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Something Old, Something New
The Challenge of COPD and the Alarming Rise of HIV/AIDS

Evelyn Victoria E. Reside, MD, FPCCP
Editor-in-Chief

The Philippine College of Chest Physicians strives to keep abreast with cutting-edge technology, the latest management approaches, and the most recent scientific information. It is indeed timely, therefore, that this issue allows us a glimpse into the more rapidly increasing scourges of chronic obstructive pulmonary disease (COPD) and human immunodeficiency virus (HIV).

In 2016, the Department of Health's National Epidemiology Center estimated that there were almost 26 new cases of HIV every day, compared to only one per day in 2008 (Department of Health, HIV/AIDS ART Registry of the Philippines, November 2016). Moreover, the number of females with HIV/Acquired Immune Deficiency Syndrome (AIDS) is increasing, and the average patient age is decreasing. To be able to look more closely at cases of HIV/AIDS with pulmonary complications, and to correlate them with their lymphocyte counts will indeed improve our knowledge of this medical condition which is still in need of much research and understanding. Hopefully, this contribution to our knowledge of HIV/AIDS will translate into more efficient medical care that will ultimately save more lives, especially since our local numbers have skyrocketed in recent years.

On the other hand, the number of articles in this issue on COPD demonstrates that the Filipino pulmonologist is not lacking interest in patients with COPD, despite the fact that it has been recognized by the Department of Health for its significant and consistent contribution to morbidity and mortality for several years running. Just like other lifestyle

conditions which are considered chronic and non-communicable, the prevalence and incidence of COPD continue to increase. In 2013, The Department of Health listed "Bronchitis" as among the country's top ten causes of morbidity, surprisingly higher on the list that tuberculosis (both pulmonary and extra-pulmonary) and dengue (Philippine Health Statistics, 2013). However, since spirometric testing may not be available throughout the archipelago, it can be surmised that these numbers may be underestimates. Indeed, once the Philippines' COPD Registry is fully implemented, we can paint a clearer, although possibly a more alarming, picture of the disease.

To wrap up this issue, the PJCD is excited to feature an article on Histoplasmosis, a fungal disease condition that is not often encountered. Considering that it is a diagnostic challenge, the case report presented here reminds us that fungal etiologies should never be overlooked in interstitial lung diseases (ILD), especially since fungal infections are treatable, thus providing much hope to patients afflicted with such a debilitating disease as ILD.

Again, as with other previous issues of the PJCD, we are proud to feature our PCCP family's humble contribution to both the local and international understanding of pulmonary disease. We encourage all young curious pulmonologists to continue searching and researching, even long after research has become a requirement. The PCCP and the PJCD is committed to attaining international recognition and indexing, and this gem of an issue definitely takes us one more step closer.

PROSPECTIVE OBSERVATIONAL STUDY

Prevalence of Chronic Obstructive Pulmonary Disease among patients previously treated for Pulmonary Tuberculosis in Manila (PreCOPT): A multi-center study

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This study was conducted in cooperation with the Department of Health Center for Health Development – National Capital Region and the Philippine College of Physicians.

ABSTRACT

Introduction: Chronic obstructive pulmonary disease (COPD) ranks as the fourth leading cause of death worldwide. In several epidemiologic studies, pulmonary tuberculosis (PTB) is currently an emerging potential risk factor in the pathogenesis and severity of COPD. This study aims to determine the prevalence of COPD among patients who were previously treated for PTB in various directly observed treatment short course (DOTS) centers in manila.

Methodology: we performed a prospective cross-sectional study using purposive sampling among patients managed in various dots centers in manila. Participants were aged ≥40 years of age, who have completed the prescribed PTB treatment and have been declared cured with no clinical evidence of relapse for at least a year at the time of the study. A diagnosis of COPD was based on the post-bronchodilator FEV1/FVC < 70 as recommended in the global initiative for chronic obstructive lung disease (GOLD). This was compared with spirometry with bronchodilator testing) from a matched population without history of PTB.

Results: Among 254 participants who were previously treated for PTB, 20.47% met the criteria for COPD with an odds ratio of 1.10 (95% ci 0.68, 1.76). This was not significantly different from the rate of 19.38% among the 227 participants without history of PTB. Majority of the patients diagnosed with COPD belong to GOLD stage III.

Conclusion: The prevalence of COPD in patients previously treated for PTB is not significant and our investigation did not show a strong association between these variables. Nevertheless, our data suggest that previous history of PTB posed a risk for development of obstructive airways disease which is predominantly severe. This may imply that in such individuals who present with dyspnea or similar suggestive symptoms warrants screening to provide appropriate intervention and optimal therapy.

Keywords: Chronic obstructive pulmonary disease, pulmonary tuberculosis

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a major cause of mortality and morbidity worldwide. It has been the fourth leading cause of death worldwide with a pooled prevalence of 6.4%, 1.8%, and 9.2%, based on the definition of chronic bronchitis, emphysema, and airflow obstruction, respectively.[1] It is projected to be the 3rd leading cause of death by year 2020.[2,3]

Environmental factors such as cigarette smoking, exposure to biomass and genetics (e.g., presence of alpha-1 anti-trypsin deficiency for non-smokers) has been established as significant factors in the development of the disease.[4] Pulmonary tuberculosis (PTB) is currently gaining attention as a potential risk factor in the pathogenesis and severity of COPD.[2,5]

In the Burden of Obstructive Lung Disease (BOLD) study done in the Philippines, the risk factors associated with COPD included the use of firewood for cooking, increased duration of farm work and a history of PTB.[4] The PLATINO study done in Latin America showed that subjects with a history of PTB were more than twice as likely to present with airflow obstruction than those without TB, even after adjustments for confounding factors by age, cigarette smoking and environmental exposures.[6]

The development of COPD in patients who were previously treated for PTB is multifactorial.[7] The infection is associated with airway fibrosis and the immune response to the mycobacteria can result in airway inflammation, which is characteristic of COPD.

This study aims to compare the profile and other characteristics of Filipino patients managed in selected Manila-based Directly Observed Treatment Short-course (DOTS) centers who have obstructive changes on spirometry against their counterparts who did not exhibit those changes. Furthermore, this study aims to describe the demographic profile of the subjects who exhibited obstructive ventilatory defects on spirometry. Lastly, it aims to determine the correlation between the severity of COPD with the period from the diagnosis of PTB to the initiation of the TB treatment, the category of the patient at the time of diagnosis, and the period from the completion of TB treatment to the conduct of the spirometric examinations.

METHODS

This was a prospective cross-sectional study conducted in the different Department of Health-accredited DOTS Centers in Manila. Patients included in the study were as follows: Filipino patients registered in the DOTS centers in Manila, aged more than or equal to 40 years, who have completed the prescribed PTB treatment, and for at least a year at the time of the study and have been declared cured with no clinical evidence of relapse. These patients must also be able to do spirometry, and able to sign an informed consent.

Patients who have at least 10 pack-years of smoking history, who were exposed to biomass fuel for more than or equal to 5 years, those who were previously diagnosed to have COPD, pregnant patients on their third trimester of pregnancy, those who were exposed to environmental and occupational factors that would predispose them to develop COPD, and those with a history of bronchial asthma were all excluded from this study.

A purposive sampling maneuver was used in this study. With an expected COPD prevalence rate of 20%, a margin of error of 5 % and the confidence level set at 95%, the minimum sample size calculated was at 254 PTB patients registered from the DOTS Centers around Manila. These were matched with 227 patients whose spirometric findings are diagnostic of COPD but who do not have PTB. The protocol was approved by the University of the Philippines Manila Research Ethics Board.

Questionnaires were given to patients to assess their demographic profile, possible risk factors for COPD, and the presence of other confounding factors which may cause obstructive changes like bronchial asthma. Tuberculosis-treatment variables

were likewise considered.

Enrolled patients were asked to perform spirometry with bronchodilator testing with 200 ug of Salbutamol delivered via metered dose inhaler. COPD was defined as a post-bronchodilator FEV1/FVC ratio of <70%. Spirometric testing was terminated if the patient developed significant light-headedness or syncope, or if sequential spirometric measurements show a greater than 20% reduction in FEV_1 that may not explained by procedural problems, suggesting maneuver-induced broncho-constriction. The severity of the obstructive ventilator abnormality was based on the post-bronchodilator FEV1 percent predicted, set by the Global Initiative for Obstructive Lung Disease (GOLD). Chest radiograph was then requested among patients included in the study whose spirometry findings showed a restrictive ventilatory defect.

Descriptive analysis was employed on the primary data. Logistic regression analysis was performed to assess the association of certain factors with airflow obstruction and odds ratio was subsequently calculated.

RESULTS

A total of 254 patients from the twelve DOTS Centers were enrolled in the study. The demographic features are depicted in Table 1.

The study participants had a male preponderance (62.2% males vs 37.8% females) with the mean age of 54.4 years. Majority of the participants belonged to a lower socio-economic status. Around 62% were able to acquire secondary level of education and slightly less than half (46.1%) were unemployed based on the Philippine Standard Classification of Education (PSCED) and the Philippine Standard Occupational Classification, respectively.

More than 90% of the patients included in the study were classified as new cases at the time of treatment in the DOTS Center (Table 2). Radiographic abnormalities noted prior to treatment were predominantly minimal in character (31.1%). Most of the patients were treated within one month from the diagnosis of PTB. Almost half were cured (48.4%) or completed treatment for PTB (49.6%).

Table 1. Demographic Profile of the Included Participants

Characteristic	N (%)
Male: Female	158 (62.2) : 96 (37.8)
Age in years, mean (range)	54.4 (39 – 78)
Educational attainment	
Tertiary	36 (14.2)
Post-Secondary Non-Tertiary/Technical-Vocational	3 (1.2)
Secondary	157 (61.8)
Primary	55 (21.6)
None	3 (1.2)
Occupation	
Service and sales workers	2 (0.8)
Craft and related trade workers	38 (15.0)
Plant and machine operators and assemblers	12 (4.7)
Elementary occupations	85 (33.5)
Unemployed	117 (46.1)
Average monthly income, n (%)	238 (93.7)
Less than P10,000	16 (6)
> 10,000 to <20,000	0
> 20,000	

Twenty-two percent of the participants showed an obstructive ventilatory defect on spirometry (Figure 1). On the other hand, more than 40% of patients previously treated for PTB had restrictive ventilator abnormality.

We also gathered data on spirometry with bronchodilation in 227 subjects from a matched population without PTB findings and with no clinical suspicion of COPD that warranted spirometry. Among these individuals, the prevalence of COPD was 19.38%. This resulted in an odds ratio of 1.10 (95% CI 0.68, 1.76). These results suggest that PTB may not be a significant risk factor for the development of COPD. The risk for COPD is only 10% higher for patients previously treated for PTB against those who did

not have a history of PTB, and statistical significance was not demonstrated.

Finally, majority (53%) of those patients diagnosed with COPD belong to GOLD Class 3 (Figure 2).

DISCUSSION

COPD is fast becoming recognized as an important cause of morbidity and mortality, utilizing a significant amount of resources in hospitalizations and medications. Aggressive campaigns have been underway to decrease exposure to established risk factors for the development of this disease.

PTB, another important global health concern, is emerging as one of the risk factors for the development of COPD. The PLATINO Study showed that the overall prevalence of airflow obstruction among those with a history of tuberculosis was 30.7%, compared with 13.9%

Table 2. Tuberculosis-related Demographics of the Study Population

Category	N (%)
Registration category	235 (92.5)
New	14 (5.5)
Relapse	2 (0.8)
Treatment after previous	1 (0.4)
treatment failure	2 (0.8)
Treatment after default	
Transfer in	
Treatment outcome	123 (48.4)
Cured	126 (49.6)
Treatment completed	3 (1.2)
Default	2 (0.8)
Trans-out	
Time interval between	
diagnosis and TB treatment	186 (73.2)
<1 month	55 (21.6)
1 to <3 months	6 (2.4)
3 to <5 months	1 (0.4)
5 to <7 months	4 (1.6)
7 to <9 months	2 (0.8)
9 to <12 months	
Radiologic abnormality on	
CXR prior to treatment	79 (31.1)
Minimal	83 (32.7)
Extensive	10 (3.9)
Normal	82 (32.3)
None	

Figure 1. Proportion of TB patients by spirometry results

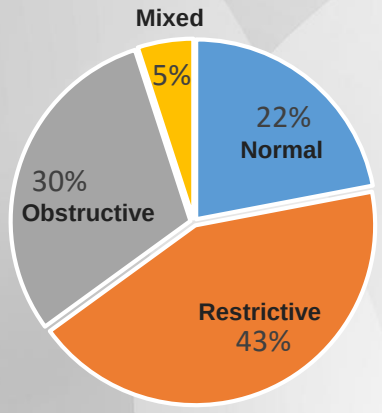
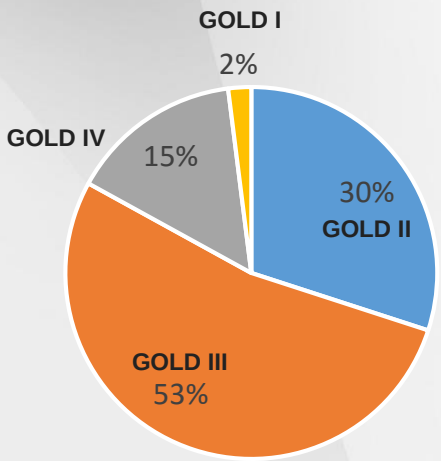


Figure 2. Proportion of TB patients by GOLD classification



among those without a history of TB.[6] It also showed that males with a medical history of tuberculosis were 4.1 times more likely to present with airflow obstruction than those without this risk factor. The PREPOCOL study conducted in five cities in Columbia also reported a strong association between a history of PTB and COPD, with an odds ratio of 2.9 (95% CI 1.6-5.5).[2] This association was even stronger than that noted with tobacco smoking (OR 2.6; 95% CI 1.9-3.5).

Our study was conducted in the different DOTS centers in Manila in an effort to confirm a significant association between pulmonary tuberculosis and an obstructive ventilatory abnormality. The prevalence rate of COPD noted in this study population was 20.47%. The prevalence of COPD in the general population with no PTB was 19.38 %, with the non-significant calculated odds ratio of 1.10, showing that prior history of PTB was not a significant risk factor in the development of COPD in this study. We did observed that in the PTB patients with COPD, majority has severe obstructive ventilator defect (FEV_1 ranging from 30-50%). These result supported the PLATINO study which showed severe grades of airway obstruction among those with history of PTB.[6]

Majority of our patient respondents were males, with a mean age of 54 years, and belonging to the lower socioeconomic strata. The TB background of patients with airway obstruction noted in this study were new cases, smear positive, treatment completed and with spirometry performed within 1-3 years from the time of completion of anti-PTB treatment. These individuals were fully managed in a programmatic setting of DOTS. In contrast, earlier landmark studies used questionnaires to establish the medical diagnosis of PTB or a history of TB as confirmed by a physician.[2,6,8]

The development of COPD in patients who were previously treated for PTB is multifactorial.[7] The infection is associated with airway fibrosis, and the immune response to the mycobacteria can result in airway inflammation, which is characteristic of COPD. The degree of obstruction is also associated with the extent of the disease, the sputum production and the length of time after the diagnosis and treatment completion.[4,9,10]

Chronic lower respiratory tract infection leads to accelerated parenchymal destruction.[8] Pulmonary tuberculosis produces caseous granulomatous inflammation resulting to tissue damage which if left untreated can result in permanent obstructive pulmonary function impairment.[11]

A common link to the pathogenesis of both conditions lies in the destruction of the pulmonary extracellular matrix (ECM), comprised of collagen and elastin, which is key to the structural integrity of the lung.[11] The damage on the ECM is mediated by matrix metalloproteinases (MMPs), which belong to a family of naturally occurring protease enzymes capable of degrading the ECM. In disease states where there is altered or unregulated activity of the MMP enzymes, there is also the chance for remodelling and subsequent damage to the lung architecture. Lipoarabinomannan (LAM), which is an antigenic component of the wall of *Mycobacterium tuberculosis*, stimulates the release of MMP-9. This results in the breakdown of collagen in the ECM and stimulates further lung damage by activation of other immune mediators such as interleukin-8 and other cytokines. This process is essential in the development of cavitary parenchymal lung damage often complicating active tuberculosis. MMP-9 levels were found to be three times higher in the serum of tuberculosis patients compared with controls with increased levels in patients with advanced disease than those with limited TB disease.

Furthermore, the activity of the specific inhibitor of MMP-1, the tissue inhibitor of metalloproteinase 1 (TIMP-1), was suppressed in

patients with PTB, resulting in unchecked MMP-1 activity and the potential for significant destruction of the ECM.[12] Similarly, tumor necrosis factor-alpha, which plays an active role in the development of tuberculous granulomas, has been demonstrated to stimulate MMP-9 secretion from the granulomas cultured from patients with active tuberculosis. There was also more MMP-9 transcription in the COPD group than in the control group. Lastly, elevated levels of TIMP-1 in COPD patients compared to controls have been demonstrated.

Endobronchial involvement of TB results in the localized and generalized bronchial obstruction, fibrosis and increased airways resistance.[12] An extrinsic bronchial compression secondary to tuberculous lymphadenopathy could also be present. Parenchymal lung destruction can affect pulmonary compliance resulting in an increased tendency for peripheral airways to collapse leading to air trapping. The airway and parenchymal abnormalities result to development of areas with decreased ventilation but with adequate perfusion. Conversely, tuberculosis also induces vascular changes in the lung leading to decreased perfusion in areas of adequate ventilation. The net result of these processes is the development of chronic airflow obstruction.

Other outcome of this study was the significant development of restrictive ventilatory abnormality (43% restrictive vs 22% obstructive). Those patients with abnormal spirometric results other than an obstructive defect were subjected to chest radiography, which showed predominantly fibrotic changes.

We acknowledge possible limitations in our study. First, due to its multi-center approach and since the enrolled study participants have already completed treatment in the DOTS clinics, encouraging them to return for a spirometric evaluation was difficult, and may have had an impact on the subjects who were ultimately included. Second, our sample size was also smaller compared to other studies with a similar objective. Third, this was a prospective study with a component of a retrospective retrieval of patients records, hence some data were already unavailable despite meticulous search and coordination with the DOTS Center staff. Lastly, the study population was selected based on predefined criteria, and may not accurately represent the general population of PTB patients.

CONCLUSION AND RECOMMENDATIONS

Our study demonstrated that the prevalence of COPD in patients previously treated for PTB is not significant and our investigation did not show a strong association between these two variables. Factors which influenced the results could have been the smaller sample size compared to earlier studies which demonstrated a positive association. Thus, we recommend studies using larger sample sizs.

Knowing the basic pathophysiologic processes that occur in a patient with PTB leading to the development of an obstructive airways disease (predominantly severe) may imply that in such individuals who may present with dyspnea or similar suggestive symptoms, a spirometric screening with post-bronchodilator study may be warranted. Confirmation of the diagnosis COPD will benefit patients in terms of early intervention and optimal management.

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CASE REPORT

Interstitial Lung Disease Secondary to Pulmonary Histoplasmosis: A Case Report

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ABSTRACT

Introduction: Interstitial lung diseases (ILDs) are associated with pathologic alterations affecting interstitial alveolar structures. Patients commonly present with dyspnea due to impaired gas exchange. There are several causes of ILD, and identification of the etiology is essential to providing appropriate management.

Case description: We present the case of a 42-year-old Filipino, initially diagnosed with ILD, who presented with progressive exertional dyspnea that started 1 year prior to admission. Chest computed tomography (CT) scan showed mediastinal lymphadenopathies with emphysematous and bronchiectatic changes, with fibrosis over the right-middle and bilateral lower lobes. Pulmonary function test revealed severe restrictive ventilatory defect. The patient was managed as a case of ILD in flare with pulmonary hypertension. Lung biopsy showed chronic lymphohistiocytic pneumonitis with focal desquamative interstitial pneumonitis-like changes where fungal elements were highly suspected. Histochemical staining with methenamine silver stain came up positive for budding yeast forms of *Histoplasma capsulatum*. Patient was started on itraconazole, resulting in clinical improvement.

INTRODUCTION

Interstitial lung diseases (ILDs) are rare manifestations of fibroblastic proliferation and infiltration of the alveolar walls. Inflammatory fibrotic infiltration within the airway and alveolar lumina and the walls of small airways, leads to the ILD's symptoms.

The most common symptom of ILD is progressive dyspnea. There is also persistent and prominent nonproductive cough associated with abnormal chest radiograph with interstitial patterns and impaired pulmonary function tests. Usually, diagnosis of ILD follows other pulmonary symptoms associated with other diseases, such as connective tissue diseases and fibrotic disorders. Clinical evaluation of ILD includes careful exploration of past medical history and potential exposures commonly from occupational and environmental agents. Identification of etiology is essential to determining prognosis and planning appropriate management. Targeted management can prevent further progression of the disease and its complications.

In this paper, we present the case of a 42-year-old male diagnosed with ILD, with the initial presenting symptom of progressive exertional dyspnea, prompting further diagnostics and later on requiring invasive management. The importance of history of potential environmental exposure to infectious agents is highlighted in this case. Histopathologic findings leading to the diagnosis of pulmonary histoplasmosis are also discussed. Likewise, diagnostics and treatment strategies on management of pulmonary histoplasmosis based on recent guidelines are discussed.

CASE PRESENTATION

This is a case of a 42-year-old male, Filipino, who was admitted at the Philippine General Hospital due to difficulty in breathing. Initially, he was clinically diagnosed as a case of ILD, presenting with exertional dyspnea that started a year prior to admission. His past medical and social history were unremarkable.

Due to the persistence and progression of dyspnea, several diagnostics were requested. Electrocardiography showed sinus rhythm with nonspecific ST-T wave changes. Chest radiography revealed bronchiectatic changes over bilateral lower lung fields, cardiomegaly, and atheromatous aorta. Pertinent chest computed tomography scan showed emphysematous changes, bronchiectasis with fibrosis over the right-middle lobe and bilateral lower lobes, and mediastinal lymphadenopathies. Spirometry showed severe restrictive ventilatory defect with no significant acute post-bronchodilator response. He was started on sildenafil along with digoxin, clopidogrel, telmisartan, and amlodipine. However, due to progression of dyspnea, the patient consulted a pulmonologist and was advised to undergo video-assisted thoracoscopic surgery (VATS) and lung biopsy. Hence, the patient was admitted.

Upon admission, patient was conscious, coherent, with mild labored breathing. Baseline oxygen saturation at room air was 79% hence started on 3 L/min oxygen support. Baseline arterial blood gas revealed mixed respiratory and metabolic alkalosis with hypoxemia. A repeat chest radiography on admission revealed bronchiectatic changes over bilateral lower lung fields, similar to his previous radiologic findings.

The patient's maintenance medications were continued, with the exception of clopidogrel.

Patient subsequently underwent VATS, lung biopsy, with chest tube thoracostomy. Intraoperative findings showed the presence of pleural effusion (approximately 300 mL) and emphysematous right upper, middle, and lower lobes, worst at the lower lobe. Samples from the right middle lobe and superior segment of right lower lobe were sent for histopathological review. On frozen section, findings included emphysematous changes with chronic interstitial inflammation in all lung segments sent, with no evidence of malignancy or granuloma.

Postoperatively, the patient was managed as a case of ILD in flare. Oxygen support then was provided at 5–6 L/min and was advised incentive spirometry. He was started on prednisone 20-mg tablet thrice a day, salbutamol with ipratropium nebulization every 4 hours, doxofylline 200-mg tablet once a day, and tiotropium via Respimat® (Boehringer Ingelheim; Germany) 1 inhalation once a day. He was also started on ketorolac 30 mg intravenously every 6 hours for the first 24 hours and etoricoxib 120 mg tablet once a day for pain control, as well as omeprazole 40 mg IV every 12 hours.

Serial chest radiography was also done because the patient was noticed to still have slight difficulty in breathing with decreased breath sounds over the right lung fields,. Chest radiography findings on the first day post-surgery revealed pneumothorax at the right hemithorax, indicating an unexpanded right lung. Chest tube output was 120 mL/day. Oxygen support of 5–6 L/min was maintained. On the second day post-surgery, patient was less dyspneic, with decreasing oxygen support requirement. Oxygen support was reduced to 3 L/min. Repeat chest radiography showed expanded right lung with minimal pneumothorax. Chest tube output (right) was decreased to 40 ml for 24 hours. Chest tube was then removed. Results of additional tests showed a negative serum antinuclear antibody and C-reactive protein.

On the third day post-surgery, patient was less dyspneic. He was discharged hemo-dynamically stable but was advised to secure bilevel positive airway pressure (BiPAP) for home use and instructed to follow up closely.

Slide review of the right-middle lobe and sup-

erior segment of right-lower lobe biopsy revealed nonspecific interstitial pneumonitis and diffuse mononuclear inflammation. Numerous alveolar macrophages were visible, as well as pulmonary arteriopathy, which were consistent with the symptoms and pulmonary hypertension of the patient.

Further examination revealed chronic lymphohistiocytic pneumonitis with focal desquamative interstitial pneumonitis-like changes, suspicious for histiocytes (Figure 1).

Fungal infection was highly suspected. Histochemical staining with mucicarmine and Grocott's methenamine silver stain were requested. Other pathologic findings were emphysematous changes, type 2 pneumocyte hyperplasia, and chronic pleuritis. Mucicarmine staining was negative but Grocott's methenamine silver stain showed budding yeast forms of histiocytes (Figure 2).

With these findings, history review of possible exposure of the patient to fungal elements

Figure 1. (A) Chronic lymphohistiocytic pneumonitis, (B) focal desquamative interstitial pneumonitis-like changes, (C) histiocytes, and (D) pulmonary arteriopathy.

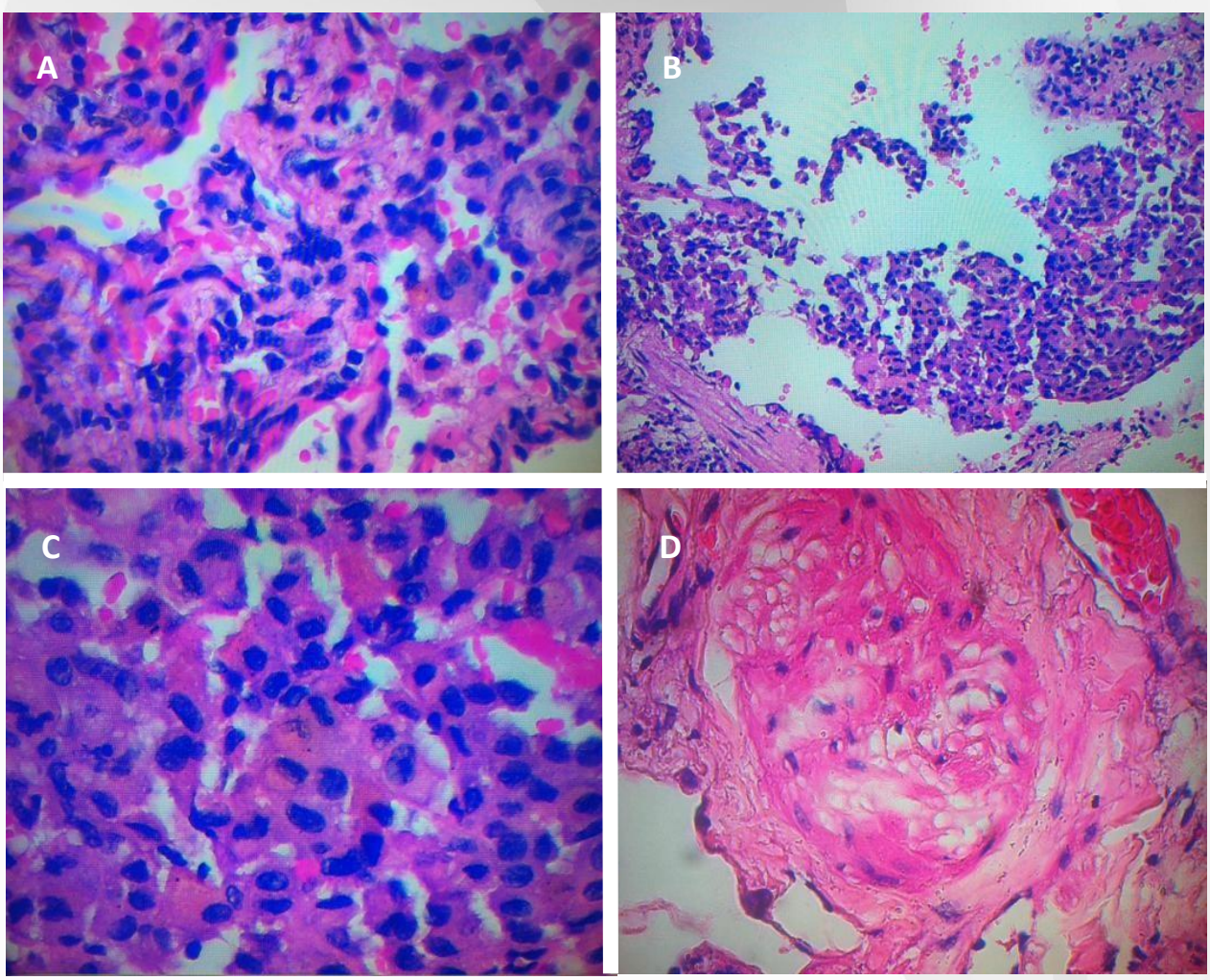
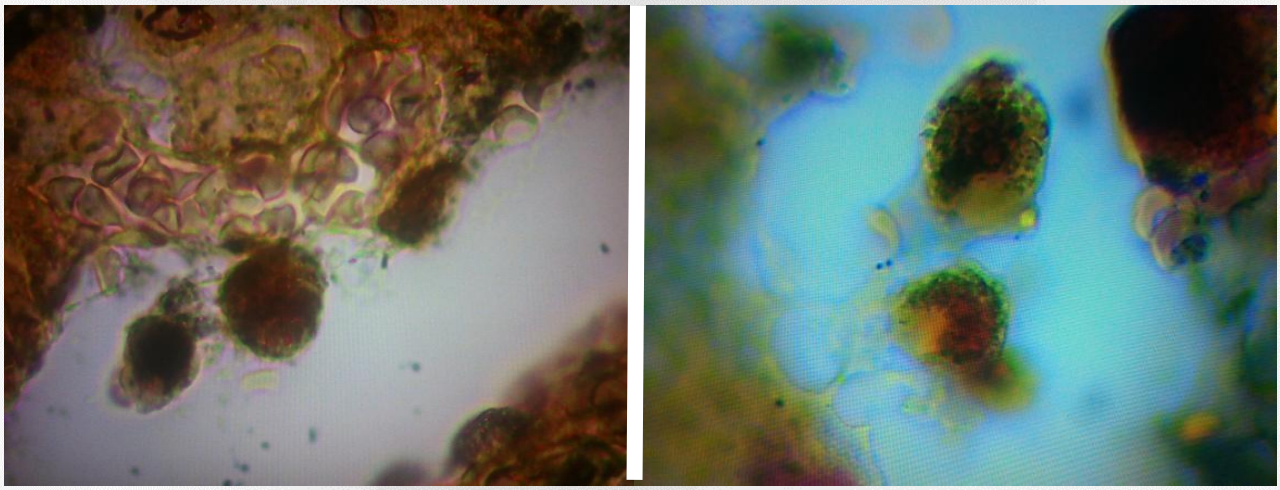


Figure 2. Grocott's methenamine silver staining of lung tissue showing budding yeast forms of *Histoplasma capsulatum*



was done. Upon follow-up the patient noted previous engagement in bear hunting activities during his stay in the United States, where he had been employed for a few years prior to the start of his symptoms. Due to this predisposing factor, the patient was started on itraconazole. Corticosteroids were slowly tapered. Tiotropium via Respimat® inhaler and use of BiPAP at home were maintained. Patient follow-up after a few months, showed marked clinical improvement, with significant reductions in dyspnea and oxygen requirement. Patient was subsequently weaned from use of BiPAP at home.

DISCUSSION

Histoplasmosis is a generalized disease that begins in the lung. It may cause progressive illness which may have fatal complications. It is an endemic mycosis distributed worldwide, most common in Central America, particularly the Ohio and Mississippi river valleys.[1] It is caused by *Histoplasma capsulatum*, a dimorphic fungus that grows in soil and as yeast in animal and human hosts. It can be transmitted through inhalation of spores from soil that is contaminated with bird droppings or bat excrement. Human-to-human transmission has not been documented. However activities associated with risk of exposure to histoplasma include spelunking, mining, excavation, construction, farming, gardening, and other soil-disrupting activities, especially in areas where the organism is highly endemic. Most cases result from sporadic exposures. Outbreaks have been associated with travel to many countries in Central America and South America, most often associated with visiting caves. In the case of our patient, his exposure was likely from outdoor forest activities in the United States.

Prevalence

Baddley et al found that the incidence of histoplasmosis in adults aged ≥65 years in the United States was 3.4 per 100,000 people.[2] However, 20% of severe illnesses were reported among healthy and young individuals.[1-3] Data on histoplasmosis prevalence in the Philippines is limited. Furthermore, data on the exact incidence and prevalence of pulmonary histoplasmosis are not available..

Immunocompromised populations and those with exposure to large inoculum of *H. capsulatum* are at high risk of symptomatic acute manifestation of pulmonary histoplasmosis. Approximately 30% of HIV/AIDS patients diagnosed with histoplasmo-

sis die from it.[3] Other risk factors include emphysema and extremes of age.

Pathogenesis and Pathophysiology

Pulmonary histoplasmosis infection occurs when microconidia of *H. capsulatum* from soil are aerosolized and inhaled into the lower airways. Macrophages recognize these infectious organisms and phagocytize them. Once inside the resident macrophages, conidia convert to yeast. During the first few weeks, yeasts multiply inside the macrophages and spread via the reticuloendothelial system. Dendritic cells line the airway and ingest and kill the yeast and present *Histoplasma* antigen to stimulate naive T-lymphocytes.

Within 2–3 weeks, a T-cell mediated immune response is generated to prevent dissemination of the disease, by assisting the effector macrophage intracellular killing of the yeast. However, this response depends on the number of cytokines, such as tumor necrosis factor-α, interferon-γ, and interleukin-12. In conditions where cellular immunity is defective, the fungi proliferate and disseminate, causing severe tissue destruction and multi-organ failure that can be fatal if left untreated.[4]

Clinical Manifestation

Incubation period is within 3–17 days for acute disease. Ninety percent of infections are asymptomatic or present with mild influenza-like illness. Some infections however, may cause acute pulmonary histoplasmosis manifested by high-grade fever, headache, nonproductive cough, chills, weakness, pleuritic chest pain, and fatigue.

Recovery 2–3 weeks after onset of symptoms occurs in most patients, although fatigue may persist. Dissemination, especially to the gastrointestinal tract and central nervous system, can occur in people who are immunocompromised.

Pulmonary histoplasmosis may mimic several diseases, such as tuberculosis and malignancy. As with our patient, patients with pulmonary histoplasmosis present with dyspnea with associated hypoxemia. And diffuse pulmonary infiltrates on chest radiograph, similar to hypersensitivity pneumonitis, are rather common.

Diagnosis

The importance of adequate history of environmental exposure is essential in diagnosing pulmonary histoplasmosis. Given an appropriate epidemiologic risk factor and a compatible clinical presentation, consider testing for the diagnosis of this condition.

In most cases of pulmonary histoplasmosis, lobar or patchy pulmonary infiltrates appear on chest imaging. It may also present as a pulmonary nodule, mediastinal or hilar lymphadenopathy or mass with or without associated pneumonia, or as a cavitary lung disease.[5]

Culture of *H. capsulatum* is still the gold standard. It is most useful in patients with chronic pulmonary histoplasmosis. Multiple sputum or bronchoalveolar lavage increases yield in most cases.[6] Since fungal cultures require longer duration of diagnosis (ie, ≥6 weeks), more rapid tests such as histochemical staining are considered.

Usual findings in biopsy of specimen with pulmonary histoplasmosis include granulomas in most cases, lymphohistiocytic aggregates, and diffuse mononuclear cell infiltrates. The use of histochemical stains (e.g., methenamine silver stain as with this patient) could show the presence of budding yeast forms, thus allowing rapid diagnosis of histoplasmosis. However, fungal staining has lower sensitivity than culture.[7] The experience of the pathologist for the recognition of *H. capsulatum* also affects the sensitivity and specificity of this diagnostic test.

In severely ill patients, the use of antigen detection enzyme immunoassay (EIA) in the bronchoalveolar lavage, blood, or urine allows rapid diagnosis of pulmonary histoplasmosis.[8] In a study done by Hage et al, *Histoplasma* antigen EIA on bronchoalveolar lavage fluid were used among patients with pulmonary histoplasmosis, where 94% of the patients tested positive for the antigen.[9] Antigen test results vary considerably according to the type of chro-

nic pulmonary disease, with sensitivities ranging from 10% for mediastinal disease, 15%–21% for chronic pulmonary disease, and 92% for disseminated disease.[10-13]

Serologic tests for histoplasma-specific antibodies include immunodiffusion test and complement fixation assays. Antibodies usually appear during the second month from the time of exposure; therefore, antibody tests may return false-negative results when measurement is done at an earlier time. The complement fixation test determines persistent antibody response from a previous episode of histoplasmosis or infection with other fungi, such as coccidioidomycosis and blastomycosis. Positive results may also occur in patients with other granulomatous diseases, such as sarcoidosis or tuberculosis.

The immunodiffusion test has been found to have higher specificity than the complement fixation test. In the former, results are reported as M or H precipitins or bands. Most patients develop an M band. The H band appears most often in patients with disseminated infection, chronic cavitary pulmonary histoplasmosis, or more severe acute pulmonary histoplasmosis. The M band becomes positive sooner and persists longer than the H band.[10] Therefore, this test may also remain positive for several years after an acute setting and does not necessarily indicate disease activity.[14] Moreover, these serologic tests may also be falsely negative in immunocompromised patients.

It is equally important to determine the appropriate diagnostic test to use, depending on the activity or chronicity of suspected pulmonary histoplasmosis. In acute diffuse pulmonary disease, there is a high fungal burden among patients presenting with diffuse infiltrates within a month after exposure. Antigen testing may provide the highest sensitivity in these cases. Antibody testing may have a negative result at this time but may have a positive result a month later.

In acute localized pulmonary disease in which patients manifest more than a month after exposure and with localized pulmonary infiltrates and/or mediastinal lymphadenopathy, fungal burden is generally lower. Antigen may be detected in 40% of the cases using urine or serum specimen.[8] Cultures and cytology of respiratory specimen may be positive in some cases. Hage et al reports that antigen testing of bronchoalveolar lavage fluid showed greater sensitivity than culture alone.[9] In chronic pulmonary histoplasmosis, serologic tests are positive, and complement fixation titers are high in most cases. Hage et al detected antigen in 7 out of 8 cases.[8]

If cultures are negative and sputum specimen cannot be obtained, a case may require bronchoscopy for obtaining adequate respiratory specimen. Direct examination of respiratory secretions, often obtained by bronchoalveolar lavage, is extremely useful. Cultures of bronchoscopy specimen were found positive in 65%–85% of cases.[15] Moreover, bronchoscopy may be necessary to establish the diagnosis in cases when less invasive tests are not diagnostic, or when the illness is so severe that it requires rapid diagnosis to provide appropriate management. In such cases, pathology or culture is positive in about 40% of patients.

When less invasive tests are not diagnostic, the main indication for surgery is the exclusion of malignancy in cases with pulmonary nodules or mediastinal lymphadenopathy.[16] However, in patients without risk factors for malignancy, follow-up with CT scan at 3–6 month intervals for 1–2 years is a reasonable approach. Lung biopsy is rarely needed and should be avoided in patients with obstructive lung disease because of the risk for surgical complications, including pneumothorax and broncho-pleural fistula, as well as bacterial superinfection.

Treatment

Clinical classifications of pulmonary histoplasmosis that may require antifungal therapy are those that are acute, chronic-cavitary, progressive, disseminated, and with mediastinal lymphadenitis. Pulmonary nodule, mediastinal granuloma, mediastinal fibrosis, broncholithiasis, and inflammatory syndromes (pericarditis, arthritis, erythema nodosum) may require treatment but not an antifungal therapy.[17]

The optimal treatment for pulmonary histoplasmosis varies according to the patient's clinical syndrome. Most infections caused by *H. capsulatum* are self-limited and require no therapy. However, patients who are exposed to a large inoculum of *Histoplasma* and those who are immunocompromised usually require antifungal therapy.

In general, itraconazole, fluconazole, voriconazole, and amphotericin B, all have *in vitro* activity against *H. capsulatum*, but clinical trials have only been conducted with itraconazole, fluconazole, and amphotericin B. Itraconazole is generally preferred for mild to moderate histoplasmosis, and our patient responded well to this medication.

Amphotericin B has a role in the treatment of moderately severe and severe infections, including those with dyspnea and hypoxemia with or without the development of acute respiratory distress syndrome.[17] It could also be a reasonable treatment option for this patient.

Fluconazole is not as active as itraconazole, so it produces less favorable results. In a study by McKinsey et al, only 54% of cases with pulmonary histoplasmosis had clinical improvement when given fluconazole.[18] Moreover, in the study by Wheat et al, development of resistance in fluconazole was found among AIDS patients with concomitant pulmonary histoplasmosis.[19] Fluconazole (400–800 mg daily) is recommended only when the patient does not tolerate itraconazole or cannot achieve adequate levels. Patients treated with fluconazole should be monitored for relapse.

The clinical practice guidelines for the management of patients with pulmonary histoplasmosis were developed and updated in 2007 by the Infectious Diseases Society of America (IDSA).[17] Patients with acute diffuse pulmonary histoplasmosis who present within a month following exposure to a large inoculum of *H. capsulatum*, as well as those with severe or moderately severe disease, warrant treatment.

In these patients, methylprednisolone 0.5–1 mg/kg/day may be given intravenously and could also be given for 1–2 weeks in addition to amphotericin B. Clinical improvement is often dramatic with this regimen, allowing transition to itraconazole to be completed within 12 weeks.

Chronic pulmonary histoplasmosis warrants treatment because persistence of infection may lead to the progressive loss of pulmonary function and may even result in death in approximately 30% of cases.[15] Amphotericin B can prevent disease progression and reduces mortality. In recent studies, itraconazole has resulted in significant clinical improvement. The recommended dose of itraconazole is a loading dose of 200 mg orally 3 times a day for the first 3 days, followed by a maintenance dose of 200 mg orally once or twice daily for at least 1 year. Some studies suggest 18–24 months of antifungal therapy, given the substantial risk of relapse. Radiographic abnormalities improve during the first year of treatment in at least two-thirds of cases but often do not resolve completely. Treatment should be continued until radiographic improvement has ceased.[18]

Those with mild to moderate pulmonary histoplasmosis—patients who have had persistent symptoms for more than a month—may be given an itraconazole loading dose of 200 mg orally 3 times daily for the first 3 days as initial therapy, followed by a maintenance dose of 200 mg twice a day orally for 6–12 weeks. Antifungal therapy may be discontinued upon resolution of pulmonary infiltrates.

Relapse occurs in 10%–20% of patients with chronic pulmonary histoplasmosis. Vigilance must be maintained upon discontinuation of treatment. While most relapses occur within 2 years of stopping therapy, follow-up should be continued for at least 5 years. Serial chest radiographs should be obtained every 6 months for the first year after treatment is discontinued, and then annually or with the recurrence of symptoms, to exclude reactivation.[17]

SUMMARY

The case of a 42-year-old male with a known case of ILD with exertional dyspnea was presented. There was persistence and progression of the patient's symptoms; hence, etiology of his disease was further investigated. The patient underwent VATS and lung biopsy, which revealed chronic lymphohistiocytic pneumonitis and focal desquamative interstitial pneumonitis-like changes. These were suspicious for fungal elements. Histochemical staining with Grocott's methenamine silver stain confirmed pulmonary histoplasmosis. With appropriate epidemiologic background of exposure to histoplasma (due to his bear-hunting activities) matched with his clinical findings, the patient was managed as a case of pulmonary histoplasmosis and was given itraconazole, which provided clinical improvement of symptoms.

Pulmonary histoplasmosis may mimic other diseases. An epidemiologic background and compatible clinical manifestation, complemented with imaging and histopathological findings, led us towards the identification of the etiology of the disease and subsequently allowed us to provide appropriate treatment.

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CROSS-SECTIONAL STUDY

Clinical Correlation of Absolute Total Lymphocyte and CD4 T-Lymphocyte Count with Pulmonary Complications of Human Immunodeficiency Virus (HIV) Seropositive Patients Seen at the Lung Center of the Philippines

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ABSTRACT

The US Centers for Disease Control and Prevention (CDC) includes CD4 counts <200 cells/μL (or CD4 <14%) as a definition of AIDS in people living with human immunodeficiency virus. This study aims to determine the correlation between absolute total lymphocyte count and CD4 T-lymphocyte count in patients presenting with pulmonary complications. Study participants include 83 patients with a median age of 30 years. Most of the patients were male, (99%), single (93%) and worked as call center agents (14%), or teachers (10%), or were unemployed (20%). All patients had HIV serotype 1. Risky behavior included engagement in both oral and anal sex (54%). Most vulnerable patients were those having unprotected sex (76%) with >5 partners (52%). The most common symptom presentation was difficulty in breathing (72%). Radiologic features showed alveolo-interstitial (30%), hazy infiltrates (16%), and reticulonodular (31%). The most common arterial blood gas interpretation was uncompensated respiratory acidosis, with various degrees of hypoxemia. The highest pulmonary complication was *Pneumocystis jirovecii* infection (50%). Ninety-four percent (94%) of the patients had a CD4 count <100 mm^3. ATLC and CD4 T-lymphocyte count were strongly correlated, with correlational coefficient of 0.77 and a p-value <0.01. Therefore, we recommend the use of ATLC as a surrogate marker of CD4 T-lymphocyte count, especially in resource-limited countries.

INTRODUCTION

The progress and decline of immunity can be monitored through the cluster of differentiation 4 (CD4; helper) lymphocyte cell count in the blood. As CD4 declines from normal levels (600–1200 cells/μL), the risk for specific opportunistic infection increases.[1,2] It has been proposed that CD4 count could be a surrogate marker for human immunodeficiency virus (HIV) infection in high-risk individuals who do not want to be tested for HIV.[1] Recent studies have suggested that even individuals with CD4 counts above 350–500 cells/μL are at elevated risk for a number of conditions that were not known as related to HIV infection.

The US Centers for Disease Control and Prevention (CDC) includes CD4 counts <200 cells/μL (or CD4 <14%) in its definition of AIDS in people living with HIV (PLHIV).[3] However, the World Health Organization (WHO) formulated its own clinical staging and case definition, developed especially for resource-constrained settings, that does not require CD4 counts.[4]

Resource-limited countries that cannot afford routine CD4 count determination rely on the total T-lymphocyte count (TLC), which is calculated from the WBC and its differential count, and is usually an immunologic marker for viral infection. There are limited studies that

suggest TLC as a surrogate marker for CD4 count. In the study by Guevarra et al, of the 13 cases of PLHIV, the CD4 level of 200 mm^3 was significantly correlated with mortality, and the mean CD4 count was 13±11.4 cells/ µL.[2] However, the TLC level and CD4 count in which opportunistic pulmonary infections set in have not yet been established.

Pulmonary complications in HIV-seropositive individuals, as reported in literature, vary upon the level of immunity.[2-5] As CD4 counts decrease, the level of pulmonary complications increases. Pulmonary tuberculosis has been reported to be the most common pulmonary infection among PLHIV. These pulmonary complications significantly affect the prognosis and survival of PLHIV.

This study aims to determine the clinical correlation of absolute total lymphocyte count (ATLC) and CD4 T-lymphocyte count with pulmonary complications of HIV seropositive patients seen at the Lung Center of the Philippines.

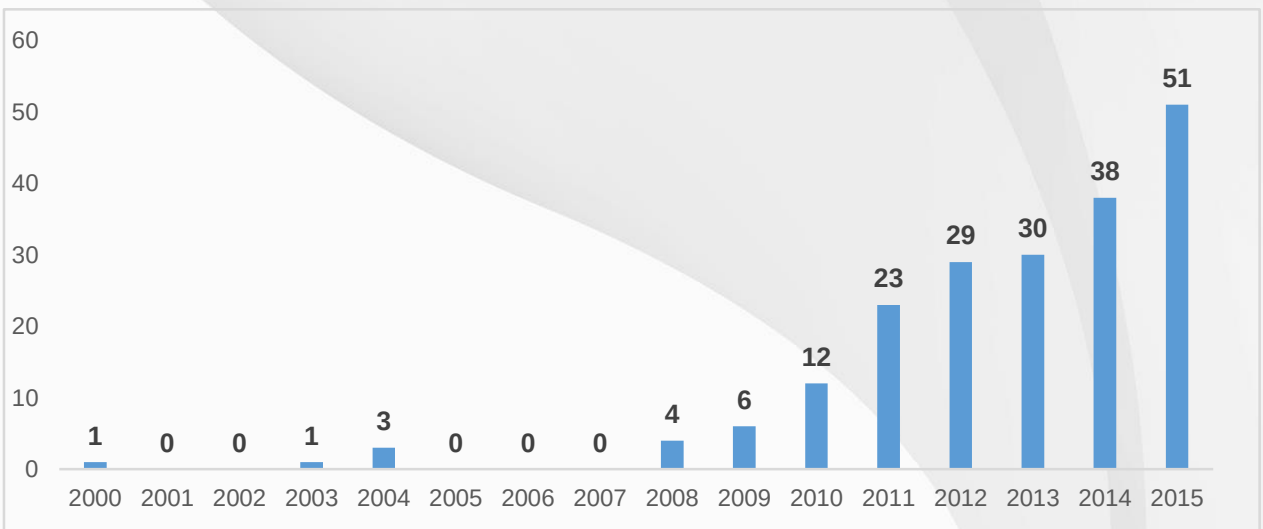
METHODOLOGY

This is a cross-sectional observational study of all HIV-seropositive patients seen at a tertiary pulmonary-subspecialty government hospital from January 2000 to September 2015. It included all newly diagnosed HIV-seropositive patients who initially presented with pulmonary symptoms at the time of diagnosis; all PLHIV who had no previous antiretroviral treatment; and all PLHIV who had ATLCs, CD4 measurements and chest radiographic imaging procedures. PLHIV with incomplete data on hospital records were excluded from the study.

We followed the patient privacy and confidentiality protocols of the Guidelines of the Declaration of Helsinki (2013), paragraph 24; CIOMS guideline 18 (2009); and ICH-GCP (1996), section 2.11.

Permission was obtained from the infection control committee, department manager of the Pathology Department, section head of the Immunology Laboratory and Institutional Ethics Review Board before initiating the conduct of the research. Only the names of the patients were copied from the Immunology Section. No documents were taken out of the laboratory. Retrieved charts from the medical records were kept strictly confidential. No information that could identify any particular patient was used in the study.

Figure 1. Frequency (n) of HIV Seropositive Individuals Diagnosed at the Lung Center of the Philippines (as of October 2015)



Study Procedure

One hundred ninety-eight charts were reviewed from the medical records of registered patients with HIV-seropositive screening by ELISA and confirmed by Western blot (Figure 1). These records were gathered from the Section of Immunology of the Department of Pathology.

Out of the 198 de-identified patients (accomplished by assigning a number to each chart), only 86 were included in this study. All had a recorded result for CD4 T-lymphocyte count and ATLC using a flow cytometer requested from the National Kidney and Transplant Institute. Three of the 86 did not have any pulmonary complications; thus, they were excluded from the study. Only 83 patients were included in the final study analysis (Figure 2).

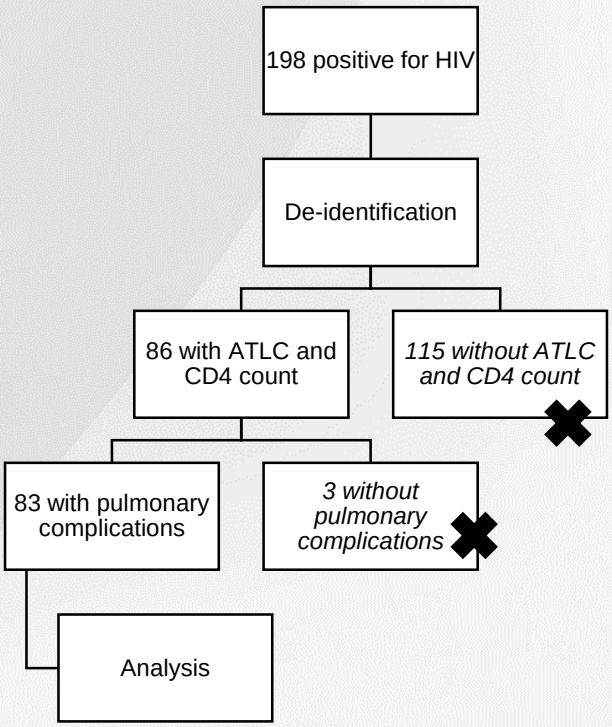
Statistical Analysis

Data were recorded and described using Microsoft Excel 2010 and Epi Info software version 3.45. Frequency distribution was measured using median with standard deviation. The correlation data of CD4 with pulmonary complications were compared with the TLC count in relation to pulmonary complications, and the correlation coefficient was calculated. The degree of correlation between CD4 count and ATLC was established using Pearson's analytical tool. Proportion of results, classified by the level of the CD4 and total lymphocyte count thresholds relevant to the clinical management of PLHIV, were analyzed. A p-value <0.05 was considered statistically significant for all statistical comparisons.

RESULTS

The demographic profile of 83 HIV seropositive patients showed that majority of them were males (99%), with age ranging from 21 to 40 years. Thirty-two percent of the entire group were 26–30 years old. The patients were predominantly single (93%), often unemployed (20%), but 14% worked as call center agents. Thirty-two percent were from Quezon City, followed by 13% from

Figure 2. Patient flow for study inclusion



Bulacan and 12% from Caloocan City. They were all positive for HIV type 1 serotype. Those with a history of sexually transmitted infection, drug use, and body piercing made up 6%, 10%, and 12% of the group, respectively (Table 1).

Majority of the patients (59%) were homosexual, engaging in both oral and anal sexual activity (54%). Twenty-five percent were bisexual, and 16% were heterosexuals. A high percentage of patients (54%) engaged in male-to-male sex. Most of the PLHIV (52%) had been with more than 5 partners (Table 2).

Difficulty in breathing (72%) was the most common symptom presented during consult and most common pulmonary manifestation. Patients also presented with cough (61%), fever (47%), active skin lesions (7%) and loose stools (5%). (Table 3).

Reticulonodular infiltrates (31%) were the most common radiologic finding. Others presented with alveolo-interstitial infiltrates (30%). Multiple radiologic findings were observ-

Table 1. Demographic Profile of HIV Seropositive Patients (N=83)

Characteristic	n (%)
Age, years	Median 30±6.29 years
21–25	16 (19)
26–30	27 (33)
31–35	16 (19)
36–40	16 (19)
41–45	6 (7)
46–50	1 (1)
51–55	1 (1)
Sex	
Male	82 (99)
Female	1 (1)
Civil Status	
Single	77 (93)
Married	3 (4)
Widow	1 (1)
Separated	2 (2)
Occupation	
Call center agent	12 (14)
Teacher	8 (10)
Supervisor/manager	6 (7)
Government employee	5 (6)
Photographer/video editor	3 (4)
Engineer	2 (2)
Other professions	17 (20)
Commercial sex worker	1 (1)
Beautician	2 (2)
Unemployed	17 (20)
Others	10 (12)
Residence	
Quezon City	27 (33)
Manila	3 (4)
Caloocan City	10 (12)
San Juan City	1 (1)
Pasay City	2 (2)
Marikina City	3 (4)
Makati City	2 (2)
Other Metro Manila cities	4 (5)
Bulacan	11 (13)
Antipolo City	3 (4)
Other provinces	15 (18)
HIV serotype	83 (100)
HIV 1	0 (0)
HIV 1 and 2	
Vices	16 (19)
Cigarette smoking	21 (25)
Alcohol	
History of STD	5 (6)
History of drug use	8 (10)
History of blood transfusion	2 (2)
Body piercing	12 (14)

Table 2. Frequency of High-Risk Behavior

Risk Factors	n (%)
Homosexual	
Oral sex	4 (5)
Anal sex	0 (0)
Both	45 (54)
Bisexual	
Oral sex	1 (1)
Anal sex	0 (0)
Vaginal penetration	0 (0)
All	20 (24)
Heterosexual	
Oral sex	1 (1)
Anal sex	0 (0)
Vaginal penetration	11 (13)
All	2 (2)
Engaging in commercial sex work	
Male to male	47 (57)
Male to female	16 (19)
Female to female	0 (0)
Unprotected sex	63 (76)
Using condom/any barrier	20 (24)
Multiple sexual partner	
2-5	20 (24)
6-9	43 (52)
10+	20 (24)

Table 3. Pulmonary Signs and Symptoms of HIV Seropositive Patients

Sign/Symptom	n (%)
Difficulty of breathing	60 (72)
Cough	51 (61)
Fever	39 (47)
Anorexia	22 (27)
Easy fatigability	24 (29)
Weight loss	19 (23)
Chest pain	1 (1)
Hemoptysis	1 (1)
Abdominal pain/loose stool	4 (5)
Rash/active skin lesions	6 (7)
Dysuria	0 (0)
Night sweats	4 (5)

ed to exist simultaneously in patients (Table 4).

The most common arterial blood gas (ABG) result was uncompensated respiratory alkalosis (51%), 27% with hypoxemia (Table 5).

Pneumocystis jirovecii pneumonia was the most frequent (51%) pulmonary complication. It was followed by pulmonary tuberculosis (41%). And any of these pulmonary complications could occur at the same time in a single patient (Table 6).

None of the patients had >200 CD4 T-lymphocyte count. Most of the patients (94%) who were seen with pulmonary complications had ≤100 CD4 T-lymphocyte count (Table 7).

The ATLC at CD4 T-lymphocyte count >100–200 mm^3 was 2.21% and with a CD4 T-lymphocyte count of ≤100 mm^3 was 0.98%. The correlation coefficient (r) was 0.77, p-value <0.01 (Table 8 and Figure 3).

There was a 24% mortality percentage for patients with CD4 T-lymphocyte level <100 mm^3 (Table 9)—specifically, <50 mm^3 per the subanalysis of the study.

DISCUSSION

In resource-limited countries such as the Philippines, CD4 T-lymphocyte count and CD8 cytotoxic cell count are not routinely requested due to its high cost.

Patients are required however to have these tests done for referral to treatment-hub hospitals, where they can start highly active antiretroviral therapy. However, not all tertiary hospitals have these tests available therefore, referral for the treatment of HIV seropositive patients is delayed. On the other hand, complete blood count with ATLC determination through flow cytometry is available at most hospitals at a low cost.

Table 4. Pulmonary Radiologic Findings in HIV Seropositive Patients

Radiologic Description	n (%)
Alveolo-interstitial	25 (30)
Hazy infiltrates	13 (16)
Reticulonodular	26 (31)
Reticular	6 (7)
Pulmonary congestion	1 (1)
Pleural effusion	6 (7)
Pneumothorax	4 (5)
Mediastinal mass	1 (1)
Consolidation	1 (1)

Table 6. Etiology of Pulmonary Complications

Pulmonary Complications	n (%)
Pneumocystis jirovecii	42 (51)
Pulmonary tuberculosis	34 (41)
Bacterial pneumonia	28 (34)
Candida/fungi	25 (30)
MDRTB	4 (5)
Histoplasma	1 (1)
Lymphoma	1 (1)
Protozoa (Escherichia coli)	1 (1)

MDRTB=multidrug-resistant tuberculosis.

Table 5. Arterial Blood Gas Results upon Consult at the Emergency Room or Outpatient Department of HIV Seropositive Patients

Arterial Blood Gas Interpretation	n (%)	Hypoxemia (PaO_2 <80 mmHg)
Respiratory acidosis, compensated	3 (4)	1 (1)
Respiratory alkalosis, compensated	20 (24)	14 (17)
Respiratory acidosis, uncompensated	1 (1)	0
Respiratory alkalosis, uncompensated	42 (51)	22 (27)
Metabolic acidosis, compensated	3 (4)	1 (1)
Metabolic alkalosis, compensated	1 (1)	0
Metabolic acidosis, uncompensated	2 (2)	1 (1)
Metabolic alkalosis, uncompensated	4 (5)	0
Normal acid-base balance	7 (8)	5 (6)

This study revealed that the majority of HIV-seropositive patients are male, single, and aged 21–30 years.. Patients who are call center agents, teachers, or unemployed have an increased risk of HIV. Majority of our study participants were from Quezon City, probably because our institution caters to residents of Quezon City. However, patients from Caloocan City and Bulacan also showed an increased percentage of PLHIV, compared to other cities and provinces.

Table 7. Level of CD4 T-Lymphocyte with Pulmonary Complication

Level of CD4 T-Lymphocytes, mm^3	Pulmonary Complications (%)
>500	0
>200–500	0
>100–200	5 (6)
≤100	78 (94)

All our participants had HIV 1 serotypes, and majority were homosexuals who engaged in both oral and unprotected anal sex. Nevertheless, bisexuals were also at high risk due to risky behaviors that were also observed among the homosexuals, i.e., most of the homosexuals and bisexuals engaged in unprotected sexual activities with male commercial sex workers. Also, Most also reported having had at least 5 sexual partners.

The most common pulmonary signs and symptoms were difficulty in breathing, chronic cough, and fever. The most common radiologic findings included reticulonodular infiltrates, alveolo-interstitial infiltrates, and haziness on bilateral lungs. The different infiltrates matched with particular pulmonary complications: most of the reticulonodular infiltrates were interpreted as pulmonary tuberculosis; alveolo-interstitial infil-

Table 8. Correlation of Level of Absolute Total T-lymphocyte Count and CD4 T-Lymphocytes Count

CD4 T-Lymphocytes, mm^3	Absolute Total T-Lymphocyte (SD)	Correlation (r)	P-value*
>500	0	0.77	<0.01
>200-500	0		
>100-200	2.21 (0.51)		
≤100	0.98 (0.78)		

Figure 3. Correlation of Absolute Total T-Lymphocyte Count and CD4 T-Lymphocyte Count

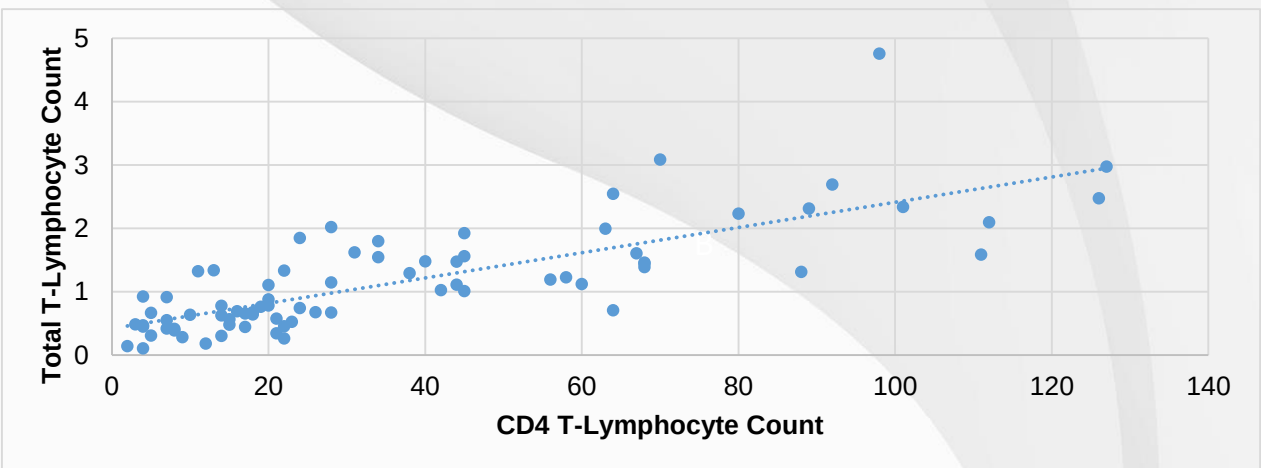


Table 9. Mortality of PLHIV with Regard to CD4 T-Lymphocyte Level

Level of CD4 T-Lymphocytes, mm^3	Mortality (%)
>500	0
>200–500	0
>100–200	0
≤100	20 (24)

trates were interpreted as pulmonary tuberculosis; alveolo-interstitial infiltrates as *P. jirovecii*; and haziness of bilateral lungs as probable bacterial pneumonia.

During the patients' initial visit to the emergency room, ABG was taken. The most common finding was respiratory alkalosis, either compensated or uncompensated. Out of 83 patients, 53% had mild to severe hypoxemia, as could be expected from patients with impending respiratory failure (the cohort had a 24% mortality rate).

The most common pulmonary complications were *P jirovecii* infection, followed by pulmonary tuberculosis. This is in contrast with other studies who reported pulmonary tuberculosis as the most common pulmonary infection.

The level of CD4 T-lymphocytes with pulmonary complications showed that majority of the infections were at the <100 mm^3 level. Furthermore, the levels of absolute total T-lymphocyte count and CD4 T-lymphocyte count were strongly correlated, with a coefficient of 0.77 and a statistically significant p-value <0.01. Finally, a mortality rate of 24% was seen in patients with a CD4 count <50mm^3.

CONCLUSION

HIV seropositive patients seen at the LCP were male, single, 21- to 30-year-old homosexuals who had engaged in unprotected sexual activities with a commercial sex worker. Most had >5 sexual partners and worked as call center agents or teachers, or were unemployed. The most common radiologic findings were reticulonodular, alveolo-interstitial, and hazy infiltrates, with respiratory alkalosis as the initial ABG result. *P jirovecii* was the most common pulmonary infection. Mortality was high among patients with CD4 T-lymphocyte count <50 mm^3 and a total lymphocyte count of 0.98%.

This study revealed a strong correlation between CD4 T-lymphocyte count and total T-lymphocyte count.

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CROSS-SECTIONAL STUDY

Clinical Profile of Patients with COPD According to GOLD 2014 Seen at the Outpatient Department of Lung Center of The Philippines

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ABSTRACT

Objectives: To determine the clinical profile of COPD patients seen at the outpatient department (OPD) of the Lung Center of the Philippines (LCP), and to establish the proportion of COPD groups according to the GOLD 2014 update.

Methodology: This is a cross-sectional, observational study done at the LCP OPD COPD clinic, using a validated questionnaire. Stratification of patients according to groups was done using pulmonary function test, reported symptoms, the modified Medical Resarch Council score, and other pertinent patient information.

Results: The mean age of COPD patients studied was 67.0 years. Most of the subjects were male (87.9%) and former smokers (86.7%). A history of tuberculosis treatment (51.5%) and hypertension (79%) were common co-morbid conditions. Patients were also taking multiple COPD medications. Most patients belonged to group D of the GOLD 2014 classification (18.8% were in group A, 21.8 % in group B, 12.7% in group C, and 46.7% to group D).

Conclusion: COPD patients seen at LCP OPD were usually elderly, male, former smokers, hypertensive, and mostly belonging to group D.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is the fourth leading cause of death in the world. It is expected to become the third leading cause of death worldwide by 2020.[1,2] It is also a major cause of chronic morbidity and mortality resulting in a substantial and increasing economic and social burden.[3] A local study in 1987 estimated that the prevalence of COPD was 3.7% based on spirometric measurements, while a later study by Idolor et al reported that the overall prevalence of COPD was 20.8 % (16.7% for Global Initiative for Obstructive Lung Disease [GOLD] stage II or higher).[4,5] The prevalence was greater in men compared to women, and increased with age.[5]

While COPD has well-defined diagnostic criteria, COPD patients constitute a heterogeneous group: COPD patients with similar airflow limitations had marked differences in symptoms (dyspnea, cough, and sputum production), rates of exacerbations, exercise capacity, and health status.[6,7] Hence, the 2014 GOLD update included airflow limitation, history of COPD exacerbations, and symptoms to classify and grade COPD severity through the four-box approach (i.e., patient group A as “low risk, less symptoms”; Group B as “low, risk, more symptoms”; Group C as “high risk, less symptoms”; and Group D as “high risk, more symptoms”) (Appendix). Stratification of patients

according to severity of COPD is important to initiate relevant treatment and is one of the most crucial aspects of the updated management guideline.[3,8,9]

With this recent update in guidelines, our primary objective is to determine the clinical profile of COPD patients seen at the OPD of the Lung Center of the Philippines. Our secondary objectives were to determine the proportion of COPD groups according to latest GOLD 2014 and evaluate the medications given to each of the COPD groups.

METHODOLOGY

This is a cross-sectional, observational study done at the Lung Center of the Philippines (LCP). It included patients who consulted at the COPD Outpatient clinic of the LCP from May 2015 to October 2015. Patients had to be aged 40 years or older, and diagnosed with COPD according to GOLD 2014 criteria. Patients who were in acute exacerbation with unstable vital signs, cancer patients, and those with a history of radiation therapy to chest or breast were all excluded.

Enrolled patients were interviewed using the American Thoracic Society (ATS) Respiratory symptom questionnaire.[10] The following data were collected: demographics, BMI, co-morbidities, smoking status, exacerbations and hospitalizations, treatment, and modified Medical Research Council (mMRC) findings. Patients were then categorized into different groups: COPD group A, B, C, and D.

Descriptive analysis was performed on all variables. Categorical variables such as age range, gender, weight classification based on BMI, smoking history, co-morbidites, and medications were summarized and expressed as frequencies and percentages. The prevalence of COPD group was computed with a 95% confidence interval. MedCalc Statistical software was used in all computations.

We conducted the study in compliance with the ethical principles set in the Declaration of Helsinki. The Institutional Ethics Review Board of the LCP reviewed and approved the study protocol and subsequent amendments. A written letter of consent and confidentiality was obtained by the investigators before data was collected.

RESULTS

The study included 165 patients. Table 1 shows the distribution of patients by GOLD 2014 classification. Class D was the most common COPD patient group (46.7%), followed by group B, (21.8%), group A (18.8%), and group C (12.7%).

Overall, 87.9% of patients were male (Table 2). Most patients were aged 60 years old and above (81.8%). Patients who belonged to group A were mostly aged 50 to 69 years old, while patients who belonged to group B, C, and D were 60 years old and above. Most patients had a BMI of 18.5 to 24.9 kg/m^2 (55.2%). The most common causative factor related to COPD was a previous or current smoking (94%), with 89.7% having over a 10 pack-years smoking history (Tables 3 and 4). Other causative factors included exposure to biomass fuel wood/charcoal (81.8%), other respiratory conditions (67.8%), occupational exposure (56.4%), and second-hand smoke (44.8%).

Hypertension was identified as a co-morbid condition in 79 patients (47.9%) (Table 5). Other

Table 1. Proportion of COPD patients by GOLD 2014 classification

Class	N	%	95% Confidence Interval	
			Lower	Upper
A	31	18.8	13.30	25.80
B	36	21.8	15.90	29.10
C	21	12.7	8.20	19.00
D	77	46.7	38.90	54.60

Table 2. Demographic profile of COPD patients by GOLD 2014 classification

Demographic	Overall (n=165)		A (n=31)		B (n=36)		C (n=21)		D (n=77)	
	N	%	N	%	N	%	N	%	N	%
Gender										
Male	145	87.9	23	74.2	34	94.4	19	90.5	69	89.6
Female	20	12.1	8	25.8	2	5.6	2	9.5	8	10.4
Age (mean 67 years)										
40 – 49	3	1.8	3	9.7	0	0.0	0	0.0	0	0.0
50 – 59	27	16.4	11	35.5	5	13.9	4	19.0	7	9.1
60 – 69	69	41.8	13	41.9	14	38.9	11	52.4	31	40.3
70≥	66	40.0	4	12.9	17	47.2	6	28.6	39	50.6
Body mass index (mean 21.2)										
<18.5	44	26.7	6	19.4	7	19.4	10	47.6	21	27.3
18 .5 - 24.9	91	55.2	19	61.3	23	63.9	9	42.9	40	51.9
25 - 29.9	20	12.1	4	12.9	5	13.9	1	4.8	10	13.0
>30	10	6.1	2	6.5	1	2.8	1	4.8	6	7.8

Table 3. Causative factors for COPD by GOLD 2014 classification

	Overall (n=165)		A (n=31)		B (n=36)		C (n=21)		D (n=77)	
	N	%	N	%	N	%	N	%	N	%
Respiratory Condition										
Asthma	24	14.5	2	6.5	2	5.6	7	33.3	13	16.9
Tuberculosis	85	51.5	12	38.7	18	50.0	12	57.1	43	55.8
Bronchiectasis	3	1.8	0	0.0	0	0.0	2	9.5	1	1.3
Smoke Exposure										
Current	12	7.3	8	25.8	4	11.1	0	0.0	0	0.0
Former	143	86.7	20	64.5	30	83.3	19	90.5	74	96.1
Never-Smoker	9	6.1	3	9.7	1	2.8	2	9.5	3	3.9
Second Hand Smoke										
Expose at Home	74	44.8	10	32.3	13	36.1	12	57.1	39	50.6
Bio Fuel Exposure										
Wood / Charcoal	135	81.8	25	80.6	29	80.6	16	76.2	65	84.4
Occupation										
Exposure to Dust	93	56.4	10	32.3	21	58.3	13	61.9	49	63.6

Never smoker: never smoked a cigarette or who smoked <100 cigarettes in their lifetime.

Table 4. Smoking History by GOLD 2014 classification

# Pack	Overall (n=165)		A (n=31)		B (n=36)		C (n=21)		D (n=77)	
	N	%	N	%	N	%	N	%	n	%
Non Smoker	9	5.5	3	9.7	1	2.8	2	9.5	3	3.9
< 10 pack years	8	4.8	4	12.9	0	0.0	2	9.5	2	2.6
>10 pack years	148	89.7	24	77.4	35	97.2	17	81.0	72	93.5

Table 5. Co-morbidities of COPD patients by GOLD 2014 classification

Associated Co-morbid conditions	Overall (n=165)		A (n=31)		B (n=36)		C (n=21)		D (n=77)	
	N	%	n	%	N	%	N	%	n	%
Hypertension	79	47.9	14	45.2	21	58.3	10	47.6	34	44.2
Diabetes Mellitus	15	9.1	1	3.2	6	16.7	1	4.8	7	9.1
Heart disease including ischemic heart disease	23	13.9	2	6.5	6	16.7	1	4.8	14	18.2
Cerebrovascular Accident	5	3.0	0	0.0	2	5.6	0	0.0	3	3.9

Table 6. Medications of COPD patients by GOLD 2014 classification

Medication	Overall (n=165)		A (n=31)		B (n=36)		C (n=21)		D (n=77)	
	n	%	n	%	n	%	N	%	n	%
SABA	55	33.3	8	25.8	13	36.1	10	47.6	24	31.2
LABA	4	2.4	1	3.2	0	0.0	1	4.8	2	2.6
SAMA	14	8.5	2	6.5	4	11.1	1	4.8	7	9.1
LAMA	49	29.7	3	9.7	5	13.9	6	28.6	35	45.5
SABA+SAMA	58	35.2	7	22.6	7	19.4	5	23.8	39	50.6
LABA+LAMA	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Methylxanthine	96	58.2	8	25.8	16	44.4	15	71.4	57	74.0
Oral corticosteroid	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
LABA+ICS	148	89.7	24	77.4	31	86.1	20	95.2	73	94.8
PD4	1	0.6	0	0.0	0	0.0	0	0.0	1	1.3
NAC	72	43.6	8	25.8	14	38.9	6	28.6	44	57.1

SABA, short acting beta agonist; LABA, long acting beta agonist; SAMA, short acting anti muscarinic; LAMA, long acting anti muscarinic; ICS, inhaled corticosteroid; PD4, phosphodiesterase-4; NAC, n-acetylcysteine.

co-morbid conditions included heart disease or ischemic heart disease (13.9%), diabetes mellitus (9.1%), and cerebrovascular accident (3%), which were mostly in group B and D.

The most commonly prescribed medications were combined inhaled long-acting beta-agonist and corticosteroid (LABA/ICS) (89.7%) and methylxanthines (58.2%) (Table 6). Phosphodiesterase inhibitors and LABAs were the least commonly prescribed medications. The combination of an inhaled LABA and LAMA, as well as oral corticosteroid, were never used in this cohort.

DISCUSSION

The profile of COPD patients seen at the LCP-OPD showed that they were: elderly, mostly male, hypertensive, former smokers, and belonging to group D of the GOLD 2014 classification.

Most of the patients in this study belonged to group D (46.7%), followed by B, A, and C (21.8%, 18.8%, and 12.7 respectively). Various studies showed that this distribution varied across different cohorts and countries.[11,12] In a study by Agusti et al on four different cohorts (COPD gene, Copenhagen study, Cocomics study, Eclipse study), the most prevalent in the general population was group A (77%), but in the secondary and tertiary care, group D (37%) was the most common.

The mean age of COPD patients was 67 (Table 1,0) somewhat close to the EPOCA study with a mean age of 69.5.[11] Other studies showed a mean age of 65, 68, 66 and 64 (COPD gene, Copenhagen, Cocomics, and Eclipse respectively).[12] All of these studies showed that COPD occurred in the elderly population. As to gender, our study showed that the prevalence of COPD in male was 87.9% which is consistent with other studies. Other cohort studies showed a male prevalence of 53, 52, 93 and 65 (COPDGene, Copenhagen, Cocomics, and Eclipse respectively).[12] The difference in gender population is probably due to an increase in tobacco use in males (47.7%) as compared to females (9.0%) in the Philippines according to GATS report .[13] Regarding Body Mass Index (BMI), most of our patients were within normal range (55.3%). However, 26.7% of our patients were noted to have a low BMI (<18kg/m^2), and mostly in group C and D (Table 1.0). There is an association of low BMI and poor prognosis in patients with COPD. It was noted that a low BMI is an independent negative determinant of survival in patients with COPD.[14]

Smoking is the most common cause of COPD.[2,9,11] In our study, 86.7% were former smokers and mostly belonging to group D. Comparing group A to group D, there was a higher percentage of current smokers in group A. This was probably because those belonging to group D had more symptoms and exacerbations. In a study by Han et al. former smoker is more prevalent in group D and less prevalent in group A. Tobacco is the main risk factor for COPD and it occurs after 20 to 25 pack years of exposure.[15] Although cigarette smoking is a risk factor for COPD, only 20 to 30% of smokers develop COPD suggesting genetic susceptibility or immunological host characteristics play an important role in disease occurrence.

De Marco et al mentioned that aside from smoking, other risk factors in developing COPD were airway hyper-responsiveness, respiratory infections in childhood, and a family history of asthma.[16] Second hand smoking can also cause COPD. In our study it was noted that 44.8 % of the subjects were exposed to second-hand smoking. According to GATS report on exposure to second-hand smoking, 39.6% of Filipinos were exposed at home daily, 36.9% were exposed at work indoors or enclosed areas, 55.3% in public transport, 33.6% in restaurants, 25.5% in government buildings and 7.6% in health care facilities.[13]

Many patients had a history of pulmona-

ry tuberculosis (TB). In a systematic review done by Byrne et al, a reported history of TB was associated with spirometry-confirmed COPD among people aged 40 years and over, and the strongest association was noted in the Philippines. The odds ratio of having COPD was over three times higher among people with a history of TB than among people without such a history.[17] In the study by Mao et al, 34.7% among COPD patients had bronchiectasis, and 12.1% of those with bronchiectasis were due to TB.[18] Complications of obstructive abnormalities in lung function develop in pulmonary TB if there is extensive parenchymal involvement. Abnormalities in lung function were significantly associated with increased duration of TB disease and age over 40. The development of airflow obstruction in TB may be caused by localized or generalized bronchial obstruction, fibrosis and increased airway resistance secondary to endobronchial involvement or bronchial compression due to lymphadenopathy.[19]

COPD occurs in elderly patients. The likelihood of co-morbid conditions in COPD increases with age. In our study it was noted that a common co-morbid condition was hypertension (47.9%). It was also noted that most of the co-morbidities seen were in patients belonging to group B and group D. This was in line with the study done by Oliveira et al, showing a high incidence of systemic arterial hypertension (55%) was noted in COPD patients, since hypertension increases linearly with age.[20] Our study also showed a high incidence of diabetes and heart disease. This may be clinically relevant, as symptoms such as dyspnea may not be secondary to COPD alone but also to underlying co-morbities, in particular, heart disease.[8]

Regarding medications prescribed, 55 out of 67 patients belonging to group A and B were given ICS/LABA. Guidelines however recommend short-acting bronchodilators as needed, while anticholinergics or as needed, and long-acting bronchodilators are considered as first-line treatments for group B.[3] Proper classification and a review of treatment guidelines should be done to decide on the most appropriate medication. According to the EPOCA study 41.9 % of the prescriptions of ICS were not prescribed correctly and conversely, in 27.8% of the cases in which they were indicated, the ICS were not prescribed.[11]

Methylxanthine were also given to groups A and B. The guidelines recommend the use of methylxanthine only in patients who remain symptomatic despite the use of inhaled long-acting bronchodilators. It is classified as an alternative medicine.[3] The high use of methylxanthines in this study may be due to economic reasons because of its lower cost.

The main limitations of this study are its observational and cross-sectional approach which is prone to recall bias. The study also used mMRC which reflects only one aspect of COPD evaluation (i.e., breathlessness). Studies noted that the distribution of COPD patients among the different groups was variable depending on whether the mMRC or COPD Assessment Test (CAT) systems were chosen.[21,22] CAT and the COPD Control Questionnaire (CCQ) are more comprehensive tools. Clinical relevance of these data would require longitudinal validation to determine how groups differ with respect to important clinical outcomes (morbidity and mortality).

CONCLUSION

COPD patients seen at LCP OPD were elderly, male, former smoker, hypertensive, and mostly belonging to group D. As to the distribution of our COPD patients, 46.7% belonged to group D, 21.8 % to group B, 18.8% to group A, and 12.7% to group C.

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APPENDIX

2014 Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification

Patient group A: Low Risk, Less Symptoms

- Patients belonging to GOLD 1 or GOLD 2 (post bronchodilator FEV 1 ≥ 50% predicted); and/or,
- 0-1 exacerbation per year and no hospitalization for exacerbation; and,
- CAT score <10 or mMRC grade 0-1

Patient Group B: Low Risk, More Symptoms

- Patients belonging to GOLD 1 or GOLD 2 (post bronchodilator FEV 1 ≥ 50% predicted); and/or,
- 0-1 exacerbation per year and no hospitalization for exacerbation; and,
- CAT score ≥10 or mMRC ≥2

Patient Group C: High Risk, Less Symptoms

- Patients belonging to GOLD 3 or GOLD 4 (post bronchodilator FEV 1 < 50% predicted); and /or,
- ≥2 exacerbations per year or ≥1 with hospitalization for exacerbation; and CAT score <10 or mMRC grade 0-1

Patient group D: High Risk, More Symptoms

- Patients belonging to GOLD 3 or GOLD 4 (post bronchodilator FEV 1 < 50% predicted); and/or,
- ≥2 exacerbations per year or ≥1 with hospitalization for exacerbation; and,
- CAT score≥10 or mMRC grade ≥2

CAT, COPD Assessment Test; mMRC, modified Medical Research Council.

RETROSPECTIVE CROSS-SECTIONAL STUDY

Bacterial Pathogens of Patients with Chronic Obstructive Pulmonary Disease (COPD) Admitted for Acute Exacerbation at the Lung Center of the Philippines in 2011–2014

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ABSTRACT

Purpose: Chronic obstructive pulmonary disease (COPD) exacerbations are associated with worsening lung function, which contributes to morbidity and diminished quality of life. Two local COPD studies have previously been done at our institution, the Lung Center of the Philippines (LCP). This follow-up study identifies common bacterial pathogens that cause exacerbations among COPD patients admitted at LCP from 2011 to 2014.

Methods: This retrospective cross-sectional study analyzes the results of respiratory cultures (ie, sputum, endotracheal aspirate, bronchoalveolar lavage, and transthoracic aspirate) taken within 3 days of the patient's admission, as recorded in the charts of 399 COPD patients. Only culture results indicating light, moderate, heavy, or predominant growth were included.

Results: The top 5 pathogens found were *Moraxella catarrhalis* (21%), *Pseudomonas aeruginosa* (16%), *Enterobacter aerogenes* (14%), *Klebsiella pneumoniae* (9%), and *Acinetobacter baumannii* (6%). *P aeruginosa*, *E aerogenes*, and *K pneumoniae* showed a variable sensitivity pattern to aminoglycosides, third- to fourth-generation cephalosporins, quinolone, carbapenems, and aminopenicillin. They showed good sensitivity patterns with meropenem and piperacillin-tazobactam. *Moraxella* sp showed poor sensitivity patterns to second-generation cephalosporins, amikacin, ciprofloxacin, and cotrimoxazole but better sensitivity patterns with co-amoxiclav and moxifloxacin. *M catarrhalis* was the most common pathogen among pure COPD patients, COPD patients with active pulmonary tuberculosis (PTB), and COPD patients with bronchiectasis. *P aeruginosa* was the most common isolate among COPD patients with coexisting lung cancer, while *E aerogenes* was the most common isolate among COPD patients with coexisting PTB and lung cancer.

Conclusion: *M catarrhalis*, *P aeruginosa*, *E aerogenes*, *K pneumoniae*, and *A baumannii* were the most common bacterial pathogens isolated from acute-exacerbation COPD patients admitted at our institution from January 1, 2011 to December 31, 2014. Alpha-hemolytic *Streptococcus* and coagulase-negative staphylococci were not included although they were previously identified by the two previous local studies, because both organisms are normal flora of the respiratory tract. These findings are comparable with the bacterial pathogens isolated by the 2 previous local studies. There is no difference in the bacterial pathogens isolated in the subgroups of COPD patients.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD), a cause of worldwide morbidity and mortality, is an important public health challenge that is both preventable and treatable. The diagnosis of an exacerbation relies exclusively on the clinical presentation of the patient, exhibiting an acute change of symptoms (baseline dyspnea, cough, and/or sputum production) beyond normal day-to-day variation.[1]

Acute exacerbations of COPD (AECOPD) are common events that often lead to hospitalization and are associated with worsened quality of life, increased healthcare costs, and increased mortality. This can be precipitated by several factors, the most common of which appear to be respiratory tract infections, either viral or bacterial. Bronchoscopic studies have shown that at least 50% of patients have bacteria in their lower airways during exacerbations of COPD.[1]

In 50%–70% of AECOPD, the pathophysiological basis is usually infectious. *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Moraxella catarrhalis*, and *Pseudomonas aeruginosa* are the most frequent bacteria isolated in acute exacerbations of COPD.[2,3,4]

Local studie.s done at the Lung Center of the Philippines (LCP) have identified alpha-hemolytic streptococci, *M catarrhalis*, *P. aeruginosa*, coagulase-negative staphylococci (CoNS) and *Enterobacter* sp as the most common pathogens cultured in COPD patients admitted for acute exacerbation.[5,6]

This study aimed to identify the top 5 bacterial pathogens isolated among COPD patients admitted for AECOPD at LCP in 2011–2014 and to compare the results with those of 2 previous local studies.

METHODOLOGY

We reviewed charts of COPD patients admitted for acute exacerbation from January 1, 2011 to December 31, 2014. Participants included adult subjects aged ≥40 years; with a smoking history ≥10 pack years; a pulmonary function test confirming the diagnosis of COPD (ie, FEV1/FVC <0.70); with or without concomitant pulmonary diseases such as pulmonary tuberculosis (PTB), bronchiectasis, PTB with bronchiectasis, and bronchogenic carcinoma; and in acute exacerbation, defined as an increase in sputum production, increased sputum purulence, and worsening dyspnea, with or without fever.

Excluded from the study were those who were <40 years old; asthmatic; with intake of antibiotics in the week prior to admission; unable to expectorate adequate lower respiratory tract specimens for examination; those with stable COPD and not in acute exacerbation; those who had poor specimens taken; or those with normal flora isolated.

Results of respiratory cultures such as sputum, endotracheal aspirate, bronchoalveolar lavage, and transthoracic aspirate taken within 3 days of admission (to rule out nosocomial infection) were analyzed. Only culture results that indicated light, moderate, heavy, or predominant growth were included. Tabulation of the offending organisms was done. Data were recorded with Windows Microsoft Excel 2010 and analyzed using Epi Info software 3.45 for frequencies and percentages.

RESULTS

The top 5 cultured pathogens were *M catarrhalis* (20.80%), *P aeruginosa* (16.04%), *Enterobacter aerogenes* (14.29%), *Klebsiella pneumoniae* (9.02%), and *Acinetobacter baumannii* (6.27%) (Table 1). Normal flora, which include alpha-hemolytic streptococci and coagulase-negative staphylococci (CoNS), were not included.

Gram-negative bacteria showed a variable sensitivity pattern toward aminoglycosides, third- to fourth-generation cephalosporins, quinolone, carbapenems, and aminopenicillin; however in our study, *P aeruginosa*, *E aerogenes*, and *K pneumoniae* had good sensitivity patterns with meropenem and piperacillin-tazobactam (Table 2).

Moraxella sp., the most common bacterial

Table 1. Organisms in Cultures of COPD Patients with Acute Exacerbations

Bacteria	Frequency (n)	Percentage
Moraxella catarrhalis	83	20.8%
Pseudomonas aeruginosa	64	16.0%
Enterobacter aerogenes	57	14.3%
Klebsiella pneumonia	36	9.0%
Acinetobacter baumannii	25	6.3%
Acinetobacter lwoffii	21	5.3%
Pantoea agglomerans	13	3.3%
Gamma-hemolytic streptococci	10	2.5%
Burkholderia cepacia	5	1.3%
Escherichia coli	3	0.8%
Stenotrophomonas maltophilia	3	0.8%
Alcaligenes faecalis	2	0.5%
Haemophilus influenza	1	0.3%
Streptococcus pneumoniae	1	0.3%
Staphylococcus aureus	1	0.3%

COPD-chronic obstructive respiratory disease.

Table 2. Antibiotic sensitivity pattern for Gram-negative isolates

	***Pseudomonas aeruginosa* (n=26)**	***Enterobacter aerogenes* (n=21)**	***Klebsiella pneumonia* (n=18)**
Amikacin	23 (88.5%)	19 (90.5%)	17 (94.4%)
Cefepime	24 (92.3%)	20 (95.2%)	15 (83.3%)
Cefotaxime	18 (69.2%)	17 (81.0%)	11 (61.1%)
Ceftazidime	22 (84.6%)	20 (95.2%)	15 (83.3%)
Ciprofloxacin	21 (80.8%)	19 (90.5%)	13 (72.2%)
Imipenem	23 (88.5%)	20 (95.2%)	14 (77.8%)
Meropenem	23 (88.5%)	20 (95.2%)	16 (88.9%)
Piperacillin-tazobactam	23 (88.5%)	19 (90.5%)	16 (88.9%)

pathogen isolated, showed poor sensitivity patterns for amikacin, cefepime, ciprofloxacin, chloramphenicol, co-amoxiclav, cotrimoxazole, penicillin G, and moxifloxacin. While both *S pneumoniae* and *H influenzae* were sensitive to cotrimoxazole (Table 3).

M. catarrhalis, *P. aeruginosa*, and *E. aerogenes* remain the most commonly isolated bacterial pathogens. *H influenzae*, which was the fifth most common bacterial pathogen identified by Limsi et al and considered to be the most common bacterial pathogen isolated among COPD patients, was only identified in 1 patient in this study; it was not among the top 5 pathogens that we identified (Table 4). Both alpha-hemolytic streptococci and CoNS were not included in this study since both are normal flora of the respiratory tract.

Of the 399 patients whose charts were reviewed, only 269 had a diagnosis of with pure COPD; 130 were associated with coexisting respiratory disease. *M. catarrhalis*, *P. aeruginosa*, and *E. aerogenes* were the 3 most common bacterial pathogens isolated from these patients. *M. catarrhalis* was the most common pathogen among pure COPD patients, COPD patients with active PTB, and COPD patients with bronchiectasis. *P. aeruginosa* was the most common isolate among COPD patients with coexisting lung cancer. While *E. aerogenes* was the most common isolate among COPD patients with coexisting PTB and lung cancer (Table 5).

DISCUSSION

Previous studies have shown that in 50%–70% of AECOPD, the pathophysiological bases are usually infectious. *H influenzae*, *S pneumoniae*, *M catarrhalis*, and *P aeruginosa* are the most frequent bacteria isolated in AECOPD.[2,3,4,7] Overall, the results of our study showed that the most common bacterial pathogens isolated during exacerbations are the

Table 3. Antibiotic sensitivity pattern for Gram-positive isolates

	Moraxella sp n=31	Streptococcus pneumonia (n=1)	Haemophilus influenza (n=1)
Amikacin	3 (9.7%)	ND	ND
Ciprofloxacin	5 (16.1%)	ND	ND
Chloramphenicol	11 (35.5)	1 (100%)	ND
Co-amoxiclav	13 (41.9%)	1 (100%)	ND
Cotrimoxazole	7 (22.6%)	1 (100%)	1 (100%)
Penicillin G	ND	1 (100%)	ND
Moxifloxacin	18 (58.1%)	ND	1 (100%)

ND=no diagnostic sensitivity test.

Table 4. Top 5 Isolated Bacterial Pathogens from Studies Done at LCP

	Limsi 2005	**Buendia 2008**	**Aspiras 2016**
Inclusive years	**2003–2004**	**2005–2007**	**2011–2014**
Alpha-hemolytic streptococci	25.8%	60.4%	
Moraxella catarrhalis	21.6%	37.6%	20.8%
Pseudomonas aeruginosa	10.2%	14.1%	16.0%
CoNS	8.7%	13.4%	
Haemophilus influenzae	7.2%		
Enterobacter aerogenes		10.9%	14.3%
Klebsiella pneumoniae			9.0%
Acinetobacter baumannii			6.3%

CoNS=coagulase-negative staphylococci; LCP=Lung Center of the Philippines.

following: *M catarrhalis* (20.80%), *P aeruginosa* (16.04%), and *E aerogenes* (14.29%). These findings are comparable with the isolated bacterial pathogens in 2 studies previously done at LCP.[5,6] Alpha-hemolytic streptococci and CoNS were not included in our study because these are both normal flora of the respiratory tract. Except for *Moraxella* sp, our findings do not match the most commonly isolated bacterial pathogens found among COPD patients with acute exacerbations, as reported in most of the previously existing literatures.[2,3,4,7] *H influenzae* and *S pneumoniae* belong to the lower tiers of pathogens isolated among COPD patients in our study.

The bacterial pathogens we isolated showed a favorable drug sensitivity pattern. Gram-negative bacterial pathogens isolated were sensitive to aminoglycosides, carbapenems, third- to fourth-generation cephalosporins, and quinolones, while *Moraxella* sp and CoNS had variable sensitivity patterns. *S. pneumoniae* and *H. influenzae* were both sensitive to cotrimoxazole. These findings suggest that the use of these antibiotics is judicious and appropriate among patients admitted for acute exacerbations.

The top bacterial pathogens isolated from this study are comparable to the bacterial pathogens isolated previously by 2 previous studies done at LCP by Limsi et al[5] and Buendia et al.[6] There are no differences in the isolated bacterial pathogens in COPD, COPD with PTB, COPD with bronchiectasis, COPD with bronchogenic carcinoma, and COPD with PTB and concomitant bronchiectasis. Alpha-hemolytic streptococci, *M catarrhalis* , *Candida* sp, *P aeruginosa*, CoNS, *E aerogenes*, *Klebsiella* sp, and *Acinetobacter* sp were the isolates identified

Table 5. Organisms Isolated Among COPD Patients With and Without Coexisting Pulmonary Diseases

	COPD Only n=269	Active PTB* n=21	Bronchiectasis* n=89	Lung Cancer* n=8	Active PTB and Bronchiectasis* n=12
Moraxella catarrhalis	58 (21.6%)	8 (38.1%)	14 (15.7%)	1 (12.5%)	2 (16.7%)
Pseudomonas aeruginosa	41 (15.2%)	5 (23.8%)	12 (13.5%)	3 (37.5%)	3 (25.0%)
Enterobacter aerogenes	38 (14.1%)	3 (14.3%)	10 (11.2%)	-	6 (50.0%)
Klebsiella pneumoniae	32 (11.9%)	1 (4.8%)	4 (4.5%)	1 (12.5%)	1 (8.3%)
Acinetobacter baumannii	15 (5.6%)	-	9 (10.1%)	1 (12.5%)	-
Acinetobacter lwoffii	9 (3.3%)	-	6 (6.7%)	3 (37.5%)	3 (25.0%)
Pantoea agglomerans	9 (3.3%)	-	4 (4.5%)	-	-
Gamma-hemolytic streptococci	7 (2.6%)	-	-	-	3 (25.0%)
Burkholderia cepacia	5 (1.9%)	-	-	-	-
Escherichia coli	3 (1.1%)	-	-	-	-
Stenotrophomonas maltophilia	3 (1.1%)	-	-	-	-
Alcaligenes faecalis	-	-	2 (2.2%)	-	-
Haemophilus influenza	-	-	1 (1.1%)	-	-
Streptococcus pneumoniae	1 (0.4%)	-	-	-	-
Staphylococcus aureus	1 (0.4%)	-	-	-	-

COPD=chronic obstructive pulmonary disease; PTB=pulmonary tuberculosis.
**In addition to COPD.*

in these studies.

One limitation of our study is that several studies have previously identified bacteria in sputum samples even among patients with stable COPD, so it is difficult to say whether the organisms that we found were true pathogens or colonizers. Also the lack of serological testing for viruses and atypical bacteria in our institution limits our study to isolating bacterial pathogens only.

AECOPD remains one of the most common causes for admission at LCP. The use of antibiotics remains controversial—certain criteria need to be met for it to be indicated. This study revisited previous studies to identify antibiogram at LCP from January 1, 2011 to December 31, 2014 and compare it with bacterial pathogens isolated previously.

We found *M. catarrhalis, P. aeruginosa*, *E. aerogenes, K. pneumoniae,* and *A. baumannii* to be the most common bacterial pathogens isolated from AECOPD patients admitted at our institution. These findings are comparable with the isolated bacterial pathogens from 2 previous studies. There is no difference in the bacterial pathogens isolated in the subgroups of COPD patients analyzed in the study.

Our results plus the data from other studies show that *M. catarrhalis*, *P. aeruginosa*, and *E. aerogenes* remain the 3 most commonly isolated bacterial pathogens that cause acute exacerbations among hospital-admitted COPD patients. If warranted, the use of antibiotics with coverage among these pathogens is prudent.

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Table 1. Demographic Data

Characteristics	Mucoid (n=33)	Purulent (n=56)	P-value
Age (years)	71.9±13.8	65.5±14.4	0.0403
Sex Male (%) Female (%)	 26 (78.79) 7 (21.21)	 46 (82.14) 13 (23.21)	 0.782
BMI (kg/m^2)	23.5±3.4	23.07±4.0	0.6473
Smoking history (pack-years)	25.6±22	34.1±27.45	0.1346
Medication use ICS + LABA (%) LAMA (%) SABA (%) LAMA + LABA (%)	 14 (42.42) 11 (33.33) 13 (39.39) 0	 40 (71.43) 17 (30.36) 9 (16.07) 4 (7.14)	 0.013 0.816 0.021 0.292
Patients with COPD (%)	32 (97.0)	44 (78.57)	0.027
Patients with bronchiectasis (%)	1 (3.0)	12 (21.43)	0.027

COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroids; LABA, long-acting beta agonists; LAMA, long-acting antimuscarinics; PY, pack years; SABA, short-acting beta agonists.

nic-bronchitis/

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CROSS-SECTIONAL STUDY

The Prevalence of Peripheral Arterial Disease among Filipino Chronic Obstructive Pulmonary Disease Patients at the Outpatient Department of the Lung Center of the Philippines

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ABSTRACT

Purpose: Chronic obstructive pulmonary disease (COPD) is a persistent airflow limitation in the airways and lungs due to noxious particles and gases. Peripheral arterial disease (PAD) is an atherosclerotic vascular disease of the lower limbs. Both are strongly connected with cigarette smoking. For this reason, our study aimed to investigate their co-existence and determining the prevalence of PAD among COPD patients seen at the Outpatient Department (OPD) of the Lung Center of the Philippines (LCP).

Methods: This was a cross-sectional study on 118 Filipino COPD patients, seen at the OPD of LCP, and with available ankle-brachial index (ABI) measurements. Information such as gender, age, smoking history, body mass index, co-morbidities, lung function parameters and ABI measurements were retrieved from patient medical records and analyzed.

Results: The prevalence of PAD in Filipino COPD patients was 19.5%. Around 61% who contracted PAD were ≥60 years old. Diabetes mellitus (p=0.001) and ischemic heart disease (p=0.05) was significantly associated to PAD. Former smoking was significantly correlated with PAD (p<0.005). Smokers who consumed at least 10 packs a year increased their chance of acquiring PAD (p=0.041). Cessation of smoking within at least 1 year (p=0.01) and 11-20 years (p=0.011) decreases the risk for PAD. The presence of PAD was significantly associated to a low forced vital capacity (p=0.214). However, an ABI of ≤0.9 showed a significant association to severity of airflow limitation values, found among moderate to severe COPD cases (p=0.001).

Conclusion: The prevalence of PAD among Filipino COPD patients was lower than in the Western countries but higher than in other Asian countries. The profile of patients with PAD were mostly ≥60 years old, with a normal BMI, consuming 40 pack-years, with or without the presence of other atherosclerotic risks and classified as moderate to severe cases of airflow limitation. Diabetes mellitus, ischemic heart disease, smoking status, pack years, smoking cessation and low FEV_1 were all significantly associated with PAD.

Keywords: *chronic obstructive pulmonary disease, peripheral arterial disease, ankle brachial index.*

INTRODUCTION

Listed as the fourth leading cause of death worldwide, with current prevalence rates of 5% - 13% globally, chronic obstructive pulmonary disease (COPD) has been predicted to rank fifth on burden of disease and the third leading cause of death all over the world by the year 2020.[1-3] Hence, it is considered an emerging public health challenge worldwide.

The major pathologic mechanism of COPD from cigarette smoking is systemic inflamemation and inflammatory changes on the vascular endothelial lining of the lungs.[4,5]

Endothelial disturbance from systemic inflammation also leads to atherothrombosis due to smoking. A two-fold increase in the risk of coronary artery disease (CAD) and a seven-fold increase in the risk of peripheral arterial disease (PAD) was linked with smoking.[6-14]

Therefore, this study aims to investigate the prevalence of PAD, defined by ankle-brachial index)[9,15,16] among Filipino COPD patients seen at the outpatient department (OPD) COPD Clinic of the Lung Center of the Philippines (LCP). It also aimed to describe these patients and determine the association between PAD and their clinical profile (e.g., pulmonary function and ABI, among others).

METHODS

This was a cross-sectional study conducted on patients seen at the OPD COPD clinic of LCP from October 1, 2013 to March 31, 2014. It included all adult patients aged 40 years old and above with a smoking history of at least 10 pack years. All have an available pulmonary function test (PFT) confirming the diagnosis of COPD. Those who are non-smokers, those who have asthma or purely restrictive lung disease, or those with no available ABI measurements were excluded.

The following information was collected from the medical records of included patients: age, gender, smoking history, body mass index (BMI), lung function test results, ABI, and co-morbidities such as diabetes mellitus, hypertension, ischemic heart disease, hypercholesterolemia and ischemic stroke. An ABIscore of ≤0.9 was used to identify patients with PAD.

Collected data was analyzed using descriptive and inferential statistics. Categorical variables were expressed as frequencies and percentages. Continuous variables were reported as means and standard deviations. Differences in proportions among categorical variables were assessed using Pearson Chi-Square Test for Independence, and Fishers Exact Test as appropriate. Measures of association were calculated using Spearman correlation for continuous variables and Cramer's V statistic for categorical data. A p-value of $\leq$0.05 was considered significant.

We conducted the study in compliance with the ethical principles set in the Declaration of Helsinki. The Institutional Ethics Review Board (IERB) of LCP reviewed and approved the study protocol and subsequent amendments prior to initiation. A written letter of confidentiality was obtained by the investigators before data was collected.

RESULTS

A total of 118 patients satisfied the inclusion criteria. Table 1 showed that the cohort consisted of 91.5% male and 8.5% females, with a mean age of 62.22$\pm$9.72 years. They had a predominantly normal BMI (60.2%). Only 35 (29.7%) were currently smokers, while 83 (70.3%) had already quit smoking. The average recorded cigarette packs consumed in a year was 55.31±29.73. Table 2 shows that former smokers had an average pack-years of 54.14 ± 28.874, while current smokers had 58.06±31.943 pack-years. Patients who had quit smoking for 1-10 years comprised 74.6% of the total population.

The most common co-existing disease among the sample was hypertension (56.8%), fol-

-lowed by diabetes mellitus (17.8%). Other co-morbidities recorded were ischemic stroke (9.3%), hypercholesterolemia (5.1%) and ischemic heart disease (5.1%). However, there were 39 subjects (33.1%) recorded without any co-morbidities.

Low forced vital capacity (FVC) was noted in 63.6% of patients.

The prevalence of PAD was 19.5% (Table 3). Table 4 shows that 61% of those with PAD were at least 60 years old, with a trend towards decreasing ABI with age without reaching statistical significance (χ^2=8.119, p=0.522). Most patients who had PAD had normal BMI (69.6%) and only 2 patients were considered to be over-

Table 1. Demographic and Clinical Profile of Included Patients (n=118)

Characteristics	Distribution		P-value
	N	%	
Age (Mean±SD=62.22 ± 9.72)			<0.001
40-49 years	15	12.7	
50-59 years	27	22.9	
60-69 years	48	40.7	
≥70 years	28	23.7	
Gender			<0.001
Male	108	91.5	
Female	10	8.5	
Body mass index			<0.001
Underweight	27	22.9	
Normal	71	60.2	
Over Weight	15	12.7	
Obese	5	4.2	
Smoking status			<0.001
Former	83	70.3	
Current	35	29.7	
Pack-years (Mean ± SD=55.31 ± 29.73)			<0.001
10-19.9	17	14.4	
20-40	23	19.5	
> 40	78	66.1	
Years of smoking cessation			<0.001
1-10	88	74.6	
11-20	22	18.6	
≥ 21	8	6.8	
Comorbidities			<0.001
Hypertension	67	56.8	
Diabetes Mellitus	21	17.8	
Ischemic Stroke	11	9.3	
Hyperlipidemia	6	5.1	
Ischemic Heart Disease	6	5.1	
None	39	33.1	
Lung function			<0.001
FEV_1 / FVC < 0.70 (Obstructive Lung Disease)	118	100	
FVC < 80 (Probable Restrictive Lung Disease)	75	63.6	
FVC ≥ 80 (No Restrictive Lung Disease)	43	36.4	

BMI, body mass index; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity.

Table 2. Average Pack-Years of Former and Current smokers

Smoking Status	Count (n)	Mean	SD
Former	83	54.14	28.874
Current	35	58.06	31.943
Total	118	55.31	29.733

weight and obese. However, the BMI distribution did not significantly differ between those with or without PAD (χ^2=2.01, p=0.571).

While more PAD cases were found among former smokers than current smokers, the difference between groups was not significant (p=0.067) (Table 4). However, the number of packs consumed in a year was directly correlated with PAD. Out of the 23 patients who developed PAD, 22 had at least 40 pack-years of smoking history. Smoking of at least 10 pack-years significantly increase the chance of having PAD (χ^2=4.809, p=0.04).

Smoking cessation of 1-10 years and 11-20 years yielded significantly decreased risk of PAD (p=0.01 and 0.011, respectively). Pearson statistics also showed that the length of smoking cessation was directly correlated with a lower occurrence of PAD (R=0.36, p<0.001).

Among the co-morbidities, hypertension was the most common disease to co-exist with PAD (68.8%) yet this disease was not significantly correlated with PAD risk (Table 4). However, diabetes mellitus was significantly associated to PAD (χ^2=17.37, p=0.001), as well as ischemic heart disease (χ^2=3.75, p=0.05). Moreover, absence of co-morbidities is not proven to significantly decrease the chance of developing PAD (p=0.061).

Table 5 showed the association between ABI and FVC. A normal ABI was associated with the absence of lung restriction (χ2=8.05, p=0.045). Other ABI categories did not demonstrate statistical differences in FVC category, most likely because of small sample sizes (55% of patients had normal ABI). Meanwhile, Table 6 shows that an ABI of ≤ 0.9 was significantly associated to severity of airflow limitation (χ^2=15.465, p=0.001).

Table 3. Peripheral Arterial Disease Prevalence

Assessment	n	%
Incompressible (ABI>1.4)	14	11.9
Normal (ABI 1.0-1.4)	65	55.1
Borderline (ABI 0.91-0.99)	16	13.6
PAD (ABI≤0.9)	23	19.5
Total	118	100

DISCUSSION

In this study, we demonstrated the following: (1) about 55% of COPD patients had normal ABI, and 19.5% had PAD; (2) the presence of atherosclerotic risks such as diabetes mellitus and ischemic heart disease were associated with the development of PAD; (3) smoking history (smoking status, amount of smoking exposure, duration of smoking cessation) has significant impact on PAD risk; and (4) PAD was significantly associated with airflow limitation severity.

The prevalence rate of PAD among Filipino COPD patients (19.5%) was lower than those in France, Israel and Spain (81.4%, 30% and 37%, respectively).[10-12] In France, the occurrence of atherosclerotic risks, namely hypercholesterolemia (68.1%), diabetes mellitus (25.6%) and hypertension (74.8%) were also much higher than in our study (5.1%, 17.8% and 56.8%, respectively).[10]

Meanwhile, prevalence of PAD among Fili-

pinos was higher than those reported in Japan, Taiwan and Korea (10%, 8% and 4.5%, respectively).[13,14,17] One possible factor for this difference was the cut-off value used (<0.9 vs ≤ 0.9 in our study). In addition, Taiwan study excluded those with symptoms and those already diagnosed with PAD.[13]

Presence of any of the atherosclerotic disease puts a patient at risk for PAD. But diabetes and smoking carries the highest relative risk for developing the disease as can be inferred from the guideline recommendation, as younger patients who are diabetic and smokers warrant an ABI measurement.[9] In our study, diabetes

Table 4. Baseline Characteristics of Filipino COPD Patients by ABI Measurements

Characteristics	Ankle Brachial Index Measurements									
Cut-off Values	>1.4		1.0-1.4		0.91-0.99		≤ 0.90			
Mean ABI ± SD (overall mean=1.15 ±0.26)	1.62 ± 0.208		1.22 ± 0.114		0.92 ± 0.12		0.84 ± 0.038			
ABI description	Incompressible (n =14)		Normal (n=65)		Borderline (n=16)		(+) PAD (n=23)		Statistical value	p value
	n	%	n	%	n	%	n	%		
Age									8.119	0.522
40-49	5	35.7	6	9.2	3	18.8	3	13.0		
50-59	0	0	15	23.1	5	31.3	6	26.1		
60-69	7	50	33	50.8	3	18.8	8	34.8		
≥ 70	2	14.3	11	16.9	5	31.3	6	26.1		
Gender									0.77	0.381
Male	1	100	61	93.8	13	81.3	20	87.0		
Female	4	0	4	6.2	3	18.8	3	13.0		
BMI	0									
Underweight	1	7.1	18	27.7	3	18.8	5	21.7	2.01	0.571
Normal	8	57.1	34	52.3	13	81.3	16	69.6		
Over Weight	3	21.4	11	16.9	0	0	1	4.3		
Obese	2	14.3	2	3.1	0	0	1	4.3		
Smoking status										
Former	9	64.3	50	76.9	7	43.8	17	73.9	28.562	< 0.01
Current	5	35.7	15	23.1	9	56.3	6	26.1	7.17	0.067
Pack-years										
10-19.9	2	14.3	13	20	2	12.5	0	0.0	4.809	0.041
20.0-40	2	14.3	14	21.5	6	37.5	1	4.3	4.175	0.043
>40	1	71.4	38	58.5	8	50	22	95.7	11.133	<0.001
Duration (years) of smoking	0									
cessation	1	92.9	39	60.0	15	93.7	21	91.3	16.248	0.01
1- 10	3	7.1	19	29.2	1	6.3	-	-	11.191	0.011
11-20	1	-	7	10.8	-	-	2	8.7	11.191	0.227
≥ 21	-									
Comorbidities										
Diabetes Mellitus	8	57.1	7	10.8	3	18.8	3	13.0	17.37	0.001
Hypertension	9	64.3	34	52.3	11	68.8	11	68.8	0.001	0.978
Hypercholesterolemia	1	7.1	2	3.1	1	6.3	2	8.7	0.78	0.38
Ischemic Heart Disease	0	0	2	3.1	1	6.3	3	13.0	3.75	0.05
Ischemic Stroke	1	7.1	3	4.6	3	18.8	4	17.4	2.2	0.138
None	3	7.7	28	71.8	2	5.1	6	15.4	7.365	0.061

COPD, chronic obstructive pulmonary disease; PAD, peripheral arterial disease; ABI, ankle brachial index; BMI, body mass index.

Table 5. Association of the Forced Vital Capacity in COPD patients with ABI measurements

Parameter	Forced Vital Capacity								Stat value	Total	P-value
	Normal ≥ 80		Mild 70-79		Moderate 50-69		Severe ≤ 49				
Age (years)	63.09±8.83		59.68±10.58		63.18±10.002		63±9.47				
FVC (% predicted)	88.35±7.02		74.29±2.33		61.37±5.36		43.5±3.94				
ABI	N	%	n	%	n	%	N	%			
>1.4 (incompressible)	5	35.7	0	0.0	7	50.0	2	14.3	5.10	14	0.164
1.0-1.4 (normal)	29	44.6	19	29.2	15	23.1	2	3.1	8.05	65	0.045
0.91-0.99 (borderline)	3	18.8	7	43.8	6	37.5	0	0.0	6.06	16	0.109
≤ 0.90 (PAD)	6	26.1	5	21.7	10	43.5	2	8.7	4.48	23	0.214
Total	43	36.4	31	26.3	38	32.2	6	5.10		118	

COPD, chronic obstructive pulmonary disease; ABI, ankle-brachial index; FVC, forced vital capacity.

Table 6. Association of Degree of Severity of Airflow Limitation in COPD Patients with ABI Measurements.

Parameter	GOLD I		GOLD II		GOLD III		GOLD IV		Stat Value	Total	p-value
	Mild ≥ 80		Moderate 50-79		Severe 30-49		Very Severe ≤ 29				
	Mean	SD	Mean	SD	Mean	SD	Mean	SD			
Age	61.22	7.293	66.53	8.987	59.54	9.97	65.75	5.285			
FEV_1	84.25	47.71	61.51	7.137	38.89	6.328	25.44	4.275			
ABI group	N	%	n	%	N	%	n	%			
>1.4 (incompressible)	1	11.1	5	13.9	7	10.8	1	12.5	0.224	14	0.974
1.0-1.4 (normal)	2	22.2	21	58.3	35	53.8	7	87.5	7.52	65	0.057
0.91-0.99 (borderline)	0	0	5	13.9	11	16.9	0	0	3.297	16	0.348
≤ 0.90 (+ PAD)	6	66.7	5	13.9	12	18.5	0	0	15.46	23	0.001
Total	9	100	36	100	65	100	8	100		118	

COPD, chronic obstructive pulmonary disease; GOLD, Global initiative for chronic obstructive lung disease; FEV_1, forced expiratory volume in 1 second; ABI, ankle-brachial index.

and ischemic heart disease were significant contributors to the likelihood of PAD. On the other hand, hypercholesterolemia and hypertension were identified as co-morbid risk factors in other studies.[10,12,13]

Previous studies have established the positive association of smoking with PAD.[17,18] As with these studies, our study found that smoking history, including magnitude of exposure and shorter duration of smoking cessation has a significant association with PAD. In addition, our data suggests that smoking cessation of less than 1 year seemed to already improve outcomes.

Reduced FVC and forced expiratory volume in 1 second (FEV_1) have been identified as a risk factors for CVD.[19,20] However, no study has found an association between FVC and PAD. In our study, a normal ABI was significantly associated to the absence of lung restriction (normal FVC). However, the inverse was not demonstrated, although low sample size could be a reason for this finding.

Prospective studies in Spain and Israel showed that COPD patients with PAD had poorer FEV_1 compared with those without PAD.[11,12] These results parallel our study, where the severity of airflow limitation is positively related with decreased ABI among those with moderate and severe COPD (p=0.001). No clear mechanism has been recognized but it has been pointed out that in the later stages of COPD, ongoing hypoxia may cause abnormal inflammatory response, as suggested by elevated CRP and cytokine levels.[14,20,21]

Some limitations were identified in our study. The results gathered were nearly all from male subjects (91.5%); applicability to women is unknown. In addition, we have not included the dyspnea severity score for COPD severity classification, which may be useful in future studies.

Our results suggest that COPD patients ≥60 years old, consuming 40 packs a year, with or without the presence of other atherosclerotic risks, and those with moderate to severe airflow limitation should be carefully assessed for PAD.

In the future, we suggest a prospective study correlating the oxygen saturation and severity of dyspnea with ABI. Other areas of research include investigations on oxidative stress genes that could further correlate COPD and PAD. Increased sample size would help establish more reliable correlations with study variables.

CONCLUSION

Filipino COPD patients who developed PAD were mostly aged 60 years old and above, with a normal BMI, consuming 40 pack years, with or without the presence of other atherosclerotic risks and were classified as moderate to severe cases of airflow limitation. The prevalence of PAD was 19.5%. Diabetes mellitus and ischemic heart disease were significant contributors to the likelihood of PAD. Smokers who consumed at least 10 packs a year significantly increase his risk of PAD (p=0.041), while smoking cessation was significantly correlated to better ABI measurement. Likewise immediate cessation of smoking within at least 1 year was associated with lower PAD risk. PAD was also associated with the severity of airflow limitation.

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