acid assessments were done and the glomerular filtration rate was estimated. Each participant was followed up at monthly clinic visits and phone calls for 450 days (15 months) and health-related outcomes of interest (cardiopulmonary-related hospitalizations and mortality) were documented.

Electrocardiography

Each participant had twelve lead electrocardiography done using General Electric Medical Systems Information Technologies MAC 1200 ST v.1.2 electrocardiograph machine and interpretation done according to standard definitions.[36]

Echocardiography

Echocardiography was done according to the American Society of Echocardiography guidelines using a General Electric Logic 5 Expert echocardiography machine.[37] "This was done by the investigator and peer-reviewed by a competent colleague blinded to the study, a third colleague acted as arbiter whenever necessary". Specifically, the right and left ventricular diameters and functions were assessed in 2-dimensional, M-modes and by Doppler in addition to pulmonary artery systolic pressure. Diastolic measurements were taken at the peak of the R wave while systolic measurements at the peak of the T wave. The ejection fraction (EF) and fractional shortening (FS) were taken as measures of systolic function. Diastolic function was evaluated by studying the filling dynamics of the left ventricle by assessing the trans-mitral "E" wave velocity (peak early mitral inflow velocity) and the "A" wave velocity (peak atrial mitral inflow velocity). The E/A ratio, E-wave deceleration time (DT) and Isovolumic relaxation time (IVRT) were taken as measures of diastolic function. The average of measurements in three cardiac cycles was taken with simultaneous electrocardiograph recording.

Definition of Terms

COPD was defined and classified according to the GOLD guidelines.[1,2]

Post Bronchodilator FEV1 in individuals with FEV1/Forced Vital Capacity (FVC) < 0.70:
GOLD 1: Mild FEV1 ≤80% Predicted
GOLD 2: Moderate FEV1 ≤50% to ≤80% Predicted
GOLD 3: Severe FEV1 ≤30% to ≤50% Predicted
GOLD 4: Very Severe FEV1 < 30% Predicted
Cardiovascular comorbidity was defined as a clinical diagnosis of a specific cardiovascular disease supported by findings from physical examination, electro-cardiography, and echocardiography.[38-41]

Statistical analysis:
Data was entered into a Microsoft Office Excel 2007 spreadsheet and analyzed using CDC Epi-Info statistical software version 7.2 and Stata statistical software version 13. Quantitative variables were summarised using mean and standard deviation (SD). Categorical variables were expressed using frequencies and percentages. The student t–test or non-parametric Mann-Whitney/ Kruskal-Wallis tests were used to compare uniformly and non-uniformly distributed quantitative data respectively (FEV1%, FEV1/FVC). The Chi-Square (X^2) test was used to test the significance of association between categorical variables (sociodemographic and clinical data). Fisher exact test was used where the frequency of a cell was <5. Linear regression analysis was used to determine the association between COPD parameters (FEV1, FEV1/FVC) and CVD comorbidity, hospitalization and mortality. Kaplan-Meier survival analysis for time to first admission and mortality were done with COPD/CVD and COPD as separate groups. Cox proportional hazard analysis was also done for hospitalization and mortality. Significance was defined as P-value < 0.05 in all cases.

Ethical consideration:
The ethical approval for the study was obtained from the Health Research Ethics Committee of JUTH (JUTH/DCS/ADM/127/XIX/5989). The nature of the study was explained in detail to each participant in the language they best understood. The researchers explained the study's nature and objectives to participants in their preferred language and obtained informed consent through signature or thumbprint. Participants were at liberty to withdraw from the study at any stage without consequence and information obtained was treated as confidential.

Results:
General characteristics of the study participants:
A total of 82 participants with spirometry-confirmed COPD were enrolled in the study, table 1. There were 39 males and 43 females. The mean age for males was 61±10 years while that of females was 60±9 years (p=0.971).

Prevalence of CVD and CVD risk factors:
Fifty-five (67.1%) of the participants had co-morbid CVD, (p<0.001). There was a statistically significant difference in the mean ages of those with CVD compared to those without (p=0.015) and also in the GOLD stages (p=0.047). The FEV1 % predicted was significantly lower in the COPD/CVD group (p<0.001). Biomass exposure was the most common risk factor for COPD (p=0.18), those with CVD had a higher smoking history although the difference was not significant (p=0.075).

Table 1: Socio-demographic and clinical characteristics of the study population

Variable	COPD/CVD$^+$	COPD/CVD$^-$	P values
Total (%)	55 (67.1%)	27 (32.9%)	<0.001
Gender			
Female	28 (50.9%)	15 (55.6%)	0.692
Male	27 (49.1%)	12 (44.4%)	
Age groups			
40-49	8 (14.6%)	5 (18.5%)	0.048
50-59	12 (21.8%)	14 (51.9%)	
60-69	22 (40.0%)	5 (18.5%)	
70-79	11 (20.0%)	3 (11.1%)	
80-89	2 (3.6%)	0 (0.0%)	
Age (mean±SD)	62 ± 10	57 ± 8	0.015
Body Mass Index	28.0 ± 6.0	26.3±3.3	0.320
Lung function			
FEV1%	48 (48.8±14.8)	70 (67.2±11.1)	<0.001
FVC%	67 (68.5±14.9)	76 (76.1±11.8)	0.105
FEV1/FVC	57.9±8.7	64.1±4.4	0.015
Risk factors			
Smoking History	14 (25.4%)	2 (7.4%)	0.075
Biomass Exposure	41 (74.6%)	15 (55.6%)	0.138
Alchohol	20 (36.4%)	3 (11.1%)	0.019
Associations			
Overweight/Obesity	32 (58.2%)	16 (59.2%)	0.999
Dyslipidemia	36 (65.5%)	8 (29.6%)	0.005
Hyperuricemia	26 (47.3%)	8 (29.6%)	0.199
Diabetes Mellitus	8 (14.5%)	0 (0.0%)	0.028

COPD/CVD: COPD with CVD comorbidity, P- (student t-test or non-parametric Mann-Whitney/Kruskal-Wallis test)

Outcomes:
The clinical outcomes in the study population after 450 days (15 months) are shown in Table 2. Those with CVD had statistically significantly higher rates for cardiopulmonary-related hospitalizations in the number hospitalized, duration of hospitalization and duration to first hospitalization, p=0.0015, 0.044, 0.05 and 0.027 respectively. A similar trend was observed for the number of cardio-pulmonary related mortalities and duration to mortality with p-values of 0.029 and <0.010 respectively.

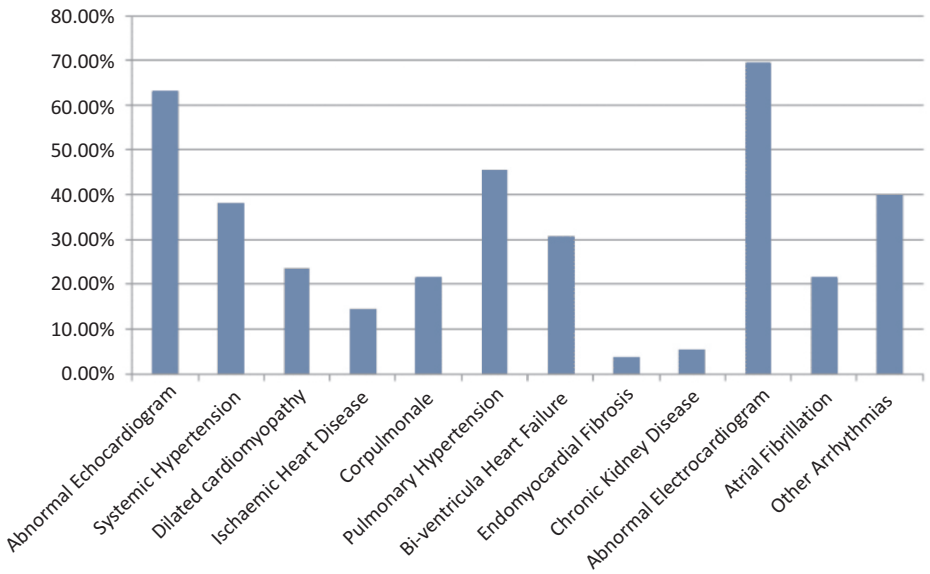


Figure 1: Burden of cardiovascular co-morbidities in the study population

Figure 1 shows the prevalence of specific CVD co-morbidities. The majority had an abnormal electrocardiogram (68.3%) and echocardiogram (63.4%). Pulmonary hypertension (46.3%) was the most common distinct CVD followed by arrhythmias (39.1%) e.g., atrial fibrillation (23.2%) and systemic hypertension (37.8%) among others.

Table 2: Clinical outcomes in the study population after 450 days of follow-up

Outcomes	COPD/CVD	COPD	P-values
Number Hospitalized	26 (47.3%)	5 (18,5%)	0.015
Number with >1 Hospitalization	15 (27.2%)	2 (7.4%)	0.044
Duration of Hospitalization (days)	9 (2 - 15)	6 (1 - 9)	0.046
Duration to First Hospitalization (days)	177 (41 - 321)	307 (64 - 408)	0.027
Number of Mortality	13 (23.6%)	1 (3.7%)	0.029
Duration to Mortality (days)	127 (105 - 255)	>321	<0.001

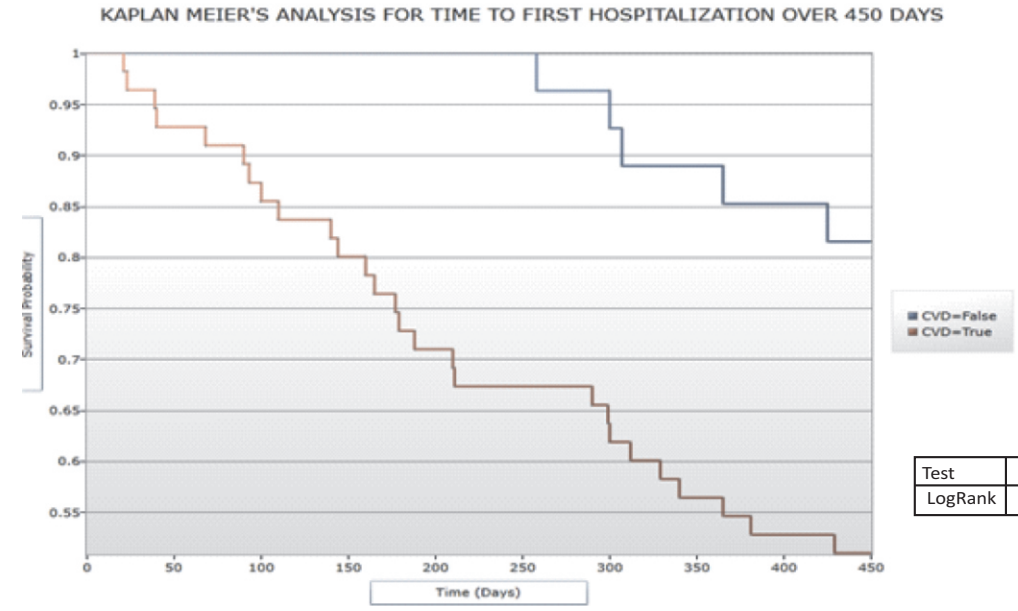
COPD/CVD: COPD with CVD comorbidity, P- (student t-test or non-parametric Mann-Whitney/Kruskal-Wallis test)

Association between COPD, CVD and Outcomes:

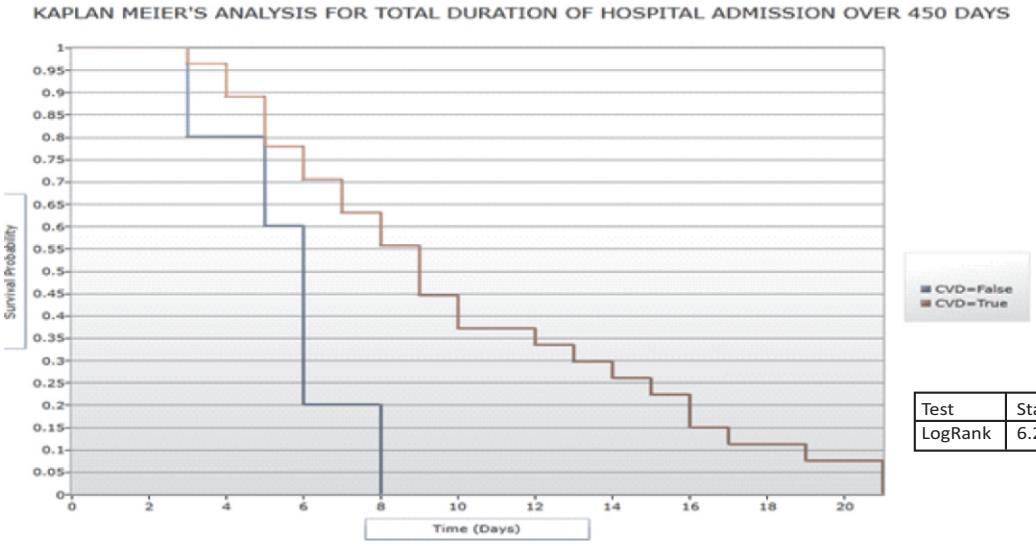
Table 3 shows the linear regression analysis for selected factors with CVD, hospitalization and mortality. For CVD co-morbidity, the relationships with FEV1 and COPD stages 3-4 were statistically significant with moderate strength of association. For hospitalization, the relationships with CVD and FEV1 predicted were statistically significant with moderate strength of association. For mortality, the relationships with age, CVD and FEV1 predicted were statistically significant with moderate strength of association. Kaplan Meier's analysis of outcomes over 450 days is shown in Figure 2. Those with CVD had a significantly lower time to the first hospitalization, higher total duration of hospitalization and lower time to mortality. Cox proportional hazard analysis of outcomes over 450 days is shown in table 4. Compared to those without CVD, those with CVD group have a 253% risk of hospitalization and 230% risk of mortality.

Table 3: Linear regression analysis of selected factors with CVD co-morbidity, hospitalization and mortality in the study population

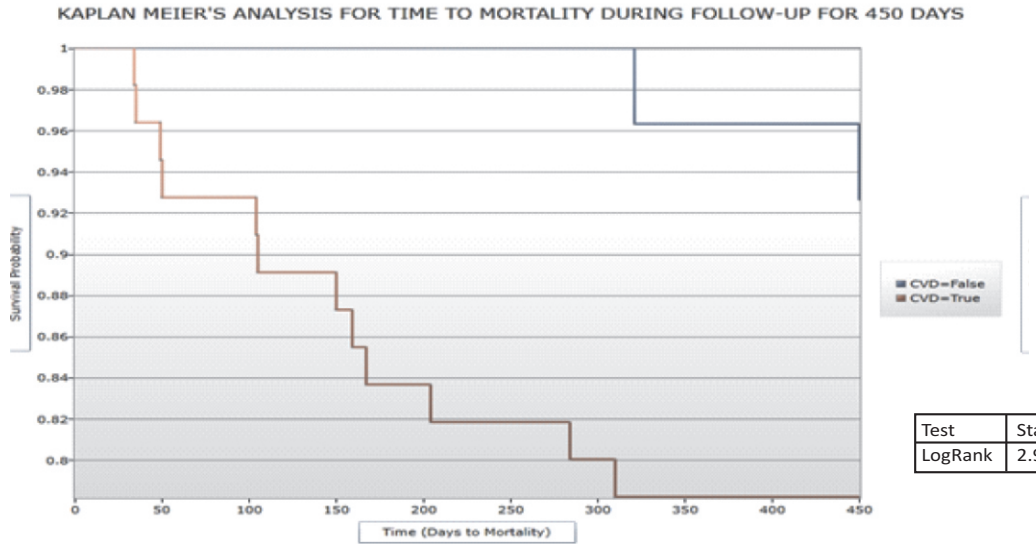
Variables (COPD)	Regression Coefficient	Correlation Coefficient (r^2)	P-value
CVD comorbidity			
Age	0.01	0.04	0.092
FEV1 predicted	-0.01	0.19	<0.001
FEV1/FVC	-0.01	0.04	0.088
COPD 3/4	0.23	0.09	0.005
Hospitalization			
Age	0.01	0.00	0.586
FEV1 predicted	-0.02	0.19	<0.001
FEV1/FVC	-0.01	0.04	0.063
CVD Comorbidity	0.18	0.06	0.013
Mortality			
Age	0.01	0.05	0.038
FEV1 predicted	-0.01	0.15	<0.001
FEV1/FVC	-0.01	0.04	0.063
CVD comorbidity	0.18	0.06	0.013



Test	Statistic	DF	P value
LogRank	7.2567	1	0.085



Test	Statistic	DF	P value
LogRank	6.2398	1	0.013



Test	Statistic	DF	P value
LogRank	2.9536	1	0.085

Figure 2: Kaplan Meier's analysis of outcomes in the study population

Table 4: Cox proportional hazard analysis of hospitalization and mortality in the study population

COPD/CVD versus COPD	Hazard Ratio	95%C.I	P-value
Hospitalization	3.534	1.359 - 9.187	0.010
Mortality	3.296	1.102 - 8.856	0.025

COPD/CVD: COPD with CVD comorbidity

Discussion

Sociodemographic and clinical characteristics of the study participants

Recent studies indicate a growing prevalence of COPD, particularly in sub-Saharan Africa, with changing sociodemographic patterns and clinical presentations.[1-6,30,34] Reports suggest that the disease is affecting a younger age group, more females, and more rural dwellers, with biomass exposure emerging as a predominant risk factor rather than smoking.[1-6,30,34] The sociodemographic characteristics of the population in this study reflect this trend. In this study, the predominant risk factor for COPD was found to be exposure to biomass, which is different from smoking, the predominant risk factor in developed nations.[1-6,30,34,42-44] This trend is attributed to increasing indoor/outdoor air pollution, epidemiologic transition, certain genetic changes, and other factors. A significant proportion of the study participants were classified as having GOLD stages 3-4, and a significant association was reported with increased CVD burden. Participants with comorbid CVD had significantly lower levels of FEV1 and FEV1/FVC. This is consistent with findings in similar studies across the globe where CVD has been linked to varying degrees of reduction in FEV1% and FVC% levels and COPD progression.[7-15,42,43,47] Some researchers now recommend that FEV1% and FVC% should be considered as established risk factors for CVD, independent of COPD diagnosis.[20-23,45-47] In terms of risk factors for COPD, this study showed an association between a history of smoking, exposure to biomass and an increased burden of comorbid CVD. Smoking and exposure to biomass are both risk factors for COPD and CVD. However, smoking poses a greater risk than exposure to biomass. Nonetheless, exposure to biomass is becoming a leading cause of COPD, especially in Sub-Saharan Africa (SSA). Some authors have reported the predilection of occurrence of some CVD in those who smoke than in those exposed to biomass and vice versa.[4-12,42-45] Patients with COPD who were exposed to biomass were more likely to develop congestive heart failure, atrial fibrillation and diabetes mellitus than those who smoked. On the other hand, smoking was found to be a stronger factor in the development of ischaemic heart disease and peripheral vascular disease than exposure to biomass. This suggests that the effects of exposure to biomass and smoking on the health of COPD patients may differ and should be taken into account when assessing their risk factors.[44] Findings in this study showed a predisposition of those with comorbid CVD to have a history of significant alcohol intake, dyslipidemia, hyperuricemia, and diabetes mellitus. Those with COPD alone had the predisposition to be obese. These findings are consistent with other similar studies.[20-23,45-47] The reason for this trend is that the risk factors of COPD and CVD are the same, and they exert their influence in a cause-and-effect way. The noxious substances found in tobacco and biomass cause chronic pulmonary and systemic inflammation with oxidative stress, which predisposes to a negative metabolic balance with consequent development of cardio-metabolic diseases.[20-23,45-47]

Cardiovascular comorbidities in COPD

Approximately 7 out of every 10 participants in this study had both COPD and CVD, with a slightly higher occurrence in males at 69.2% compared to 65.1% in females. This trend is consistent with findings from similar studies.[7-17,47-50] Reports indicate that COPD patients with comorbid CVD in Africa experience higher morbidity and mortality rates than Caucasians, possibly due to limited resources and clinician awareness.[1-3,7-17] As expected, a significant proportion of the study participants had abnormal electrocardiograms (69.5%) and echocardiograms (63.3%). These abnormalities can occur early, even in asymptomatic patients, due to shared risk factors and pathophysiologic mechanisms between the respiratory and cardiovascular systems.[1-3,7-17,45-50] They are considered early markers of CVD and poor prognostic factors. The most common CVD comorbidities identified in this study were pulmonary hypertension (45.5%), arrhythmias (40%), systemic hypertension (38.2%), bi-ventricular heart failure (30.9%), dilated cardiomyopathy (23.6%), corpulmonale (21.8%), atrial fibrillation (21.8%), ischaemic heart disease (14.5%), chronic kidney disease (5.5%) and endomyocardial fibrosis (3.6%). Previous studies have found that the pattern of comorbid CVD varies depending on location.[1-3,7-17,45-50] In Caucasians, the predominant CVD comorbidities are ischaemic heart disease, systemic hypertension, atrial fibrillation and heart failure while it is more diverse among Africans. This diversity may be due to factors such as the prevalence of biomass as a risk factor, epidemiologic transition, the high burden of infectious diseases and parasitic infestations, genetic predisposition to excessive chronic inflammatory stress and oxidative stress found in Africans among other factors.[11-14,16-37,45-50]

Clinical outcomes in COPD

According to the literature, patients with COPD who have comorbidities of CVD experience poor clinical

outcomes. The results of this study are in line with the literature. After a follow-up of 450 days, significant statistical differences were found between participants with and without CVD in terms of the number of hospitalizations, duration of hospitalization, time taken to first hospitalization, number of mortalities, and time taken to mortality. CVD is one of the leading causes of morbidity and is responsible for over 50% of the mortality in patients with COPD. Over 15 months, the hospitalization rate was 47.3% versus 18.5%, the mortality rate was 23.6% versus 3.7% and the average life expectancy was 127 days versus >321 days respectively in the subgroup with CVD compared to those without. From this, it is inferred that CVD comorbidity significantly worsens all levels of clinical outcomes in patients with COPD, particularly in those of African origin for multiple reasons.[1-3,12] In addition, comorbidities are the rule rather than the exception in COPD.[7,11,12,18-20,31] These co-morbidities are responsible for about 70% of the mortality caused by COPD with CVD accounting for at least 50% of the mortality in COPD.[7,11,12,18-20,31] Sidney et al reported a more than twofold increased risk for CVD-related hospitalization and mortality in patients with COPD compared with those without.[31] The observed association between COPD and CVD may be explained, at least in part, by shared risk factors and complex pathophysiologic interactions among other reasons.[22,23, 42-47]

Factors associated with and predictors of CVD in COPD:

The findings of this study show that there is a significant association between exposure to biomass, reduction in FEV1% and FEV1/FVC% ratio, and COPD GOLD stage 3/4 with an increased burden of CVD comorbidity. This means that the severity of CVD comorbidity worsens as the COPD stage increases, and reduction in FEV1% and FEV1/FVC% ratio are important determinants of CVD comorbidity in COPD patients.[7-15,42,43,47] Similar findings were obtained when factors affecting hospitalization and mortality were analyzed. It's been observed that the likelihood of cardiovascular morbidity and mortality increases with worsening FEV1, and the rate of FEV1 loss independently predicts mortality.[7-15,42,43,47] FEV1 is ranked second to smoking and above blood pressure and cholesterol as a predictor of all-cause and cardiovascular mortality.[27-29] The co-existence of COPD and CVD has serious implications for the management of these patients, and understanding their association may enable improved risk prediction and targeted therapies for patients at a higher risk of CVD. Overall, the high prevalence of CVD in COPD patients underscores the need for greater physician awareness and appropriate management.

Conclusion

Cardiovascular comorbidities are common in patients with COPD in our environment. They adversely affect morbidity, hospitalization rates, prognosis and mortality. It is recommended that patients with COPD be routinely evaluated for cardiovascular comorbidities and managed accordingly. This will significantly reduce morbidity and mortality in the patients.

Limitations: The study is limited because it is a single centre hospital-based study with limited numbers and findings may not be generalizable across different populations.

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