Echocardiographic Findings of Left Ventricular Function of Chronic Obstructive Pulmonary Disease (COPD) Outpatients in a Tertiary Training Hospital in Tacloban City

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ABSTRACT

The recent understanding of COPD has advanced from being a primarily lung disease to a systemic illness with extra-pulmonary manifestations including cardiovascular disease. Besides right-sided heart failure, there is increasing evidence that left ventricular dysfunction may also develop as a consequence of COPD. The present study identified the echocardiographic findings of left ventricular function of COPD patients at the Divine Word Hospital Outpatient Department. Thirty-seven stable outpatients who had confirmed COPD by post-bronchodilation spirometry were included in this exploratory cross-sectional analytical study. The participants then underwent 2D echocardiography. Of the 37 participants, 59.46% were found to have normal LV systolic function but with evidence of LV diastolic dysfunction. GOLD class 2 and class 3 participants (moderate to severe airflow limitation) were more likely to have LV diastolic dysfunction compared to GOLD class 1 (*OR* of 2.25 and 1.60 respectively). GOLD class 2 participants were also more likely to have abnormal LV geometry (*OR* 1.69) than GOLD class 1. In conclusion, echocardiographic evidence of unrecognized heart failure, with preserved ejection fraction (HFpEF) in particular, was observed in more than half of the participants.

CHAPTER 1

INTRODUCTION

A. Background of the Study

COPD is currently the third leading cause of death worldwide in 2019 (WHO, 2022). The breathlessness associated with COPD has considerable impact on the quality of life of patients. In a study on the burden of obstructive lung disease in the Philippines, the prevalence of COPD in a rural community was at least 20.8% for GOLD stage I and at least 16.7% for GOLD stage II (Idolor et al., 2011).

COPD is a well-recognized common co-morbid condition among patients with other illnesses. Besides the understanding that it is a primarily lung disease, COPD has also recently been understood as a systemic illness in itself with extra-pulmonary manifestations such as unintentional weight loss, skeletal muscle dysfunction, osteoporosis, depression, and an increased risk of cardiovascular disease (Agusti et al., 2008). The forced expiratory volume in 1 second (FEV1) by spirometry is the standard determinant of COPD severity. In one recent study, deteriorated FEV1 levels have also been shown to be associated with presence of impaired left ventricular (LV) function (Heidorn et al., 2022). Beta-blockers play a central role in the management of LV dysfunction. However, the presence of COPD has been found to be the reason for beta-blocker avoidance among physicians managing patients with LV dysfunction as in heart failure with co-existing COPD. Conversely, long-acting beta2-agonist bronchodilators has also been under-prescribed among COPD patients with comorbid heart failure in the general practitioners setting (Pirina et al., 2017).

However, in the latest guidelines for the management of heart failure by the AHA/ACC/HFSA, COPD is not listed as among identified risk factors for the development of heart failure. Although the same

guidelines recognize that COPD is among the co-occurring chronic conditions among health insurance beneficiaries with heart failure (2022 AHA/ACC/HFSA Heart Failure Guidelines). Cardiovascular diseases remain to be under-recognized and under-treated among COPD patients despite current evidence indicating the increased risks for cardiovascular diseases among COPD patients (Morgan et al., 2017).

To augment the current understanding between COPD and cardiac function, this present study is developed to examine the LV function using echocardiography of stable COPD patients in relation to the GOLD classification of severity of airflow limitation.

B. Research Question

What are the echocardiographic findings of LV function of COPD patients at Divine Word Hospital Outpatient Department?

C. Significance of the Study

This study shall primarily provide local data on the echocardiographic findings of LV function in COPD in the Philippine setting. At the time of writing, there has been no published article that provided data on the subject. In particular, results of this study shall be of importance to the following stakeholders:

1. To the clinicians, the study shall provide basis for decision-making in screening for cardiac abnormalities, such as signs of heart failure, among COPD patients with or without overt cardiovascular diseases.

2. To healthcare policymakers, the study shall provide local data on the echocardiographic findings of LV function among COPD patients which may form basis for future revisions of existing or development of new guidelines in the management of COPD in the country.
3. To local researchers, the study shall provide local data for future local studies on cardiovascular diseases among Filipino COPD patients.
4. To international researchers, the study shall provide data on the echocardiographic findings of LV function among COPD patients with Filipino ethnicity residing in their country of origin.
5. To the community, the results of the study may serve as basis in developing programs for health promotion among at-risk population for COPD and disease prevention among COPD patients from developing overt cardiovascular diseases.

D. Scope and Limitations of the Study

This study shall investigate on the echocardiographic findings of LV function using the Ejection Fraction, Diastolic Dysfunction Grade, Mitral E Velocity, Mitral e', Mitral E/e' Ratio, LA Volume Index, and TR Jet (Pulmonary Artery Pressure) and LV geometry as parameters, among COPD patients seen at the Outpatient Department of Divine Word Hospital, Tacloban City. The study shall be conducted from March 1, 2022 to October 31, 2022 when Alert Level of Covid-19 Transmission was at its lowest in the city. Due to its cross-sectional design, the study shall not be able to investigate on the influence of the duration of illness on the echocardiographic findings of LV function.

E. Objectives of the Study

General Objective:

This study aims to describe the demographic profile of and the echocardiographic findings of LV function among COPD patients in the Outpatient Department of Divine Word Hospital.

Specific Objectives:

1. Describe the demographic profile of the participants in terms of:

    1.1. Age

    1.2. Sex

    1.3. Smoking history

    1.4. Exposure to non-tobacco related substances

    1.5. Respiratory symptoms

    1.6. GOLD classification of COPD severity of airflow limitation by FEV1 values

    1.7. COPD Assessment Test (CAT) score

    1.8. Modified Medical Research Council (mMRC) Dyspnea score

    1.9. Number of years since diagnosis of COPD

    1.10. Self-reported comorbidities

    1.11. History of Covid-19 infection and severity

    1.12. History of Covid-19 vaccination

    1.13. Occupation

    1.14. Present therapy

    1.15. Vital signs

    1.16. Oxygen saturation

1.17. Body Mass Index (BMI)

2. Determine the LV function of the participants using echocardiography in terms of the following parameters:

2.1. Ejection Fraction (EF)

2.2. Diastolic Dysfunction Grade

2.3. Mitral E Velocity

2.4. Mitral e'

2.5. Mitral E/e' Ratio

2.6. Left Atrial Volume Index (LAVI)

2.7. Tricuspid Regurgitation (TR) Jet (Pulmonary Artery Pressure)

2.8. Left Ventricular (LV) Geometry

3. Correlate the echocardiographic parameters of LV function with GOLD classification of severity of airflow limitation by FEV1.

F. Definition of Terms

Chronic obstructive pulmonary disease (COPD) –a heterogeneous lung condition characterized by chronic respiratory symptoms (dyspnea, cough, sputum production) due to abnormalities of the airways (bronchitis, bronchiolitis) and/or alveoli (emphysema) that cause persistent, often progressive, airflow obstruction. Based on the GOLD criteria, its diagnosis requires spirometry to confirm the presence of non-fully reversible airflow limitation as a post-bronchodilation FEV1/FVC ratio of less than 0.70.

GOLD -stands for Global Initiative for Chronic Obstructive Lung Disease (GOLD), a group of healthcare professionals that publishes and revises the clinical practice guidelines in the diagnosis, management and prevention of COPD

Spirometry -a pulmonary function test which is effort-dependent used to assess for obstructive pathophysiology as seen in COPD

FEV1 -in spirometry, it stands for forced expiratory volume in 1 second which is the amount of air that can be forced out from the lungs in one second.

FVC -in spiromtery, it stands for forced vital capacity which is the amount of air that can be forcefully expired after maximal inspiration.

FEV1/FVC ratio -a value derived from spirometry as an evidence of airway obstruction. A value of < 70% is diagnostic of obstruction.

COPD Assessment Test (CAT) score -a self-rating tool used in the stratification of severity of dyspnea in COPD

Modified Medical Research Council (mMRC) Dyspnea scale -a self-rating tool used in the stratification of severity of dyspnea in COPD

2D Echocardiography or Transthoracic Echocardiography or Echocardiography -a non-invasive ultrasound technique to visualize the heart and assess its function

Ejection Fraction -the percentage of blood pumped out of the heart in each contraction of the left ventricle. Value is derived from the formula = stroke volume divided by end-diastolic volume.

Diastolic dysfunction grade -degree of diastolic dysfunction as determined by transthoracic echocardiography. Grade I is impaired relaxation. Grade II is pseudonormalization. Grade III is reversible restrictive filling. Grade IV is irreversible restrictive filling.

Mitral E Velocity -measure of early mitral inflow velocity, expressed in m/sec

Mitral e' -measure of mitral annular early diastolic velocity, expressed in m/sec

Mitral E/e' Ratio -a measure of left ventricle filling pressures in the evaluation of diastolic dysfunction

LA Volume Index -a measure of size of the left atrium. It is derived from left atrial volume divided by body surface area, expressed in mL/m^2

TR Jet (Pulmonary Artery Pressure) -refers for tricuspid regurgitant jet method, a method in estimating pulmonary artery pressure.

CHAPTER 2

REVIEW OF RELATED LITERATURE

Chronic obstructive pulmonary disease (COPD) is a chronic disease condition characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases, particularly tobacco. Its prevalence is higher in age 40 years and above than less than 40 years and that the current trend in prevalence and mortality is a shift from male-prevalent disease in the past to an equally prevalent disease between males and females (Gold Report, 2020). It is currently the third leading cause of death worldwide, next only to ischemic heart disease and stroke (WHO, 2020). With the current classification of severity of airflow limitation using GOLD criteria, the risk of exacerbations was 17-fold for GOLD 4, 5-fold for GOLD 3, and 2-fold for GOLD 2, compared to individuals with GOLD 1 (Ingebrigtsen, 2015).

The associated morbidity in COPD increases with age however it is unclear if healthy aging still leads to COPD or if age is rather a reflection of cumulative insults to the lungs throughout life (Gold Report, 2020). In a review of recent studies on the mechanisms linking ageing and COPD, Mercado and colleagues note that increase in cellular senescence, stem cell exhaustion, increased oxidative stress, alteration in the extracellular matrix and a reduction in endogenous anti-ageing molecules and protective pathways such as autophagy have all been found in COPD (Mercado et al., 2015). Of principal importance for the present study is the discovery of cellular senescence of endothelial progenitor cells (EPC).

More than a decade ago, Asahara and colleagues are able to identify progenitor cells that differentiate into endothelial cells that localize at sites of ischemia participating in neoangiogenesis (Asahara et al., 1997). Since the discovery of these cells, the present understanding of how blood vessels

are formed and repaired has improved leading to the new concept that blood vessels are also formed by the contribution of bone marrow-derived EPCs in addition to the fully differentiated resident endothelial cells, which were thought to be the only mechanism in angiogenesis for decades (Tepper et al., 2003). Thus, EPCs are essential in maintaining endothelial integrity and in the repair process in areas of vascular damage.

However, among smokers and COPD patients, Paschalaki and colleagues have found that there is increased DNA damage and accelerated senescence of EPCs in these groups compared to healthy non-smokers and that these damaged EPCs are ineffective in repairing vascular damage and maintaining vascular integrity; which in turn, may be involved in endothelial dysfunction among COPD patients (Paschalaki et al., 2013).

As a systemic illness in itself rather than just a primarily lung disease, COPD has been found to have extra-pulmonary manifestations such as unintentional weight loss, skeletal muscle dysfunction, osteoporosis, depression, and an increased risk of cardiovascular disease (Agusti et al., 2008). The cardiovascular disease (CVD) traditionally associated with COPD has been the right ventricular failure secondary to pulmonary hypertension (Chaouat et al., 2008). However in the recent years, a number of studies have also attempted to establish association between COPD and other CVD entities, particularly left ventricular dysfunction.

Left ventricular (LV) dysfunction has been recognized in 32% of deteriorating COPD patients in one study (Render et al., 1995). Among outpatient elderly participants with stable COPD without documented heart failure, 20.5% have been found with unrecognized heart failure (Rutten et al., 2005). However in the latter study, the participants had declared comorbidities such as ischemic heart disease,

hypertension, diabetes mellitus which are also risk factors for heart failure per se. In one study, only 28.4% of COPD patients had no associated comorbidities. The median number of comorbidities was 2 per patient, with higher number of comorbidities in GOLD B and D patients. Hypertension, obstructive sleep apnea, dyslipidemia, ischemic heart disease, anxiety and depression, under-nutrition, osteoporosis, and diabetes were among the identified comorbidities (Raherison et al., 2018).

In another review on COPD and cardiac diseases, the following has been identified as the 3 most frequent cardiac comorbidities, namely: heart failure, ischemic heart disease, and atrial fibrillation. The review states that there is no evidence that heart failure with reduced ejection fraction (HFrEF) or heart failure with preserved ejection fraction (HFpEF) should be treated differently in the presence of COPD and that heart failure should be treated based on the usual guidelines. The review states that beta-blockers are under-prescribed due to perceived concerns regarding adverse effects on pulmonary function, despite clear survival benefits in HFrEF and the safety profile of cardio-selective beta-1 adrenoceptor antagonists (Roversi et al., 2016).

In a meta-analysis on the risk of cardiovascular comorbidity in COPD, Chen and colleagues have found that patients with COPD were more likely to be diagnosed with CVD, including a 2-5 times higher risk of ischemic heart disease, arrhythmia, heart failure, diseases of pulmonary circulation, and diseases of the arteries, compared to patients without COPD. There is also one-third higher risk of hypertension and diabetes in COPD patients versus non-COPD (Chen et al., 2015). In one large prospective study, the prevalence of CVDs was highest in participants with forced expiratory volume in 1 second (FEV1) < 50% in both COPD and asthma-COPD overlap, as well as higher blood pressures and higher prevalence of diabetes mellitus among the said participants (Ingebrigsten et al., 2019). The FEV1 value measured by spirometry is the standard determinant of COPD severity of airflow limitation. In another more recent study,

deteriorated FEV1 levels have also been shown to be associated with presence of impaired left ventricular (LV) function (Heidorn et al., 2022).

In a recent study on LV diastolic dysfunction and COPD, it has been found that there is a high prevalence of masked heart failure with preserved ejection fraction (HFpEF) in non-severe COPD with exertional dyspnea, free of overt cardiovascular disease (Cherneva et al., 2021). In the outpatient setting, the coexistence of COPD and chronic heart failure (CHF) has also been studied. It has been found that the prevalence of CHF among the surveyed COPD patients was 11.9%, and conversely the prevalence of COPD among known CHF patients was 31.5% (Griffo et al., 2017).

On the association between COPD and CVD as comorbid conditions, it has been recognized that patients with comorbid COPD and CVD experience high rates of morbidity, including worse quality of life, dyspnea and exercise tolerance and a higher risk for hospitalization (Rabe et al., 2018). Patients with both COPD and CHF had the highest 90-day mortality rate of 25.74% compared to patients with either COPD or CHF alone as well as when compared to patients without both diseases (Ying Dai et al., 2020).

In a study on the echocardiographic abnormalities in patients with COPD at their first hospital admission, cardiac alterations were present in 64% of patients specifically right ventricle enlargement (30%), pulmonary hypertension (19%), left ventricle (LV) enlargement (6%), LV systolic dysfunction (13%), LV diastolic impairment (12%) and left atrial dilatation (29%); the authors as well has concluded that echocardiography should be considered in the assessment of patients with clinically significant COPD considering the prognostic and therapeutic implications of cardiac comorbidity (Freixa et al., 2012). In a meta-analysis of studies on diastolic dysfunction in patients with COPD, there were no differences in left ventricular ejection fraction between COPD and non-COPD population. However, patients with COPD

were more likely to have LV diastolic dysfunction as established by echocardiographic parameters (Zhyvotovska et al., 2019).

Current recommendations on the evaluation of LV systolic function by 2D echocardiography utilizes the ejection fraction (EF) computed using the modified Simpson's rule. Normal values in males were observed to be 52-72%, whereas in females 54-74% (Lang et al, 2015). Currently recommended echocardiographic variables for identifying diastolic dysfunction are: (1.) annular e' velocity: septal e' < 7 cm/sec, (2.) lateral e' < 10 cm/sec, (3.) average E/e' ratio > 14, (4.) LA volume index > 34 mL/m^2, and peak tricuspid regurgitation (TR) velocity > 2.8 m/sec. Left ventricular diastolic function is normal if more than half of the available variables do not meet the cutoff values for identifying abnormal function. Left ventricular diastolic dysfunction is present if more than half of the available parameters meet these cutoff values (Nagueh et al., 2016). Because patients with reduced LV ejection fractions (LVEFs) also have impaired diastolic function, the evaluation has a different focus than in patients with normal LVEF (>= 50%). The main reason for evaluating diastolic function in patients with reduced EFs is to estimate LV filling pressure (Lang et al., 2015).

Even without known cardiovascular disease, COPD patients in one study were found to have significant changes in LV geometry, resulting in concentric remodeling (Pela, 2016). The more negative pleural pressures, resulting from pulmonary hyperinflation, increased LV transmural pressure augmenting LV wall stress. This increased stroke work and was suggested to be the mechanism involved in the development of increased LV mass seen in COPD patients (Smith, 2013).

While it has been evident that COPD and CVD share risk factors, predominantly smoking, two particular pathophysiological links between COPD and CVD have been identified: (1) lung hyperinflation,

which is thought to compromise cardiac function by an increased pressure in the cardiopulmonary system, right ventricular dysfunction, impaired left ventricular filling, and reduced cardiac output; and (2) systemic inflammation caused by chronic or intermittent hypoxia, which in turn are linked to development of arterial stiffness, a predictor of cardiovascular events. The authors however state that the mechanisms underlying these associations are not fully well understood. The authors also point out the limitation of recommendations offered by current guidelines for the management of CVD in COPD and that CVDs are often underdiagnosed and under-treated in COPD patients (Rabe et al., 2018).

While COPD is recognized as among the co-occurring chronic conditions in health insurance beneficiaries with heart failure, it is not listed among identified risk factors for the development of heart failure (2022 AHA/ACC/HFSA Heart Failure Guidelines). In a study on the prevalence and management of COPD and heart failure comorbidity in the general practitioners setting, only 40.1% of COPD patients with heart failure received beta-blocker therapy compared to 68% among heart failure patients who were on beta-blockers. The authors in the latter study identified the presence of COPD to be the reason for beta-blocker avoidance among physicians managing patients with LV dysfunction as in heart failure with co-existing COPD. Conversely, long-acting beta2-agonist bronchodilators were also under-prescribed among COPD patients with comorbid heart failure in the general practitioners setting (Pirina et al., 2017).

Because of the recognizable morbidity and mortality associated with COPD and CVD, the active detection and management of comorbidities in COPD has been advocated (Rabe et al., 2018). The identification of both COPD and heart failure at an early stage is considered essential in order to optimize control of both diseases and reduce their associated morbidity and mortality risks (Pirina et al., 2017).

Despite emerging evidence of its existence, the association between LV dysfunction, either systolic or diastolic, and COPD and the mechanism underlying such have not yet been fully understood and remained a subject for ongoing studies. Because of the associated links between COPD and CVD, particularly LV dysfunction and heart failure, in foreign studies, medical practitioners in the locality must also be aware of the existence of a possible similar association among Filipinos.

Locally published data on COPD and its association with CVD are limited. One particular study that looked into the disparate rates to develop COPD and CHF among Asian ethnic groups and Pacific islanders, including the Filipino race, has been conducted by foreign investigators and the setting was in Hawaii, U.S.A. In that study, the authors have investigated the transition rates from having either CHF or COPD to developing both by race or ethnicity. The authors have been able to demonstrate that there are differences in rates of progression to having both diseases among different ethnic groups which may influence the differences of the prevalence of patients with COPD and CHF (Davis et al., 2016). However, the said study has not examined the possible causes underlying the observed disparities in rates of disease progression, and that the observation was made while the subjects are outside their countries of origin with different living conditions. A connection between COPD and CVD among Filipinos in the home country is yet to be established on paper.

The breathlessness associated with COPD has considerable impact on the quality of life of patients as shown in a study on the burden of obstructive lung disease in the Philippines. It has been found that the prevalence of COPD in a rural community was at least 20.8% for GOLD stage I and at least 16.7% for GOLD stage II (Idolor et al. [BOLD Study], 2011). Because of the paucity of local data on COPD among Filipinos, considering the associated morbidity and mortality of the disease in the country, the Philippine College of Chest Physicians has designed a five-year landmark study on the profiles of COPD patients

nationwide, called the COPD Profile and Survival Study (CPASS) that started in 2016 (PNHRS, 2017). This landmark study is in its final year and nearing completion as of this writing.

As presented above, the link between COPD and CVD is slowly being established in foreign countries and in foreign population. Present data on the existence of similar associations between COPD and CVD in the Philippines among Filipinos are still limited. This present study shall utilize the common non-invasive diagnostic techniques employed in the clinical setting, 2D echocardiography and spirometry, and shall examine the evidence of association between echocardiographic findings of LV function and COPD severity among COPD patients in the outpatient setting.

CHAPTER 3

METHODOLOGY

A. Research Design

This was an exploratory cross-sectional analytical study of COPD outpatients.

B. Research Setting

The study was conducted and completed at the Divine Word Hospital (DWH), Tacloban City, Philippines. A tertiary teaching hospital, it currently has a 179-bed capacity and is duly accredited by the Philippine College of Physicians to conduct a Residency Training Program in its Department of Internal Medicine.

C. Study Sample

In order to maximize the sample size for this study, all stable outpatients referred for assessment of breathlessness and diagnosed to have COPD confirmed by spirometry during the study period, March 1, 2022 to October 31, 2022, who fulfil the inclusion criteria will make up the sample size.

D. Research Subjects

This study shall include COPD outpatients who qualify based on the following criteria:

Inclusion Criteria

Male or female

Age > 40 years old

Diagnosed with COPD using the GOLD criteria of spirometry findings of FEV1/FVC ratio < 0.70 post-bronchodilator

Exclusion Criteria

Non-COPD patients

COPD patients without spirometric confirmation of airflow limitation

E. Data Collection

A data collection form was constructed to record information utilized in this study, which included: demographic data (age, sex, smoking history, exposure to non-tobacco related substances, respiratory symptoms, GOLD classification of COPD severity of airflow limitation by FEV1 values, COPD Assessment Test (CAT) score, Modified Medical Research Council (mMRC) Dyspnea score, number of years since diagnosis of COPD, self-reported comorbidities, history of Covid-19 infection and severity, history of Covid-19 vaccination, occupation, present therapy, vital signs, oxygen saturation, body mass index (BMI)) and the echocardiograph report parameters.

Letter requesting approval of the conduct of this study and a copy of the approved research protocol were sent to the DWH Hospital Administrator, Medical Director, and Chairpersons of the Department of Internal Medicine and of the Outpatient Department.

Confirmed COPD patients visiting clinics at the Outpatient Department of DWH were invited to participate in the study. Informed consent forms were accomplished by the participants who were then interviewed for the demographic information using the data collection form. Vital signs upon interview were recorded. Participants who fulfilled the inclusion criteria underwent nasopharyngeal swabbing for

Rapid Antigen Test (RAT) for SARS-CoV2 as a precautionary measure in the Covid-19 pandemic. Only participants with negative or non-reactive RAT results qualified to participate in the study. Qualified outpatients underwent spirometry performed by a respiratory therapist. The post-bronchodilator FEV1 values were recorded in the participant's data collection form. The participants were then scheduled for 2D transthoracic echocardiography at the Cardiopulmonary Unit (CPU) of the DWH within 1 month from the day the FEV1 was measured. The study used the GE Vivid T8 echocardiography machine, which had regular calibration quarterly in a year. The echocardiogram was interpreted by a single echocardiographer who was not directly involved in the writing of this research paper. The following parameters in the echocardiogram were recorded in the data collection form:

1. Ejection Fraction
2. Diastolic Dysfunction Grade
3. Mitral E Velocity
4. Mitral e'
5. Mitral E/e' Ratio
6. LA Volume Index
7. TR Jet (Pulmonary Artery Pressure)
8. LV Geometry

F. Data Analysis

Continuous variables were summarized as means, standard deviations, and ranges. Categorical variables were presented in frequencies and percentages. LV function parameters by echocardiography were summarized as means, including 95% confidence interval estimates, and ranges by patient groups

according to COPD GOLD classification of airflow limitation severity by FEV1. In account of the small sample sizes, Kruskal-Wallis Tests were used to determine presence of statistically significant global differences between LV function parameters across different COPD GOLD classification; when found to be statistically significant, Tukey's post-hoc pairwise difference tests were used to determine which COPD GOLD classifications had different LV function parameters. LV geometry was dichotomized into normal and not normal, wherein association with COPD GOLD classification was assessed using multivariate Fisher's Exact Test and Mantel-Haenszel Test for homogeneity or equality of odds ratios with GOLD 1 (mild airflow limitation, FEV1 >= 80% predicted) COPD as reference. Likewise, 95% confidence interval estimates were computed for percentages, odds of abnormal LV geometry, and corresponding odds ratios. When a statistically significant association exists, chi-square residuals were computed to determine association patterns. Similarly, diastolic dysfunction was dichotomized to be no Doppler evidence of diastolic dysfunction and combined Grades 1 to 4 diastolic dysfunction; similar statistical approach were applied. Results of the statistical treatments were interpreted accordingly using a 5% level of significance.

CHAPTER 4

RESULTS AND DISCUSSION

RESULTS

The study had a total of 37 participants. The demographic profile of the participants is presented in Table 1, stratified by normal LV systolic and diastolic functions, normal LV systolic function but with diastolic dysfunction, and systolic LV dysfunction.

Table 1. Demographic Profiles

Baseline Characteristics of Study Population	**Normal LV systolic function and no evidence of LV diastolic dysfunction**	**Normal LV systolic function but with evidence of LV diastolic dysfunction**	**With evidence of LV systolic dysfunction**	**Total**
	14 (37.84%)	**(Diastolic Dysfunction Grade >/= 1) 22 (59.46%)**	**(Ejection Fraction < 55%) 1 (2.70%)**	**(N = 37)**
Age in years Mean (SD)	69.36 (11.39)	72.86 (9.12)	78 (--)	71.68 (9.97)
Sex				
Male, n (%)	14 (38.89%)	21 (58.33%)	1 (2.78%)	36 (97.29%)
Female, n (%)	0 (0%)	1 (100%)	0 (0%)	1 (2.70%)

Occupation, n (%)				
Farmer	3 (37.50%)	5 (62.50%)	0 (0.00%)	8 (21.62%)
Vehicle driver	3 (42.86%)	4 (57.14%)	0 (0.00%)	7 (18.91%)
Office worker	3 (37.50%)	4 (50.00%)	1 (12.5%)	8 (21.62%)
Police officer	1 (33.33%)	2 (66.67%)	0 (0.00%)	3 (8.10%)
Housekeeping	1 (50.00%)	1 (50.00%)	0 (0.00%)	2 (5.40%)
Construction worker	0 (0.00%)	2 (100.00%)	0 (0.00%)	2 (5.40%)
Civil engineer	1 (100.00%)	0 (0.00%)	0 (0.00%)	1 (2.70%)
Fire officer	0 (0.00%)	1 (100.00%)	0 (0.00%)	1 (2.70%)
Fisherman	0 (0.00%)	1 (100.00%)	0 (0.00%)	1 (2.70%)
Homemaker	0 (0.00%)	1 (100.00%)	0 (0.00%)	1 (2.70%)
Lawyer	1 (100.00%)	0 (0.00%)	0 (0.00%)	1 (2.70%)
Market vendor	1 (100.00%)	0 (0.00%)	0 (0.00%)	1 (2.70%)
Teacher	0 (0.00%)	1 (100.00%)	0 (0.00%)	1 (2.70%)
Self-reported Comorbidities				
No comorbid condition	2 (33.33%)	4 (66.67%)	0 (0.00%)	6 (16.21%)
Hypertension	12 (40.00%)	17 (56.67%)	1 (3.33%)	30 (81.08%)
Diabetes Mellitus	7 (53.85%)	5 (38.46%)	1 (7.69%)	13 (35.13%)
Dyslipidemia	6 (50.00%)	5 (41.67%)	1 (8.33%)	12 (32.43%)
Heart Failure	2 (66.67%)	1 (33.33%)	0 (0.00%)	3 (8.10%)
Coronary/Ischemic Heart Disease	1 (50.00%)	0 (0.00%)	1 (50.00%)	2 (5.40%)
Lung Cancer	0 (0.00%)	1 (100.00%)	0 (0.00%)	1 (2.70%)
PTB, on treatment	0 (0.00%)	1 (100.00%)	0 (0.00%)	1 (2.70%)
Bronchial Asthma	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0%)
Hyperthyroidism	1 (50.00%)	1 (50.00%)	0 (0.00%)	2 (5.40%)
Chronic Cerebrovascular Disease (remote stroke)	2 (100.00%)	0 (0.00%)	0 (0.00%)	2 (5.40%)
Chronic Kidney Disease (not on RRT)	4 (100.00%)	0 (0.00%)	0 (0.00%)	4 (10.81%)

Prostate Cancer	0 (0.00%)	1 (100.00%)	0 (0.00%)	1 (2.70%)
Smoking history in pack-years				
Mean (SD)	58.36 (57.92)	39.32 (33.37)	20	50.12 (49.71)
Median (Range)	37 (0 - 245)	30.5 (0, 112)		31 (0 - 245)
History of Exposure to Non-tobacco substances				
Yes, n (%)	15 (65.22%)	8 (34.78%)	0 (0.00%)	23 (62.20%)
No, n (%)	7 (50.00%)	6 (42.86%)	1 (7.14%)	14 (37.80%)
Number of years since diagnosis				
Newly diagnosed (less than 1 year)	7 (41.18%)	10 (58.82%)	0 (0.00%)	17 (45.94%)
1 year to less than 5 years	6 (35.29%)	10 (58.82%)	1 (5.89%)	17 (45.94%)
More than or equal to 5 years	1 (33.33%)	2 (66.67%)	0 (0.00%)	3 (8.10%)
Current GOLD Classification of Airflow Limitation Severity of participants				
GOLD 1 (Mild)	3 (42.86%)	3 (42.86%)	1 (14.29%)	7 (18.91%)
GOLD 2 (Moderate)	4 (30.77%)	9 (69.23%)	0 (0.00%)	13 (35.14%)
GOLD 3 (Severe)	5 (38.46%)	8 (61.54%)	0 (0.00%)	13 (35.14%)
GOLD 4 (Very Severe)	2 (50%)	2 (50%)	0 (0.00%)	4 (10.81%)
History of Covid-19 Infection				
Infected and recovered, n (%)	0 (0.00%)	6 (100.00%)	0 (0.00%)	6 (16.21%)
Asymptomatic case, n (%)	0 (0.00%)	2 (100.00%)	0 (0.00%)	2 (33.33%)
Mild case, n (%)	0 (0.00%)	1 (100.00%)	0 (0.00%)	1 (16.67%)
Moderate case, n (%)	0 (0.00%)	3 (100.00%)	0 (0.00%)	3 (50.00%)
Severe case, n (%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Critical case, n (%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
No prior infection, n (%)	14 (45.16%)	16 (51.61%)	1 (3.23%)	31 (83.78%)
Covid-19 vaccination status				

Fully Vaccinated, n (%)	11 (36.67%)	18 (60.00%)	1 (3.33%)	30 (81.08%)
Partially Vaccinated, n (%)	1 (100.00%)	0 (0.00%)	0 (0.00%)	1 (2.70%)
Not vaccinated, n (%)	2 (33.33%)	4 (66.67%)	0 (0.00%)	6 (16.21%)
Symptoms				
Chronic cough, n (%)	14 (37.84%)	22 (59.46%)	1 (2.7%)	37 (100%)
Chronic dyspnea, n (%)	12 (40%)	17 (56.67%)	1 (3.33%)	30 (81.08%)
Chronic sputum production, n (%)	1 (3.13%)	30 (93.75%)	1 (3.13%)	32 (86.48%)
Recurrent chest pain, n (%)	2 (40%)	3 (60%)	0 (0.00%)	5 (13.51%)
Recurrent paroxysmal nocturnal dyspnea, n (%)	0 (0%)	3 (100%)	0 (0.00%)	3 (8.10%)
Recurrent orthopnea, n (%)	1 (50%)	1 (50%)	0 (0.00%)	2 (5.40%)
Modified Medical Research Council Dyspnea score				
0-1	2 (50%)	2 (50%)	0 (0.00%)	4 (10.81%)
$\geq$ 2	12 (36.36%)	20 (60.61%)	1 (3.03%)	33 (89.18%)
COPD Assessment Test (CAT)				
<10	12 (40%)	17 (56.67%)	1 (3.33%)	30 (81.08%)
$\geq$ 10	2 (28.57%)	5 (71.43%)	0 (0.00%)	7 (18.91%)
Exacerbation History (exacerbation in the past year resulting in hospitalization)				
With exacerbation	2 (40%)	3 (60%)	0 (0.00%)	5 (13.51%)
No exacerbation	12 (37.5%)	19 (59.38%)	1 (3.13%)	32 (86.48%)
Present therapy				
CCB, n (%)	6 (40%)	9 (60%)	0 (0.00%)	15 (40.54%)
ACE inhibitors/ARBs, n (%)	8 (42.11%)	10 (52.63%)	1 (5.26%)	19 (51.35%)
Beta-blockers, n (%)	7 (31.82%)	14 (63.64%)	1 (4.55%)	22 (59.45%)
Diuretics, n (%)	2 (40%)	3 (60%)	0 (0.00%)	5 (13.51%)
Bronchodilators, n (%)	11 (36.67%)	18 (60%)	1 (3.33%)	30 (81.08%)

Inhaled corticosteroid/LABA combination, n (%)	4 (36.36%)	7 (63.64%)	0 (0%)	11 (29.72%)
LABA/LAMA combination, n (%)	12 (34.29%)	22 (62.86%)	1 (2.86%)	35 (94.59%)
Home oxygen therapy, n (%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Physical Examinations				
Blood pressure in mmHg				
Systolic, mean (SD)	124.55 (18.703)	117.86 (17.18)	140.00	122.43 (18.17)
Diastolic, mean (SD)	75.91 (10.98)	72.14 (9.75)	90.00	74.86 (10.70)
Heart rate in bpm, mean (SD)	84.32 (14.33)	70.29 (6.81)	69.00	78.59 (13.64)
Respiratory rate in cpm, mean (SD)	18.91 (1.151)	19.14 (1.29)	22.00	19.08 (1.28)
Temperature in ^{o}C, mean (SD)	36.71 (0.30)	36.79 (0.35)	37.00	36.74 (0.32)
Oxygen saturation by pulse oximetry (at room air), mean (SD)	96.00% (2.00%)	96.14% (1.61%)	97.00%	96.08% (1.82%)
Body Mass Index (BMI) in kg/m^2, mean (SD)	23.48 (3.94)	23.45 (3.05)	29.40	23.63 (3.65)

The mean age of the participants was found to be 71.68 (SD = 9.97), and majority of them were males (36, 97.29%). Of these, 59.46% (22) were found to have normal LV systolic function but with evidence of LV diastolic dysfunction while 37.84% (14) have normal LV systolic function and no evidence of LV diastolic dysfunction. One participant (2.7%) exhibited evidence of LV systolic dysfunction.

A large proportion were farmers (8, 21.62%) and office workers (8, 21.62%), followed by vehicle drivers (7, 18.91%) and police officers (3, 8.10%). The most common comorbidity reported were hypertension (30, 81.08%), diabetes mellitus (13, 35.13%) and dyslipidemia (12, 32.43%).

As to smoking history, the median pack-year was 31 with a range from 0 to 245 pack-years. Majority of the participants also reported exposure to non-tobacco substances (23, 62.20%).

Participants with newly diagnosed COPD (17, 45.94%) and those diagnosed from 1 to 5 years (17, 45.94%) had equal proportion, while only 8.10% (3) of the participants had been diagnosed with COPD for more than 5 years.

Based on the GOLD classification of airflow limitation, higher proportion of participants had moderate (13, 35.14%) and severe (13, 35.14%) airflow limitations, while 7 (18.91%) had mild airflow limitation. Only 10.81% (4) had very severe airflow limitation.

Of the 37 participants, only 6 (16.21%) had history of COVID-19 infection of which 3 (50%) had moderate cases while the rest had mild (1, 16.67%) and asymptomatic (2, 33.33%) infection. Majority of the participants were fully vaccinated (30, 81.08%) against COVID-19 and 1 (2.70%) was only partially vaccinated. Six (16.21%) were not vaccinated.

Common symptoms reported by the participants include chronic cough (37, 100%), chronic sputum production (32, 86.48%), and chronic dyspnea (30, 81.08%). As to the dyspnea score, majority of them had mMRC scores ≥ 2 (33, 89.18%) and CAT scores < 10 (30, 81.08%). Only few participants (5, 13.51%) reported exacerbations in the past year resulting in hospitalization.

As to the medications, majority of the participants were maintained on LABA/LAMA combination therapy (35, 94.59%), bronchodilators (30, 81.08%), beta-blockers (22, 59.45%) and ACEi/ARB (19, 51.35%).

For the vital signs, the mean systolic and diastolic BP were 122.43 mmHg (*SD* = 18.17) and 74.86 mmHg (*SD* = 10.70), respectively. The average heart rate was 78.59 bpm (SD = 13.64). The average respiratory rate was 19.08 cpm (*SD* = 1.28) and mean oxygen saturation was 96.08% (*SD* = 1.82%). The average temperature was 36.74 ^{0}C (*SD* = 0.32). Mean body mass index of the participants was 23.63 kg/m^2 (*SD* = 3.65).

Left Ventricular (LV) Function Parameters

Table 2-1 shows the summary of the echocardiographic parameters of LV function of the participants stratified by GOLD classification of airflow limitation by FEV1.

Table 2-1 Echocardiographic parameters of LV function per GOLD Classification

This table shows the participants' mean values of echocardiographic LV function parameters grouped according to GOLD classification.

GOLD Classification of Airflow Limitation Severity by FEV1 n, (%)	**Echocardiographic Parameters of LV Function** mean, (range), [95% Confidence Interval for the Mean]					
	Ejection Fraction	**Mitral E Velocity** m/sec	**Mitral e'** m/sec	**E/e' Ratio**	**LA Volume Index** mL/m^2	**TR Jet (PAP)** mmHg
Mild (FEV1>= 80% predicted) 7	63%, (30%-76%) [51%, 75%]	0.815714 (0.65-1.1) [0.69, 0.94]	0.094286, (0.06-0.12) [0.08, 0.11]	9.271429, (5.4-14.2) [6.50, 12.04]	30.66667 (21-51) [23.82, 41.61]	31 (6-58) [15.48, 46.52]

Moderate (FEV1 50-79% predicted) 13	69%, (58%-80%) [65%, 73%]	0.771538 (0.6-1.1) [0.67, 0.87]	0.095385 (0.06-0.14) [0.08, 0.11]	8.419231 (6-13.3) [6.97, 9.87]	25.23077 (14-44) [20.19, 30.27]	15.92308 (7-45) [10.27, 21.58]
Severe (FEV1 30-49% predicted) 13	67% (53%-76%) [63%, 71%]	0.789231 (0-1.2) [0.61, 0.97]	0.08 (0-0.12) [0.06, 0.10]	9.584615 (0-20) [6.88, 12.29]	23.23077 (8-45) [18.01, 28.45]	19.61538 (8-44) [14.77, 24.46]
Very Severe (FEV1< 30% predicted) 4	67% (60%-76%) [59%, 75%]	0.8 (0.7-0.9) [0.71, 0.88]	0.095 (0.07-0.12) [0.07, 0.12]	9.625 (7.5-11.6) [7.42, 11.83]	26.75 (12-52) [9.04, 44.46]	11.75 (7-22) [4.76, 18.74]
p-value **(Kruskal-Wallis Test)**	*0.8548*	*0.8292*	*0.6465*	*0.7313*	*0.2420*	*0.0798**
INTERPRETATION	No significant differences	No significant differences	No significant differences	No significant differences	No significant differences	Some evidence of (statistical) significantly higher TR Jet (PAP) among GOLD 1 participants compared to both GOLD 2 and GOLD 4 participants.

Using Kruskal-Wallis test on the parameters of LV function stratified according to their GOLD classification of airflow limitation, there was very little statistically significant findings which could be made owing to the very small sample size. Indeed, in Table 2-1, no apparent patterns emerged across

comparisons for the first 4 echocardiographic parameters presented. For LA Volume Index, while it appeared that Mild (or GOLD 1) had higher mean than the rest, the small sample size led to high uncertainties surrounding the estimates of the mean. Only with TR Jet (PAP) where some (weak) evidence of statistically significant differences was found, where clearly Mild (or GOLD 1) had the highest value. This was notably significant only at alpha (significance level) of 10%, again owing to the small sample size.

Left Ventricular (LV) Dysfunction

Table 2-2 shows the summary of the diastolic dysfunction grades among participants with normal systolic function. In this table, the single participant with evidence of systolic dysfunction (EF < 55%) was excluded in the analysis since systolic dysfunction already implies the presence of diastolic dysfunction and the presence of clinical heart failure (with reduced ejection fraction). Rather, the objective of this table is to identify association between GOLD classification of airflow limitation severity and diastolic dysfunction among participants who were not in clinical heart failure with reduced ejection fraction (HFrEF) at the time of examination. Hence, the sample size used in this table is N = 36.

In the analysis of the diastolic dysfunction grades among participants (Table 2-2), the values were dichotomized into having no evidence of diastolic dysfunction and with evidence of diastolic dysfunction (Table 2-2a). This was necessary to facilitate statistical analysis given that some of the cells had zero entries. Grades 1 to 4 diastolic dysfunction were clustered into “with evidence of diastolic dysfunction” as shown in Table 2-2a. Fisher’s Exact test was then applied.

Table 2-2 Diastolic Dysfunction

This table shows the frequency of diastolic dysfunction grade ***among participants with normal systolic function*** *as determined by echocardiography grouped according to GOLD classification.*

GOLD Classification of Severity of Airflow Limitation by FEV1 N = 36	**Diastolic Dysfunction** **N = 36**				
	No Doppler evidence of diastolic dysfunction (Grade 0)	**Grade 1 diastolic dysfunction**	**Grade 2 diastolic dysfunction**	**Grade 3 diastolic dysfunction**	**Grade 4 diastolic dysfunction**
Mild (FEV1 > = 80% predicted) 6	3	3	0	0	0
Moderate (FEV1 50-79% predicted) 13	4	9	0	0	0
Severe (FEV1 30-49% predicted) 13	5	8	0	0	0
Very Severe (FEV1 < 30% predicted) 4	2	2	0	0	0

Table 2-2a Diastolic Dysfunction

*This table shows the frequency of participants **with normal systolic function** stratified into having **no evidence of diastolic dysfunction** and **with evidence of diastolic dysfunction** on echocardiography and grouped according to GOLD classification.*

GOLD Classification of Severity of Airflow Limitation by FEV1 N = 36	**Diastolic Dysfunction** **N = 36**	
	No Doppler evidence of diastolic dysfunction (Grade 0) N (%), [95% Confidence Interval for %]	**With Doppler evidence of diastolic dysfunction (Grades 1 to 4)** N (%), [95% Confidence Interval for %]
Mild (FEV1 > = 80% predicted) 6	3 (50%) [12%, 88%]	3 (50%) [12%, 88%]
Moderate (FEV1 50-79% predicted) 13	4 (31%) [9%, 61%]	9 (69%) [39%, 91%]
Severe (FEV1 30-49% predicted) 13	5 (38%) [14%, 68%]	8 (62%) [32%, 86%]
Very Severe (FEV1 < 30% predicted) 4	2 (50%) [7%, 93%]	2 (50%) [7%, 93%]
p-value **(Fisher's Exact Test)**	*0.856*	
INTERPRETATION	No statistically significant association between GOLD Classification of Severity of Airflow Limitation by FEV1 and Diastolic Dysfunction according to normal (Grade 0) or not normal (Grades 1 to 4).	

Using the Fisher's Exact test, no statistically significant association was observed between the GOLD classification of airflow limitation severity and diastolic dysfunction.

Table 2-2b Likelihood of LV diastolic dysfunction across GOLD classification of severity of airflow limitation

This table shows the odds ratio analysis of the likelihood of having an LV diastolic dysfunction across the GOLD classification of severity of airflow limitation with GOLD 1 as the reference.

GOLD Classification of Severity of Airflow Limitation by FEV1	**Odds **of Diastolic Dysfunction*** (95% Confidence Interval)	**Odds Ratio** (95% Confidence Interval)
Mild (FEV1 > = 80% predicted) GOLD 1	1.00 (0.20, 4.95)	*Reference*
Moderate (FEV1 50-79% predicted) GOLD 2	2.25 (0.69, 7.31)	2.25 (0.28, 17.96)
Severe (FEV1 30-49% predicted) GOLD 3	1.60 (0.52, 4.89)	1.60 (0.21, 12.03)
Very Severe (FEV1 < 30% predicted) GOLD 4	1.00 (0.14, 7.10)	1.00 (0.07, 14.40)
p-value **(Mantel-Haenszel Test)** ***Test of Homogeneity (Equal Odds)***	*0.8359*	
INTERPRETATION	No statistically significant differences in odds of having (Grades 1 to 4) diastolic dysfunction across different GOLD Classification of Severity of Airflow Limitation by FEV1 with Mild (GOLD 1, FEV1 >= 80% predicted) as reference.	

Utilizing odds ratio, results showed that those participants with moderate airflow limitation (GOLD 2) were more likely to have abnormal diastolic function (or dysfunction) compared to patients with mild airflow limitation (GOLD 1) (*OR* = 2.25). Similarly, patients with severe airflow limitation (GOLD 3) were also more likely to have diastolic dysfunction compared to those with mild airflow limitation (*OR* = 1.60). On the other hand, having very severe airflow limitation (GOLD 4) did not predict diastolic function (*OR* = 1.0). This latter observation was due to very limited number of sample participants.

Left Ventricular (LV) Geometry

Table 2-3 shows the summary of the LV geometry observed in the participants. Due to the limited number of sample, the LV geometries were dichotomized into either normal or abnormal (Table 2-3a) to facilitate statistical treatment using Fisher's Exact test. Concentric remodeling, concentric left ventricular hypertrophy, eccentric left ventricular hypertrophy, dilated LV and small LV geometries were clustered into "not normal" as shown in Table 2-3a.

Table 2-3 Left Ventricular Geometry

This table shows the participants LV geometry as determined by echocardiography grouped according to GOLD classification.

GOLD Classification of Severity of Airflow Limitation by FEV1 N = 37	**LV Geometry** N = 37					
	Normal	**Concentric Remodeling**	**Concentric Left Ventricular Hypertrophy**	**Eccentric Left Ventricular Hypertrophy**	**Dilated LV**	**Small LV**
Mild (FEV1 > = 80% predicted) 7	3	1	1	1	1	0
Moderate (FEV1 50-79% predicted) 13	4	8	0	0	0	1
Severe (FEV1 30-49% predicted) 13	7	5	0	1	0	0

Very Severe (FEV1 < 30% predicted) 4	2	2	0	0	0	0

Table 2-3a Left Ventricular Geometry

*This table shows the participants LV geometry on echocardiography reclassified into **normal** and **not normal** and grouped according to GOLD classification.*

GOLD Classification of Severity of Airflow Limitation by FEV1 N = 37	**LV Geometry** N = 37	
	Normal N (%), [95% Confidence Interval for %]	**Not Normal** N (%), [95% Confidence Interval for %]
Mild (FEV1 > = 80% predicted) 7	3 (43%) [10%, 82%]	4 (57%) [18%, 90%]
Moderate (FEV1 50-79% predicted) 13	4 (31%) [9%, 61%]	9 (69%) [39%, 91%]
Severe (FEV1 30-49% predicted) 13	7 (54%) [25%, 81%]	6 (46%) [19%, 75%]
Very Severe (FEV1 < 30% predicted) 4	2 (50%) [7%, 93%]	2 (50%) [7%, 93%]
p-value **(Fisher's Exact Test)**	*0.701*	
INTERPRETATION	No statistically significant association between GOLD Classification of Severity of Airflow Limitation by FEV1 and LV Geometry according to normal or not normal.	

The Fisher's Exact test did not show significant association between GOLD classification of airflow limitation severity and LV geometries.

Table 2-3b Likelihood of abnormal LV geometry across GOLD classification of severity of airflow limitation

This table shows the odds ratio analysis of the likelihood of having an abnormal LV geometry across the GOLD classification of severity of airflow limitation with GOLD 1 as the reference.

GOLD Classification of Severity of Airflow Limitation by FEV1	**Odds **of abnormal LV Geometry*** (95% Confidence Interval)	**Odds Ratio** (95% Confidence Interval)
Mild (FEV1 > = 80% predicted) GOLD 1	1.33 (0.29, 5.96)	*Reference*
Moderate (FEV1 50-79% predicted) GOLD 2	2.25 (0.69, 7.31)	1.69 (0.24, 12.08)
Severe (FEV1 30-49% predicted) GOLD 3	0.86 (0.29, 2.55)	0.64 (0.10, 4.34)
Very Severe (FEV1 < 30% predicted) GOLD 4	1.00 (0.14, 7.10)	0.75 (0.06, 10.03)
p-value **(Mantel-Haenszel Test)** ***Test of Homogeneity (Equal Odds)***	*0.6929*	
INTERPRETATION	No statistically significant differences in odds of having abnormal LV geometry across different GOLD Classification of Severity of Airflow Limitation by FEV1 with Mild (GOLD 1, FEV1 >= 80% predicted) as reference.	

Utilizing odds ratio, results revealed that participants with moderate airflow limitation (GOLD 2) were 1.69 more likely to have abnormal LV geometry than those with mild airflow limitations (GOLD 1) only. On the other hand, participants with severe (GOLD 3) (*OR* = 0.64) and very severe (GOLD 4) (*OR* = 0.75) airflow limitations were less likely to have abnormal LV geometry compared to those with mild airflow limitations (GOLD 1). This latter observation might relate to the limited number of sample participants.

DISCUSSION

The baseline characteristics of the study participants showed the predominance of males, all of whom had chronic exposure to cigarette smoke with long-standing symptoms of chronic cough, sputum production and dyspnea. Top occupations observed in the participants were of the outdoor setting, presumably predisposing them to exposure to industrial and vehicular smoke. These characteristics were consistent with the described prevalence of the disease in the current GOLD Report.

The study population were comprised mainly by participants in the GOLD 2 and 3 classifications of severity of airflow limitation, moderate and severe respectively, whose mean CAT scores were less than 10. Average vital signs observed overall were within normal acceptable limits. These findings suggested the clinically stable condition of the participants upon presentation for the study. However, this also meant that the recruitment of COPD outpatients in the very severe airflow limitation (GOLD 4) class might be limited since this group would more likely to have disease exacerbations, thus likely to need in-patient management rather than be seen as outpatient.

Most commonly reported comorbidities of the participants were hypertension, diabetes mellitus, and dyslipidemia, all of which were known independent cardiovascular risk factors. The presence of these reported comorbidities were reflected on the maintenance medications the majority of the participants were on, i.e. LABA/LAMA combination therapy, bronchodilators, beta-blockers, and ACEi/ARBs, in decreasing order of frequency. Only 16.21% of the participants had no self-reported known comorbidities. This proportion was lower compared to the 28.4% COPD patients with no associated comorbidities in one study (Raherison et al., 2018).

On echocardiography, 22 of the participants (59.46%) were found to have evidence of LV diastolic dysfunction while their ejection fractions were still within normal limits. Only 1 of these 22 participants (4.54%) had heart failure as a reported known comorbidity. Therefore, 21 of the total 37 participants or 56.76% had evidence of LV diastolic dysfunction with normal ejection fraction, indicative of an unrecognized heart failure with preserved ejection fraction (HFpEF). One of the total 37 participants (2.70%) was identified to have reduced ejection fraction but was not previously known to have heart failure as a comorbidity, thus indicative as well of an unrecognized heart failure with reduced ejection fraction (HFrEF). Taken together, 59.46% of the participants had unrecognized heart failure, of which 95.45% had HFpEF and 4.55% had HFrEF. The presence of unrecognized HFpEF and HFrEF among the participants in this study supported the recent findings of high prevalence of masked heart failure with preserved ejection fraction (HFpEF) in non-severe COPD with exertional dyspnea, free of overt cardiovascular disease (Cherneva et al., 2021). The 59.46% prevalence of unrecognized heart failure in the present study was higher than the prevalence of 11.9% reported by Griffo et al. in the outpatient setting (Griffo et al., 2017). The associated comorbidities in the participants who exhibited evidence of LV diastolic dysfunction in our study were hypertension (56.67%), diabetes mellitus (38.46%) and dyslipidemia (41.67%).

Examined independently of one another, the respective echocardiographic parameter values of ejection fraction, mitral E velocity, mitral e' velocity, E/e' ratio, and LA volume index did not differ significantly across GOLD classifications of severity of airflow limitation (GOLD 1 through 4). The TR jet (PAP) values however showed statistically significant difference, though weak, across the GOLD classifications noting GOLD 1 to have higher values. This latter observation might suggest the presence of pulmonary arterial hypertension, which is a common sequela of long-standing COPD, in this proportion of

participants. However, given the weak statistical significance, this latter observation might still be inconclusive. The statistical significance might improve utilizing a bigger sample of participants.

Current guidelines recommended that the determination of diastolic dysfunction be based on the composite assessment of the herein measured echocardiographic parameters of LV diastolic function (Nagueh, 2016). Therefore, the composite assessment of LV diastolic dysfunction, which was expressed in grades, was more clinically relevant to be interpreted rather than taking the parameters individually and independently of one another.

Odds ratio analysis of the diastolic dysfunction grades demonstrated an increased likelihood for GOLD 2 and GOLD 3 participants to have diastolic dysfunction compared to GOLD 1 participants. A recent meta-analysis of studies on diastolic dysfunction in patients with COPD had shown that COPD patients were more likely to have LV diastolic dysfunction compared to non-COPD patients as established by echocardiographic parameters (Zhyvotovska et al., 2019). However, the authors had not stated whether this likelihood increases with increasing severity of the airflow limitation (i.e. higher GOLD class). In our present study, the GOLD 4 participants did not exhibit an increased likelihood to have a diastolic dysfunction which might be due to the low number of participants in this particular GOLD class.

In the aspect of LV geometry, one study found significant alterations in LV geometry, particularly concentric remodeling, among COPD patients even when cardiovascular disease was excluded (Pela, 2016). Pulmonary hyperinflation associated in COPD was the identified mechanism causing altered LV mass (Smith, 2013). In our present study, GOLD 2 participants exhibited an increased likelihood to have an abnormal LV geometry on echocardiography in general. However, the identification of the relationship

between GOLD classification and specific abnormal LV geometry was not possible due to the limited number of participants.

This present study was the first, to the best of our knowledge, to investigate on the echocardiographic findings of LV function in COPD among Filipinos in the outpatient setting in the country.

CHAPTER 5

CONCLUSION AND RECOMMENDATIONS

CONCLUSION

Based on the findings of the study, the following conclusions were drawn:

1. Echocardiographic evidence of unrecognized heart failure, with preserved ejection fraction (HFpEF) in particular, was observed in more than half of the participants, which may augment symptoms of dyspnea or breathlessness practically attributed solely to COPD.

2. Echocardiographic parameters of LV systolic and diastolic function showed absence to weak correlation with GOLD classification of severity of airflow limitation when considered independently of one another.

3. GOLD class 2 and 3 participants had increased likelihood to have evidence of diastolic dysfunction on echocardiography compared to GOLD class 1 participants.

4. GOLD class 2 participants exhibited an increased likelihood to have an abnormal LV geometry on echocardiography compared to GOLD 1 participants.

RECOMMENDATIONS

With the present findings in this study, the researchers highly recommend the following:

1. That patients with a diagnosis of COPD, especially with comorbidity of hypertension, diabetes mellitus or dyslipidemia, be evaluated for underlying heart failure with preserved or reduced ejection fraction that may contribute to the symptom of dyspnea or breathlessness.

2. That addressing both COPD and heart failure may improve control of symptoms of dyspnea and breathlessness, which are common to both disease entities.

3. That in higher GOLD classification of severity of airflow limitation, echocardiography be considered to be included in the diagnostic workup of outpatients.

4. That further studies be made on the current subject involving a bigger sample population to better reveal associations between GOLD classification of severity of airflow limitation and LV function among Filipino COPD patients.

5. That long-term studies be made on the prognostic impact of LV dysfunction, either systolic or diastolic, on the natural history of and management outcome in COPD.

(REFERENCES)

(APPENDICES)

(To include Cat and mmrc scores)