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From the necessary to the impossible

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

"Start by doing what's necessary, then what's possible; and suddenly you are doing the impossible."

– Saint Francis of Assisi

This quote from St. Francis of Assisi accurately sums up the journey of the Philippine Journal of Chest Diseases (PJCD) from its inception, its ups and downs, and hopefully to its successful recognition and indexing in the Western Pacific Region Index Medicus (WPRIM). Looking back, the road to this present issue was a long and winding one, with several snags and hitches, but the color and the challenges along the way are giving the journal its history and character.

Our Issue Number 3 for the year recognizes the scientific work of our members and fellows-in-training, who continue to nurture their passion for research and support the journal in the process. Most of the articles in this issue focus on pulmonary infections and obstructive lung disease, and sensibly so, since year after year for the last several years, Pneumonia and COPD have remained significant respiratory illnesses in the Philippines. According to the 2014 Philippine Health Statistics from the Department of Health, Respiratory Tuberculosis (TB), TB Other Forms, Bronchitis, and Acute Lower Respiratory Tract Infections and Pneumonia continue to figure prominently in our national morbidity and mortality data.[1] Because of this, it is no surprise that data abound on these respiratory conditions. However, since these illnesses continue to persist among the top leading causes of morbidity and mortality, it is evident that our clinical data and research outcomes have yet to be translated into meaningful public health steps to create significant change in our country's health profile.

It is easy to consider the hospital and the clinic to be entirely separate from the public health domain. But it is evident that, despite their differences, they need to be synergistic—one feeding off the other to create healthier communities. The clinician-researcher will have various resources available to him or her, and these will be different from the tools of the public health physician, but they should be working towards the same goal: the data gathered and analyzed by the clinician-researcher must be useful for application in the field, and vice versa, and if not, and questions abound, then that sets the stage for further research.

For it is equally important to know what happens to our patients after they are discharged from our hospitals, or exit our clinics—when they reach home and re-integrate into their communities at home and at work. Sometimes what happens to our patients outside of our hospitals and clinics are even more significant than we think, especially considering the factors

of infectious diseases, exposure to second- and even third-hand smoke, climate change, environmental air quality, not to mention cultural dimensions of health behavior and the effects of family structure.

Although cigarette consumption has decreased from 10.6 sticks daily per smoker in 2009 to 7 sticks per day per smoker in 2015,[2] it is difficult to say that this was the direct effect of either the Sin Tax Law or the Graphic Health Warnings Act, or both, or neither one. Indeed, research is still lacking on the actual effects of these legislative milestones, although admittedly this will take considerable time and resources to fully investigate. Moreover, much research has been done on antimicrobial effects of the various bugs (old and new) causing pneumonia and other respiratory infections, but up-to-date local data are lacking for topics such as physician prescribing habits and preferences for antibiotics, and immunization profiles of the elderly.

Admittedly though, much has been gained by the Sin Tax Law in terms of pushing forward the Department of Health's agenda. But this influx of money to support the medical needs of indigent patients and the growth and development of our country's health facilities should be accompanied by an equally robust research environment, more so for the evaluation and monitoring of the effectivity and responsiveness of our public health programs.

I am fully aware that this type of public health research may not be the most inviting, or the most common, for the clinician-researcher, but they can and should be done. There was also a time in the past when the movers behind the PJCD never talked about indexing, but it can and should be done.

Let us stretch our creativity and think out of the usual research box. The challenge is not just to lose ourselves in mounds of patient charts to review them for historical data, or to expectantly wait for patients to report for scheduled follow-up visits for a pharmaceutical clinical trial; but rather, an equally great challenge is to roll up our sleeves and look to communities for answers to our questions. And perhaps then, once we have the patient and community together—the forest AND the trees—the seemingly impossible dream of a healthy Philippines will become more possible.

References:

1. Asuncion IL, Benegas-Segarra A. 2014 Philippine Health Statistics. Manila: Department of Health; 2014.
2. Kalusugan Pangkalahatan 2010-2016: An Assessment Report. Manila: Department of Health; 2016.

CASE SERIES

Case series: Pathologies of the respiratory system during pregnancy

Rianne dela Cruz, MD; Sherry Gail Jaloro, MD; Jewel Cordelle Nuñal, MD; Ma. Kriselda Karlene Tan, MD; Ralph Elvi Villalobos, MD; Lenora Fernandez, MD, FPCCP; Albert Albay, Jr., MD, FPCCP; Jubert Benedicto, MD, FPCCP

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ABSTRACT

The pregnant female may experience a multitude of physiologic changes that are a unique occurrence only in pregnancy and a significant proportion of these alterations may involve the respiratory system. Pregnancy may also bring about differences not only in the normal functioning but also on the diseased state leading to some diseases being worsened or exacerbated by pregnancy, while some being improved. Because of the unique interplay of these factors in pregnancy, it is important for pulmonologists to be acquainted with the different conditions that are common in pregnant patients, for the timely and proper management is paramount to a successful pregnancy and healthy mother and infant. Here, we present three unique cases, each highlighting different commonly encountered diseases in pregnancy, together with the proper management plan for each case.

CASE 1: ASTHMA IN PREGNANCY

M.M is a 37-year-old female, G3P2 (2002), 9 3/7 weeks age of gestation (AOG), who complained of dyspnea. She had a past history of childhood bronchial asthma and would take as-needed salbutamol tablet for exacerbations. She denies worsening of symptoms during her present pregnancy. Her last exacerbation was 1 month prior to admission, where she was prescribed maintenance inhaled salmeterol/fluticasone with poor compliance. She has no known triggers. Her two previous pregnancies were both full term and uneventful.

Both parents are asthmatics. No other heredofamilial disorders noted. She was a previous smoker with a 1-pack-year smoking history. She does not drink alcoholic beverages. She is currently unemployed.

One week prior, she complained of cough associated with progressive shortness of breathing occurring daily and nightly awakenings due to dyspnea. She self-medicated with oral salbutamol as needed with slight relief of symptoms.

On the day of admission, there was worsening of dyspnea and she was rushed to the emergency room, where she was noted to be lethargic and in respiratory distress. Vital signs were as follows: blood pressure (BP) of 160/90 mmHg, heart rate (HR) of 130 beats per minute (bpm) and respiratory rate (RR) of 40 cycles per minute (cpm). Her oxygen saturation was 69% at room air. There was note of wheezes in all lung fields. The patient was promptly intubated and hooked to mechanical ventilation. She was nebulized with salbutamol (3 doses) and given intravenous (IV) hydrocortisone 100 mg and magnesium sulfate 2 g IV bolus. She was then transferred to the medical intensive care unit (ICU).

In the ICU, piperacillin-tazobactam 4.5 g IV 8-hourly and azithromycin 500 mg once daily were initiated after infiltrates on chest x-ray were noted. She was then referred to the pulmonary medicine service.

On the second hospital day, the patient had no dyspnea and had stable vital signs. She was

able to tolerate continuous positive airway pressure (CPAP) mode, with an FiO_2 of 30%, with pressure support of 4 mmH20, positive end-expiratory pressure of 5 mmH20 and rapid shallow breathing index of 45. Her arterial blood gases were unremarkable. She was then extubated and transferred to the medical ward the next day.

The final diagnosis was acute respiratory failure type I secondary to status asthmaticus; community-acquired pneumonia (CAP), high risk; uterine pregnancy, 9 3/7 weeks AOG.

Discussion

Respiratory physiology during pregnancy

During normal pregnancy there is a 20% increase in oxygen consumption and a 15% increase in the maternal metabolic rate. These demands are met by several physiologic changes during pregnancy.[1] To compensate for the increased oxygen demand of pregnancy, minute volume is increased by 40%–50%. This hyperventilation is due to an increasing tidal volume which are due to the stimulatory effect of progesterone on the respiratory center.[2]

With the progress of pregnancy, the circumference of the lower chest wall increases by 5-7 cm with an increase in the anteroposterior and transverse diameters, resulting in widening of costal angle from 68° to 103°. This compensates for the eventual elevation of the diaphragm because as the uterus enlarges, it pushes the diaphragm upward approximately 4-5 cm, resulting in a reduction in the functional residual capacity (FRC) by about 18%. Because of this change, pregnant women more rapidly desaturate during hypopneic periods due to loss of reserve lung volume.[3] Pregnancy does not change forced vital capacity (FVC), forced expiratory volume in one second (FEV1) or peak expiratory flow rate (PEFR). As in the general population, FEV1 and PEFR during pregnancy correlate well with asthma symptoms and exacerbations making them acceptable measurements to help monitor asthma control.[4]

Minute volume/ventilation and total volume both increase by 30%-50%.

Effect of pregnancy on asthma

As a consequence of pregnancy-associated immunological and clinical changes, asthma improves in approximately one-third of pregnant women, remains the same in one-third and worsen in the rest.[5] The underlying immunological mechanisms are mostly unknown and biomarkers predicting deterioration are lacking.

The prevalence of bronchial asthma varies between 3%-9% of all pregnancies and approximately 6% of patients get hospitalized due to acute exacerbation. Worsening of asthma during pregnancy is related to the baseline asthma severity. Schatz et al[6] enrolled 1,739 pregnant asthmatics before 26 weeks of gestation and classified them into mild, moderate and severe disease groups. They noted that 51.9% of those in the severe group have an asthma exacerbation, 25.7% of the moderate group and 12.6% of the mild group.[6]

Despite the lack of studies directly addressing possible mechanisms, several authors have proposed that maternal hypoxia, inflammation, asthma exacerbation, smoking and altered placental function may contribute to poor pregnancy outcomes in females with asthma. These mechanisms lead to low birth weight, preterm labor, preeclampsia and caesarean delivery.[7]

In the local setting, a study done in our institution showed that both maternal and neonatal outcomes are compromised among pregnant asthmatics as compared to pregnancies not complicated by asthma. Pregnant asthmatics were significantly more likely to have preeclampsia, caesarean delivery and longer hospital stay. They are significantly more likely to have preterm infants, lower mean birth weight and longer neonatal hospital stay.[8] Table 1 summarizes the results of this study.

Table 1. Pregnancy outcomes between pregnant and non-pregnant asthmatics in the Philippine General Hospital (2000)

Outcome	Asthmatics(%) N=184	Control N=205	RR (95% CI for RR)	P Value	Adjusted RR
Caesarean Section	56(30.47%)	3(1.5%)	20.8 (6.62<RR<65.3)	<0.0001	15.59 (4.65-52.29) P<0.001
Preeclampsia	19 (10.3%)	3(1.5%)	2.12 (2.06<RR<23.5)	0.000157	9.78 (2.79-34.2) p=0.004
Length of hospital stay >3 days	97(53%)	87(42%)	1.24 (1.01<RR<1.53)	0.0426	2.10(1.29-3.41 p=0.0026
Gest. HTN	8 (4.3%)	3 (1.5%)	2.97 (0.8<RR<11.03)	0.087	NS
Forceps	15 (8.2%)	17(8.3%)	0.98 (0.51<RR<1.91)	0.96	NS
PROM	4(2.2%)	2(1.0%)	2.23 (0.41<RR<12.02)	0.43	NS
Placenta Previa	1(0.5%)	0(0%)	—-	—	NS
Intubation	1(0.5%)	0	—-	—	NS
Preterm	27 (14.7%)	9(4.4%)	3.34 (1.61<RR<6.92)	0.00048	3.46 (1.57-7.64) p=0.0021
Length of Neonatal Stay >3D	91(49%)	93(45%)	1.09 (0.88<RR<1.34)	0.4197	1.76 (1.12-2.77) p=0.0143
Low birth weight <2.5 kg	41(22%)	32(16%)	1.43 (0.94<RR<2.17)	0.0924	NS
SGA	21 (11.4%)	34 (16.6%)	0.69 (0.41<RR<1.14)	0.144	NS
LGA	3 (2.5%)	3 (2.5%)	0.62 (0.21<RR<1.81)	0.376	NS

RR=relative risk; HTN=hypertension; PROM=premature rupture of membranes; SG=small for gestational age; LGA=large for gestational age; NS=not significant.

Management of exacerbations during pregnancy

Treatment is no different from the emergency management of acute severe asthma outside pregnancy that includes repetitive administration of inhaled short acting B-agonists, with early introduction of systemic corticosteroids and oxygen support.[9] These patients should be closely monitored and their treatment titrated according to their response to medications administered.[10]

For pregnant patients with status asthmaticus requiring intensive care, approach to mechanical ventilation is of particular concern.[11] The clinical criteria for intubating a pregnant patient are similar to those in nonpregnant patients and include increased work of breathing, mental status deterioration, hemodynamic instability and inability to protect the airway or manage secretions. The physiologic changes of pregnancy should be taken into account such as increase O2 demand, respiratory alkalosis, decrease in FRC and decrease in respiratory compliance. The presence of mucosal edema, capillary engorgement and

increase in breast size, warrant a 0.5mm smaller endotracheal tube compared to nonpregnant of similar height and age.[12] Although a PaO2 of 55mmHg and SpO2 of 88% would be tolerated in the general population, adequate fetal oxygenation requires a PaO2 of 70mmHg, which responds to a maternal SpO2 of about 95%.[13]

In general, a slow respiratory rate, low tidal volume, high peak inspiratory flow rate are set to allow greater time for exhalation of the tidal volume and therefore prevent air trapping.[14]

Management of stable asthma in pregnancy

The management strategy is complex and should be carried out for a long period. It includes an objective evaluation of maternal and fetal clinical conditions, avoidance or control of triggering factors, pharmacological treatment and educational and psychological support.[15] Follow-up in the clinic once every 1–2 weeks until asthma is controlled and then monthly throughout pregnancy

All pregnant asthmatic women should be up to date on influenza and pneumococcal vaccines as respiratory infections are frequent triggers for asthma exacerbation. They should avoid nonimmunologic triggers and reduce exposures to allergens.

Asthma in pregnancy needs to be treated and drugs are necessary, since uncontrolled asthma represents a risk factor to both the mother and the fetus. Only 0.7% of drugs carry a Pregnancy Risk Category A classification and the vast majority are in B and C. In particular, 66% of all medications with a pregnancy category are now in Pregnancy Risk Category C. Table 2 summarizes the drug classes of commonly used asthma drugs.

The management of asthma during pregnancy should be based upon objective assessment of symptom control, risk factors for poor asthma outcomes. Treatment of asthma is the same as in non-pregnant asthmatics based on the stepwise approach to asthma control.[10] Inmost w omen, asthma reverts back to the pre-pregnancy level of severity within 3 months after delivery. All asthma medications should be continued during pregnancy and lactation.[7]

Table 2. Summary of pregnancy category of commonly used asthma drugs in pregnancy.

Drug Class	Pregnancy Category
Beta-agonists	Category C
Anticholinergics	Category C
Inhaled Corticosteroids	Category B
Leukotriene Receptor Antagonists	Category B
Cromolyn	Category B
Methylxanthine	Category C
Systemic Corticosteroids	Category C (Category D in first trimester)

Category B=Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women.
Category C=Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
Category D=There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

Patients' education is mandatory to optimize the outcomes of therapy in asthmatic patients. However, in the case of pregnant women, strict and repeated reassurance on the significance and safety of a regular therapy for controlling airway inflammation is definitely essential to ensure adequate compliance.

CASE 2: TUBERCULOSIS (TB) IN PREGNANCY

A.B. is a 25-year-old woman, G2P1 (1001), on her 29th week of pregnancy, with regular prenatal check-ups at a local health center. She was treated for 6 months for smear-positive TB in 2008, after which there was documentation of sputum smear conversion was documented.

Two weeks prior, she complained of cough with greenish sputum, anorexia, malaise and undocumented fever. She also had watery, non-mucoid, non-bloody diarrhea (2-3 bowel movements per day). She was given cefuroxime and metronidazole for 2 weeks, but the symptoms persisted. While fetal movements were perceived to be normal and no vaginal bleeding or spotting was noted, the persistence of symptoms prompted consult at the obstetric admitting section (OBAS).

She was received at the OBAS awake, alert, ambulatory and not in cardiorespiratory distress. She was cachectic and had dry oral mucosa. No cervical lymphadenopathy was noted. She had equal chest expansion and crackles on bilateral lower lung fields. She was tachycardic but has regular rhythm and has poor skin turgor with delayed capillary refill time.

Abdominal examination done by the perinatologists showed a fundic height of 22 cm and fetal heart tones appreciated at the left lower quadrant. No uterine contractions were noted. Internal exam revealed a normal external genitalia, parous vagina and a cervix that was 1-cm dilated but uneffaced.

She was managed as a case of acute gastroenteritis with signs of dehydration, CAP, preterm labor, to rule out gastrointestinal and pulmonary TB.

She was given cefixime and metronidazole as antibiotics, nifedipine as tocolytic and dexamethasone. Upon further workup, her sputum, stool and urine AFB all yielded positive results. She was managed as bacteriologically-confirmed TB and given isoniazid, rifampicin, pyrazinamide and ethambutol pending the results of sputum TB culture. Streptomycin was deliberately not given due to the feared risk of ototoxicity in the developing fetus.

On her 34th week of gestation, she had labor pains and fetal monitoring showed fetal distress hence an emergency cesarean section was performed. She gave birth to a live baby boy, 2.5 kg, small for gestational age, APGAR 8,9. The anti-TB regimen was continued and the baby was also given isoniazid prophylaxis despite negative gastric aspirate GeneXpert. The patient and her son are soon discharged asymptomatic and on regular follow-up at te outpatient department.

Discussion

Global and local burden of TB in pregnancy

Because of the complex issues surrounding pregnant patients, the World Health Organization has identified TB in pregnancy as a key target area to keep focus on to reach the 2030 End TB strategy.[16] The Southeast Asian region has the second highest burden of TB in pregnant women with an estimated 2.4 cases per 1,000 pregnant women and contributes to 31% of the global prevalence of TB.[17] In the region, the Philippines has the second highest prevalence rate of TB in pregnant women, after Cambodia.

In recent years, a significant proportion of deaths due to TB occur in pregnant women and because of improving obstetric care in the recent years, deaths due to obstetric causes have been declining, while deaths from infectious causes (especially TB) in pregnant women are on the rise.[18,19]

Pathophysiology of TB in pregnant women

The risk of TB in pregnant women is two-fold. One is the detrimental effects of TB in a pregnant woman and the other is the seemingly adverse effects of pregnancy itself to the progression of TB. It has also been shown that pregnancy itself confers and increased risk for TB compared to the general population. One study done in the UK showed an almost 1.7 times increased risk of contracting TB in pregnant women compared to the non-pregnant female population.[20]

In pregnant women, there is a blunted TH1 pro-inflammatory response by the body, which leads to either masking or more severe symptoms,

increased susceptibility to new infections and increased probability of reactivation.[21]Pregnant patients are no different compared to the general population in terms of symptoms, with the most common presentation still chronic cough, fever and anorexia.

However, diagnosis of TB can be difficult in pregnant women for a variety of reasons. Physiologic changes of pregnancy may mask symptoms of TB. It may be difficult to recognize anorexia and malaise because these two symptoms are more often attributed to the pregnancy itself. It is also difficult to assess weight loss during pregnancy.[22]

TB in pregnant women has been shown to increase the risk of intrauterine growth retardation, premature birth and low birthweight. It is important to emphasize that late treatment of TB in pregnant women leads to worse outcomes, including 10x increased risk of dying. Women with active TB during the third trimester has a 15% risk of transmitting their infection to their newborns.

Diagnosis of TB in pregnant women

Because of the non-specific presentation of TB in pregnant women, timely diagnosis is essential for the successful treatment of TB. The diagnosis of TB in pregnant women is not different compared to the non-pregnant population. The standard diagnostic test is two sputum AFB smears and if one is positive, then it is considered bacteriologically confirmed TB.

However, in the era of rapid diagnostic tests, the role of GeneXpert is becoming more popular, although the Clinical Practice Guidelines for the Diagnosis, Treatment, Prevention and Control of Tuberculosis in Adult Filipinos – 2016 Update has not yet considered the GeneXpert as a first-line test for diagnosis of TB in pregnant women.[23] Nonetheless, in a study done specifically in pregnant women, GeneXpert was found to be more sensitive than standard AFB smears (80.8% vs 50.0% for AFB smear) and is as specific (97.1% vs 100%).[24]

With regards to radiologic examinations in pregnancy, it has long been established that chest x-ray with abdominal shield is considered low risk for adverse events in both the mother and the fetus during pregnancy,[25] but the risk is not zero. Therefore, in pregnant patients, chest-xray should only be used to diagnose TB if all other non-invasive tests are inconclusive.

Treatment of TB in pregnancy

Treatment of TB in pregnant women adhere to these two basic tenets: (1) “A successful TB treatment is essential for a successful pregnancy” and; (2) “The dangers of untreated TB is much worse than the dangers of anti-TB medications.” All first line drugs except streptomycin are safe in pregnancy. Only ethambutol is considered category A but pyrazinamide, isoniazid and rifampicin also have excellent safety profiles.[26] However, streptomycin is associated with ototoxicity in the developing fetus. The standard regimen is the same as the general population and an alternative regimen is 2 months of HRE followed by 7 months of HR.

Unlike the first-line medications, the second-line anti-TB medications are more toxic both to the mother and fetus and more careful planning is warranted. A referral to a specialty center is warranted for cases of multidrug-resistant TB in a pregnant patient.[27] Pregnancy warrants an increase in the frequency of monitoring (monthly alanine transaminase examinations) during TB treatment because pregnancy confers increased risk for isoniazid-induced hepatotoxicity.[28]

Breastfeeding and neonatal care of infants of mothers with TB

Breastfeeding is an important aspect in the care of the newborn. Numerous studies have shown that all first-line and second-line drugs

are safe to give in breastfeeding mothers because their concentrations are too low to cause harm in the infant. It is also important to note that, while anti-TB medications are excreted in small amounts in breastmilk, TB bacilli can be secreted in significant amounts. Therefore, it is recommended that a mother infected with TB should undergo 2 weeks of anti-TB treatment before she can commence breastfeeding.[29]

In terms of neonatal care, it is suggested that if the infant has a positive GenXpert result (from gastric aspirate), the baby should undergo a full course of treatment for TB. Infants with no evidence of active TB infection should still be given isoniazid prophylaxis for 6 months, especially if the mother has TB up to the third trimester.

CASE 3: PULMONARY PROCEDURAL CONSIDERATIONS DURING PREGNANCY

J.B. is a 27-year-old female who was pregnant (32 weeks AOG), G1P0, who came in for hemoptysis. Five years prior, she was diagnosed with sputum-positive PTB and treated for 6 weeks with Category I PTB treatment, with subsequent sputum conversion. Two years later, she complained of nonproductive cough, with no associated fever or night sweats. She consulted at a local hospital and was managed as a case of sputum-negative TB with Category II treatment. There was recurrence of nonproductive cough after a year and Category II treatment was repeated. She then became pregnant with the present pregnancy. *However,* she complained of cough with intermittent hemoptysis. A chest x-ray showed an aspergilloma, thus prompting the present consult.

On physical examination, she was awake, comfortable and not in distress. Her vital signs were as follows: BP of 110/70 mmHg, HR of 92 bpm, RR of 20 cpm and O_2 saturation of 97%. Breath sounds were decreased on the left lung fields. Other physical examination findings were unremarkable. At this time, the patient was diagnosed with a left upper lung mass, aspergilloma for consideration; PTB with bronchiectasis; uterine pregnancy at 32 weeks AOG (G1P0).

A multidisciplinary conference was conducted to discuss JB's case. The consensus was to bring the pregnancy to term and do elective Caesarean section. A chest computerized tomography (CT) scan and subsequent surgery for the aspergilloma was planned after delivery. No TB retreatment was initiated at this time due to negative results of TB workup.

JB was able to carry her pregnancy to term and delivered a live baby girl. She was undergoing preparations for lung resection surgery at the time of writing.

Respiratory diagnostic and procedural issues in pregnancy

A pulmonary function test (PFT) was requested in anticipation of a lung resection surgery due to the diagnosis of aspergilloma. Normal pregnancy is a physiological state that does not require PFT.[30] During the first and second trimester, the lung function is relatively normal. During the third trimester, the pulmonary function becomes compromised with a decrease in PEFR. The usual problem with doing a PFT in pregnant patients is not in performing the test, but in interpreting and reporting the results against normal or nonpregnant reference ranges. Furthermore, it is not advisable to do a pulmonary function test in pregnant patients with pre-eclampsia or a cervical cerclage. Finally, parity has no effect on lung function until the woman has delivered three times. Thereafter, a slight compromise in lung function is seen.[31,32]

Bronchoscopy aids in the diagnosis and management of patients, pregnant or non-pregnant, presenting with hemoptysis. However, it has its own specific risks, including those related to the procedure and those from conscious sedati-

on.[33] Risks related to conscious sedation include medication-related teratogenesis, induction of premature labor, maternal cardiac arrhythmias, depressed mental status with resultant hypoventilation, airway vulnerability, possible pulmonary aspiration and respiratory distress. Risks related to the performance of the procedure itself include barotrauma, pneumothorax, hypoxemia, airway hyper-reactivity, pulmonary hemorrhage, systemic hypotension and hypertension.

Medications commonly used in pregnant women such as lidocaine, beta-2 agonist, submucosal epinephrine, midazolam and propofol must be used cautiously and in low doses only. The maximum recommended dose of 4% Lidocaine topical solution should be less than 300mg and should not exceed 4.5 mg per kg body weight.

Beta-2 agonists have an FDA Pregnancy Risk category of C and must not be used routinely. If needed, minimally required dose should be given. Submucosal injection of epinephrine should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus. Midazolam (Category D) is the preferred benzodiazepine for flexible bronchoscopy, but should only used when absolutely necessary, in low doses and with caution.

Initial assessment of the patient prior to bronchoscopy must include previous instances of complicated conscious sedation and allergies. During the general physical examination, specific attention must be given to assess airway patency. During the procedure, continuous monitoring with intermittent sphygmomanometry, cardiac rhythm, rate monitoring and pulse oximetry (to maintain 97%-100% O2 saturation) are recommended. Capnography is optional but the general goal is to avoid hypoventilation during the procedure. There are no formal recommendations regarding fetal heart monitoring during flexible bronchoscopy.[34]

Emergent bronchoscopy in pregnancy should be performed if lifesaving regardless of the stage of pregnancy or status of the fetus. However, it must be done in close coordination with the obstetrician and the perinatologist. Non-emergent bronchoscopy should be postponed until the patient has given birth, if possible, or if there is a good chance of delivering a viable healthy newborn after 28 weeks of pregnancy. One may also consider using new technology to substitute for bronchoscopy such as 3D CT or virtual bronchoscopy.

Treatment of aspergilloma during pregnancy

Treatment of aspergilloma during pregnancy remains controversial and problematic, with little consensus amongst experts mainly because of the variability of the underlying lung disease process. Aspergillomas may resolve clinically without overt pharmacologic or surgical intervention in up to 10% of patients. The major justification for surgery and arterial embolization is the risk of life-threatening hemoptysis, which has an associated mortality of 5%-10% or greater.[35]

There has paucity of literature regarding thoracic resectional surgery on pregnant women. The problem confronting the surgeon is whether pulmonary resection could be performed during gestation with safety to the mother and fetus. Available literature shows that in the presence of standard indications, pulmonary resection may be safely performed on patients, even on the second trimester of pregnancy, with only a 0%-8% fetal mortality and at most 3% maternal mortality.[36]

In pregnant women who are poor surgical candidates, medical treatment options are limited due to toxicity and teratogenicity issues, as well as lack of available data on safety in pregnancy. Amphotericin B is the agent on which the most information is available, and is

the agent of choice for all serious fungal infections in pregnancy, including aspergilloma. Fetal toxicity is rare, maternal toxicity is similar to non-pregnant patients, and animal studies do not show teratogenicity. Hemoptysis can usually be controlled with oral tranexamic acid. If hemoptysis is significant, bronchial artery embolization is recommended and should be performed by an experienced interventional radiologist. Recurrence of hemoptysis is common if antifungal therapy is not given and optimized and may be a sign of antifungal failure.[37]

CONCLUSIONS

By reviewing these cases, we have come to understand that normal pregnancy is a physiologic state. During this time, the respiratory tract undergoes profound changes as a result of maternal adaptation to pregnancy. It was shown that a variety of these changes are important to recognize whether part of the normal physiologic adaptation to pregnancy to correlate with the pregnant patient's symptoms.

It was also highlighted that caring for a pregnant mother also entails care for the patient's fetus, therefore both benefits and risks must be weighed to ensure a beneficial environment for both patients.

A lot of pulmonary cases plague our pregnant patients and it is indeed important to review them and take into consideration each little intricacy that is unique.

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CASE REPORT

Overlapping Overlaps: A Case Report

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ABSTRACT

Chronic respiratory diseases such as interstitial lung disease (ILD), chronic obstructive pulmonary disease (COPD) and obstructive sleep apnea (OSA) have been known to overlap. In fact, the co-existence of COPD and OSA in a patient has been described as Overlap syndrome. Overlapping pulmonary problems increase morbidity and mortality and usually require close monitoring, prompt therapy and a multidisciplinary approach to management. Furthermore, the co-existence of these three conditions in a patient is rare. Here we report the case of a patient with Overlap syndrome with overlapping ILD due to autoimmune disease.

THE CASE

History

This is the case of a 30-year-old female, unmarried, from Quezon City, who was admitted due to dyspnea.

In 2013, she was initially diagnosed with pulmonary hypertension (PH) after complaining of dyspnea and bipedal edema on routine check-up. On physical examination, there was note of a PA lift and fixed split S2. Chest radiograph revealed a prominent right pulmonary artery. Echocardiography revealed preserved left ventricular (LV) function with a LV ejection fraction (LVEF) of 67%, good wall motion and contractility and normal resting systolic function. However, there was an elevated tricuspid regurgitation (TR) jet at 39 mmHg, with no atrial dilatation and pericardial effusion. The diagnosis was mild PH and she was treated with phosphodiesterase (PDE)-5 inhibitor, to which she was compliant.

On annual surveillance echocardiography, a decrease in LVEF from 67% to 59%, worsening of PH with increasing TR jet from 39 mmHg to 81mmHg, a dilated right ventricle, flattening of the interventricular septum during systole and dilated right atrium (RA) were noted--all points to RA volume overload seen in PH. She was advised to undergo right heart catheterization, but she refused. The PDE-5 inhibitor was shifted to an endothelin receptor antagonist, which improved her symptoms.

Furthermore, high-resolution computerized tomography (HRCT) of the chest done in 2014 revealed findings suggestive of interstitial lung disease (ILD) (Figure 1).

One week prior, she experienced easy fatigability accompanied by non-productive cough. Symptoms were aggravated by movement and relieved by rest. She did not note any fever, bipedal edema, orthopnea or chest pain. She consulted a private physician, and a complete blood count (CBC) revealed a hemoglobin of 147 mg/dL, hematocrit of 46, platelet count of 239 cells/mm^3, and a white blood cell (WBC) count of 7.91 cells/mm^3 (with normal differential counts). Urinalysis revealed proteinuria (+4), 6 red blood cells/high power field (hpf) and 1 WBC/hpf. Chest x-ray was done and signed out as bibasal pneumonia (Figure 2). She was given cefuroxime and azithromycin for 5 days, which afforded relief of the cough.

However, 3 days prior, easy fatigability per-

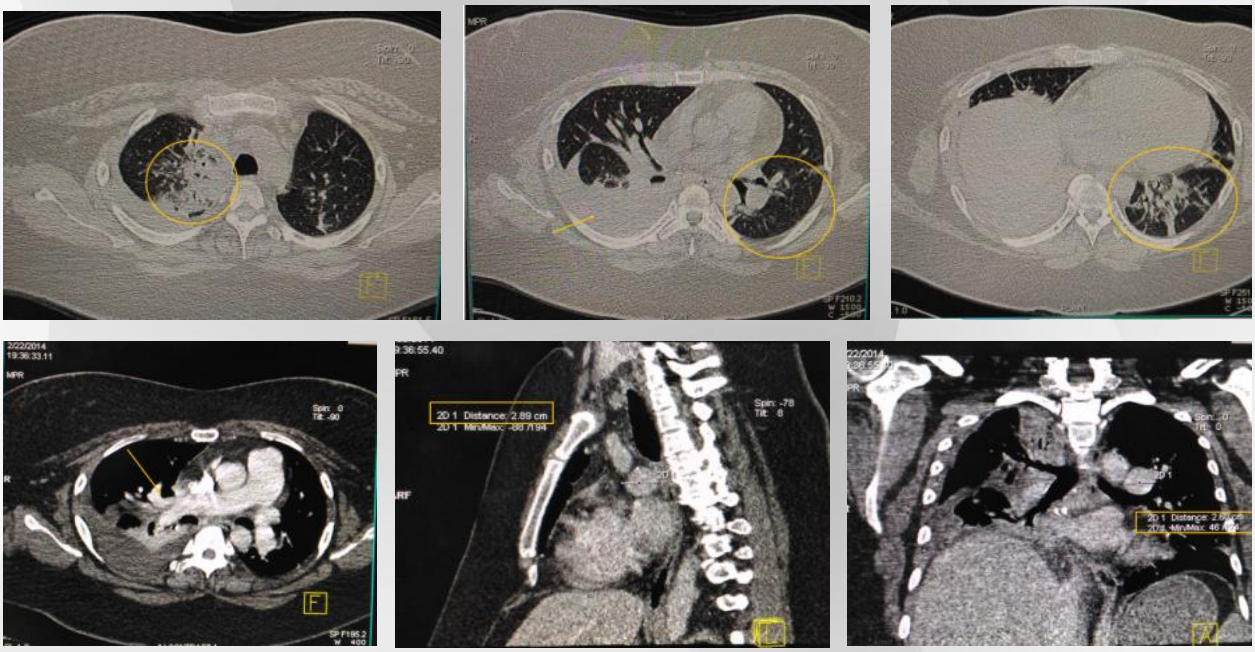

Figure 1. High-resolution computerized tomography of the chest. **Top row:** The parenchymal window reveals ground glass opacities in the right upper lobe; beginning honeycomb changes on the left middle lung field up to the basal segments; and pleural effusion. **Bottom row:** The mediastinal view shows cardiomegaly and dilated pulmonary arteries (right-2.89 cm; left=2.60 cm).

sisted, now accompanied by increased somnolence. Companions noted increase in sleeping time accompanied by anorexia and body malaise. She also experienced dyspnea on exertion. There were no aggravating or relieving factors, and she did not seek any consult nor took any medications. Over the next few days, her symptoms progressed, thus prompting consult.

Of note, she is hypertensive and was diagnosed with systemic lupus erythematosus (SLE) on July 2003, initially presenting as alopecia, rash, arthritis, anemia, thrombocytepenia and proteinuria. Further work-up revealed that she was positive for anti-nuclear antibody (ANA), anti-double stranded DNA and anti-ribonucleoprotein (anti-RNP). She was referred to the National Kidney and Transplant Institute, where a kidney biopsy done confirmed lupus nephritis compatible with membranous glomerulonephritis. She was treated with the following maintenance medications: hydroxychloroquine, prednisone, aspirin, supplemental calcium and irbesartan.

She is a previous smoker with a 20-pack-year smoking history, stopping in 2003.

Review of systems revealed no symptoms attributable to a flare of SLE, but noted unquantified weight gain.

Admission and hospital course

Upon admission, she was conscious, coherent, stretcher borne, in cardiorespiratory distress, with the following vital signs: blood pressure of 140/80 mmHg, heart rate of 92 beats/min, regular respiration with a rate of 28 cycles/min, body temperature of 37ºC, and an O2 saturation at room air of 92%. Her body mass index was 37.

Examination of the chest revealed symmetric expansion, equal tactile and vocal fremiti,

resonant on percussion, bibasal crackles and bilateral wheezes. The cardiac examination showed a jugular vein pressure of 4.5 cm at a 30-degree angle, adynamic precordium, apex beat at the sixth intercostal space, left anterior axillary line, RV heave, PA lift, no thrills, a loud P2 and no murmurs. The abdomen was flabby and had non-bulging flanks, normoactive bowel sounds, tympanitic on percussion, soft and non-tender with no hepatosplenomegaly. She had grade 1 bipedal pitting edema but no cyanosis.

On admission, the initial diagnosis was community-acquired pneumonia, moderate risk; cor pulmonale; to rule out acute coronary syndrome (ACS); chronic obstructive pulmonary disease (COPD), in acute exacerbation; obstructive sleep apnea (OSA) risk; to consider overlap syndrome; SLE, not in flare; ILD probably due to connective tissue disease (CTD); obesity class II; hypertension stage II.

The patient was immediately given supplemental oxygen (4 L/min). Arterial blood gas (ABG) revealed partially compensated respiratory acidosis with inadequate oxygenation with supplemental oxygen.

Troponin I was not elevated, and 12-lead electrocardiography showed a normal sinus rhythm with no ischemic changes, thus ruling out ACS. CBC showed leukocytosis (12 WBC/mm^3), with 90% segmenters. Serum sodium, potassium and creatinine were all normal.

She was treated with broad spectrum intravenous antibiotics to address the pneumonia; diuretics to relieve pulmonary congestion; and systemic steroids and short-acting bronchodilators to address the obstructive airway disease. The patient was unable to provide a good sputum specimen for examination despite sputum induction.

During her hospital stay, her dyspnea persisted and sleeping time and bibasal wheezes increased. Serial ABGs showed uncompensated respiratory acidosis with more than adequate oxygenation with supplemental oxygen. She was then placed on non-invasive mechanical ventilation (NIMV), which improved her ventilatory status (ABG showing uncompensated respiratory alkalosis with more than

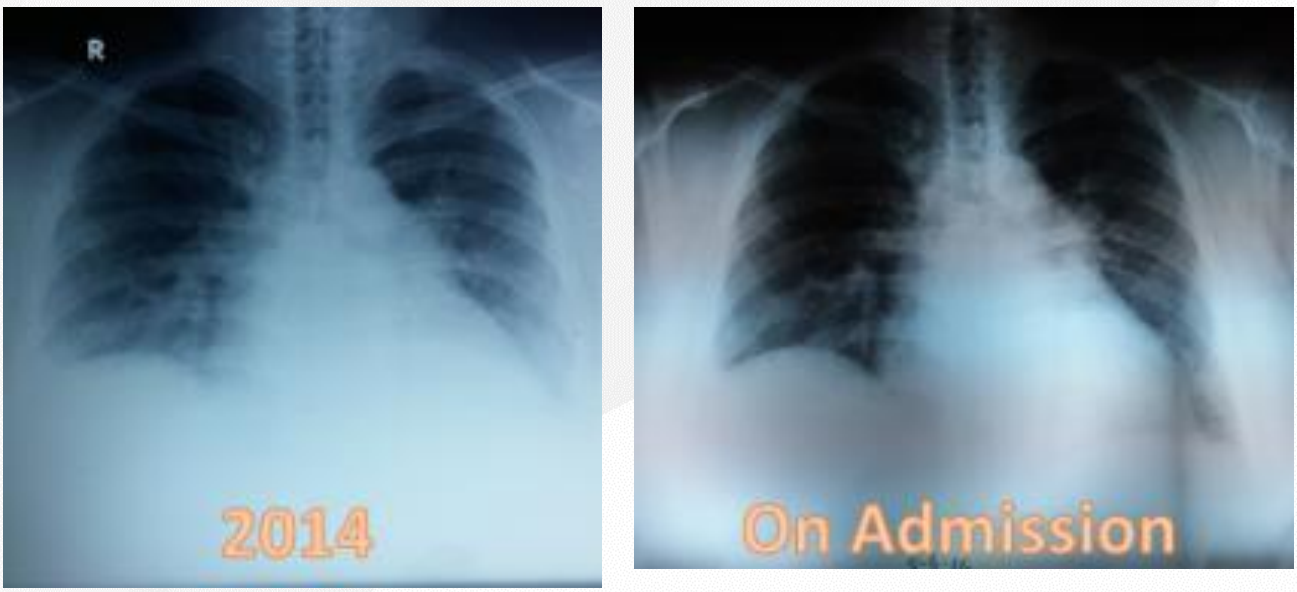

Figure 2. Chest radiograph on admission revealed no significant change from her previous films. Widening of the hilar structures and persistent lower lobe infiltrates are evident.

adequate oxygenation with supplemental oxygen). She improved over the next few days and she was eventually weaned off from ventilator support and discharged stable and improved on the 5th hospital day. Home medications included a combined long-acting beta-agonist (LABA) and long-acting muscarinic antagonist (LAMA) and PDE-5 inhibitor. She was also advised surveillance of ILD and PH through chest CT scan and 2D echocardiography.

Outpatient assessments and follow-up

The underwent spirometry and sleep polysomnography on follow-up. Spirometry revealed a scooped-out pattern on the expiratory limb of the flow-volume loop.

FEV1/FVC was 90.7%, with decreased FEV1 (1.07 L) and FVC (1.18 L). FEF 25-75 was low at 1.91 L/s. The low FVC was interpreted as due to a restrictive ventilatory defect or residual volume hyperinflation. The exaggerated concavity of the expiratory part of the flow volume loop and low FEF 25-75% were interpreted as suggestive of obstructive ventilatory defect. The patient was not able to tolerate post-bronchodilator studies, lung volume studies and diffusing capacity of the lungs for carbon monoxide (DLCO) studies; hence, were not conducted. The final spirometry reading was "suspect very severe underlying obstructive ventilatory defect, cannot rule out restrictive ventilatory defect."

Polysomnography revealed multiple hypopneic and apneic episodes, with a respiratory disturbance index of 7/hour. These episodes were accompanied by desaturations of up to 92%, which resolved with continuous positive airway pressure (CPAP). During pressure titration, resolution of hypopnea with improvement of oxygen saturation to 98% and decrease in the frequency of desaturations were noted at a CPAP level of 8-9 cm H_2O. This was interpreted as "mild OSA with effective CPAP level at 9 cmH_2O".

With the confirmation of COPD and OSA, the patient was diagnosed with Overlap Syndrome was confirmed. She was advised to initiate corrective therapy by using CPAP at starting pressure of 9 cmH_2O with oxygen supplementation, which improved her symptoms. Medically guided weight reduction and sleep hygiene measures were also recommended.

DISCUSSION

According to Murray, PH is seen in 12-28% of patients with SLE.[1] The clinical presentation is the same as with other PH patients, with the most common symptom being dyspnea. It is strongly associated with Raynaud's phenomenon, elevated rheumatoid factor titre, anti-phospholipid antibodies, and as found in this patient, anti-RNP.

The patient also had underlying ILD, as diagnosed by HRCT. In these patients, ILD usually presents as reticular infiltrates on chest radiograph, but is best diagnosed via HRCT, being non-invasive and more sensitive for mild or early disease.[2] Common patterns seen in ILD caused by SLE are ground glass opacities, septal thickening, fine reticular interstitial markings and honey-combing changes prominent on the posterior and basal segments of the lung. Patterns seen on HRCT can help qualify disease severity and prognosticate natural course.

Using the scoring system by Assayag et al, there was presence of all patterns of ILD in our patient with more than 75% lung involvement.[3] These connote an increased risk of morbidity and mortality due to a rapid decline in lung function, increased decline in exercise tolerance, and progressive hypoxia.

The presence of ILD also predisposes the patient to other pulmonary conditions, including pulmonary embolism, lung cancer, OSA, and COPD.[1] COPD was highly considered also because of the presence of autoimmune disease. Due to chronic inflammation and T cell activation, around 2%-5% of patients with SLE develop COPD, with around 5% developing COPD within the first year of SLE diagnosis.[4,5] The usual age at diagnosis is between the second and fourth decade of life.[6]

The patient also had OSA and was advised

corrective therapy using CPAP with oxygen supplementation. Medically guided weight reduction and bariatric procedures may also be considered for such patients. Sleep hygiene such as a regular sleep schedule and avoidance of sedatives must also be advised. For such patients, future surgeries with sedation may require perioperative CPAP.

Pulmonary conditions are known to overlap, as in this patient, who had ILD, PH, COPD and OSA. However, most literature document only the overlap of COPD with either OSA or ILD.[7-20] Literature on the triumvirate of ILD, COPD and OSA is scant.

Patients with ILD are at risk of hypoxemia due to the architectural changes in the lungs, and up to 88% of ILD patients have a form of nocturnal desaturation and sleep disturbance, mainly attributable to symptoms such as cough.[7] Sleep disturbance is correlated with the FEV1 and FVC, and symptoms usually resolve with supplementation with CPAP. Patients with ILD who develop OSA are likewise at higher risk of developing PH.[8]

ILD and COPD syndrome was first described by Auerbach 30 years ago.[21] COPD is seen in 5%-10% of patients with ILD, commonly in those with idiopathic pulmonary fibrosis, and is alternatively known as combined pulmonary fibrosis emphysema.[18] The exact correlation is unknown but is believed to be due to chronic inflammation in the interstitium, later affecting the airways. The overlap is usually seen in younger females with rheumatoid arthritis over scleroderma and mixed CTD. Literature on ILD and COPD in SLE is scarce. Treatment of COPD in ILD is geared towards treatment of the underlying disease contributing to ILD.[10] In this case, administration of immunomodulators and oxygen therapy will provide relief of symptoms.

The co-existence of COPD and OSA is termed by Dr David Flenley in 1985 as Overlap syndrome.[22] OSA usually develops in the later stage of COPD. Overlap syndrome has since been used regardless of the relative burden to one condition with the other. Carratu et al observed that 15% of COPD patients have some form of OSA, with prevalence rising to 43% among those with Stage IV disease.[12] Conversely, Greenberg et al noted that patients with OSA has a COPD prevalence of 7.6%.[13] It is important to recognize Overlap syndrome, as it increases the risk of morbidities such as hypoventilation and respiratory failure, as we as mortality.

Overlap of ILD, COPD and OSA

In patients with ILD and COPD, there is increased fibrosis, disruption of normal lung architecture, and decrease in lung compliance leading to increased ventilation/perfusion mismatch. These changes increase minute ventilation and work of breathing, which is constant both in the wake and sleep state. In the presence of OSA, sleep may serve as an additional stressor to respiration. Oxygen desaturation may be more profound during sleep because of muscle atonia. These changes may worsen concomitant PH.

Additionally, hyperinflation due to air trapping in COPD contributes to impaired contractile function of the diaphragm. Patients with COPD have increased minute ventilation and frequently rely on accessory muscles to aid ventilation. Thus, ventilation can fall dramatically during sleep and particularly in rapid eye movement (REM) sleep when muscle activity decreases. In studies, desaturations are frequent among patients with FEV1/FVC <65%, and increasing severity of obstructive disease is associated with more severe desaturations during sleep.[11-15,19,20]

Since Overlap syndrome is rare, no diagnostic algorithm or guideline. However, Zamarron et al recommended that Overlap syndrome should be suspected in COPD patients complain of headache upon awakening, excessive daytime sleepiness, snoring and breathing pauses, and obesity.[19] In patients with OSA, one should

suspect overlap COPD when one presents with signs and symptoms of cor pulmonale and polycythemia vera. OSA screening may be done using the STOPBANG, Epworth and Berlin questionnaires, with STOPBANG and Epworth having the highest sensitivity. The diagnosis of OSA must be confirmed by full polysomnography. Other pulmonary function tests such as ABG, spirometry with lung volume study and DLCO can help prognosticate outcome. Cardiopulmonary exercise test can also predict morbidity and mortality outcomes.

The optimal treatment of overlap syndrome is unknown. Few clinical trials have been undertaken, and no large studies have compared long-term outcomes between randomized therapies. Medications to control COPD exacerbation are still a mainstay. Inhaled LABA/LAMA with or without inhaled corticosteroids are important to keep the airways open. Oxygen therapy for at least 18 hours is advocated especially in the presence of severe PH. Nocturnal oxygen supplementation can likewise correct nocturnal desaturation in mild to moderate COPD and OSA.

Hypnotics or sedatives to help patient achieve REM sleep are advocated especially in severely symptomatic patients. Cognitive behavioral therapy, weight reduction and lifestyle modification are mainstays of therapy in Overlap syndrome. Smoking cessation and decrease in alcohol consumption must be emphasized and adherence to therapy must be stressed. Pulmonary rehabilitation to improve exercise tolerance may also help in improving FEV1 of these patients.

Positive airway pressure (PAP) in the form of CPAP, biphasic PAP (BIPAP), and NIMV. CPAP remains the gold standard of treatment for OSA and Overlap Syndrome, as it could increase in upper-airway resistance that occurs during sleep, potentially unload the respiratory muscles, and decrease hypoventilation, oxygen consumption or carbon dioxide production by the respiratory muscles. Alternatively, CPAP may offset intrinsic positive end-expiratory pressure in severe COPD. The 5-year survival of among patients with Overlap syndrome who use CPAP is 71% as compared to 34% in those who do not use CPAP.[19,20]

A subset of patients with stable COPD who may benefit from NIMV include those with daytime hypercapnia and super-imposed nocturnal hypoventilation. The effects of BIPAP have not been specifically evaluated since there is a difference between inspiration PAP and expiration PAP in maintaining alveolar ventilation and reducing carbon dioxide partial pressure.

There is little literature on the epidemiology of Overlap syndrome. However, it must be noted that all three disease entities share a common pathophysiology of hypoxemia, which can accelerate the disease process and decline in respiratory function of the patient, leading to higher cardiac events and respiratory failure.

In summary, we discussed the overlap of ILD, COPD and OSA in a patient with SLE. It is important to know the correlation of these diseases and to recognize signs and symptoms early for the timely institution of appropriate treatment.

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CROSS-SECTIONAL STUDY

Prevalence of Asthma-COPD Overlap Syndrome (ACOS) in Patients Presenting with Asthma or COPD in the OPD of the UP-PGH Section of Pulmonary Medicine: A Pilot Study

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ABSTRACT

Background: Asthma and COPD has significant overlap, which is known as Asthma-COPD Overlap Syndrome (ACOS). The exact prevalence of ACOS is still unknown. ACOS patients have a higher risk of exacerbation; thus, they must be identified.

Methodology: This was a single-center cross-sectional study. Asthma and COPD patients at the OPD were identified and included until the computed sample size of 54 COPD patients and 53 asthma patients was reached. Demographic profile of patients were determined. Spirometry done and patient was classified as having asthma, COPD or ACOS. The prevalence of ACOS was also computed.

Results: Asthma and COPD patients had a mean age of 56.42 $\pm$ 11.74 years and 66.63 $\pm$ 9.53 years, respectively. The mean age of ACOS patients was 65.32 $\pm$ 8.58 years. All patients were above age 40 years. Majority with asthma were females (69.44%), while majority with COPD (92.5%) and ACOS (63.64%) were males. Pulmonary tuberculosis (PTB) prevalence was 5% (asthma), 41% (COPD) and 48% (ACOS). Only 13.9% with asthma smoked, while 97.5% of COPD and 62.2% of ACOS patients smoked. Mean smoking history was 4.72 $\pm$ 14.67, 50.6 $\pm$ 30.28 and 32.23 $\pm$ 37.65 pack-years, respectively. The overall prevalence of ACOS was 22.45%. Those with asthma had a higher prevalence of ACOS (26.53%) compared to those with COPD (18.37%). ACOS was most common in those aged 50-59 years old.

INTRODUCTION

Asthma is defined as a heterogeneous disease characterized by chronic airway inflammation with a history of wheeze, shortness of breath, chest tightness and cough that vary over time and intensity, with variable expiratory airflow limitation.[1] Chronic obstructive pulmonary disease (COPD), on the other hand, is defined as enhanced chronic inflammatory response in the airways and lungs to noxious particles or gases.[2] Although asthma and COPD are different entities, it has been increasingly recognized that these two diseases have significant overlap and is now known as Asthma-COPD Overlap Syndrome or ACOS.[3] This subset of patients is reported to have a higher risk of exacerbations and hospitalization; thus, they have to be identified as more aggressive management is recommended for patients with ACOS.

The exact prevalence of ACOS in our country has not yet been determined but is said to be approximately 15-25% worldwide among patients diagnosed with obstructive airways disease.[4] Patients with ACOS have worse outcomes and greater health care utilization.[3,5] There have been several arguments whether this overlap really exists or it is just a phenotype of

COPD. Although the British Hypothesis states that asthma and COPD are two different disease entities, the Dutch Hypothesis supports the increasingly observed overlap between these two diseases stating that asthma and bronchial hyper-responsiveness predispose to COPD later in life and that asthma, COPD, chronic bronchitis and emphysema are different expressions of a single airway disease.

Several methods to diagnose ACOS have been proposed. Soler-Cataluña et al diagnosed ACOS based on three major and 2 minor criteria.[6] The major criteria included a very positive bronchodilator test with increase in FEV1 ≥ 15% and ≥ 400 mL, eosinophilia in sputum, and personal history of asthma. Minor criteria included high total IgE, personal history of atopy, and positive bronchodilator test with increase in FEV1 ≥ 12% and ≥ 200 mL on two or more occasions. However, these major and minor criteria were not sensitive nor specific. Another study done by Louie et al used the following major criteria for ACOS: a physician diagnosis of asthma and COPD in the same patient; history or evidence of atopy such as hay fever, elevated total IgE; age 40 years or more; smoking >10-pack years; and, postbronchodilator FEV1 < 80% predicted and FEV1/FVC < 70%.[6] Minor criteria used in their study included ≥ 15% increase in FEV1 or ≥ 12% and ≥ 200 mL increase in postbronchodilator treatment with albuterol. Other studies have attempted to diagnose ACOS among patients with asthma or COPD, but their diagnostic criteria have not been validated.

The prevalence of ACOS has also been a topic of debate since it is highly variable if categorized based on age group. A cohort study by Amir et al reported the prevalence of ACOS at 19.9%, and that prevalence increases with increasing age: 3.4% in patients 30 to 39 years old, 17.2% in patients 50 to 59 years old, and 37.9% in patients 60 years old and above.[7]

The Global Initiative for Asthma (GINA) and Global Initiative for Chronic Obstructive Lung Disease (GOLD) has come together to come up with a report on ACOS which is intended as a general guide for health professionals on diagnosis and management approach.[3] The aim of the consensus-based report on ACOS was made to assist clinicians to identify those patients who have chronic airflow limitation and distinguish asthma from COPD and ACOS. A stepwise and syndromic approach to diagnose patients with chronic airways disease is recommended. There are several features that would favor one diagnosis over the other. For instance, the age of onset of asthma is usually during childhood, symptoms may vary over time and lung function may be normal between symptoms.[1] On the other hand, COPD is usually diagnosed in patients >40 years of age, with chronic and usually continuous symptoms, and with persistent airflow limitation even between symptoms.[2] The usual age of diagnosis of patients with ACOS is ≥ 40 years but many had symptoms in adulthood.[3] Respiratory symptoms are persistent but variability in some patients may be prominent and as with COPD, lung function between symptoms is usually characterized by persistent airflow limitation.

Although spirometry is essential for diagnosis or exclusion of chronic airflow limitation, it may have a more limited value in distinguishing between asthma with fixed airflow limitation, COPD and ACOS.[3] Spirometric variables that are consistent with ACOS are as follows: post-bronchodilator FEV1/FVC < 0.7 is usually present; FEV1 ≥ 80% predicted is compatible with diagnosis of mild ACOS; FEV1 < 80% predicted is an indicator of severity of airflow limitation and risk of future events such as mortality and exacerbations; post-bronchodilator increase in FEV1 ≥ 12% and 200 mL from baseline consistent with reversible airflow limitation is common and more likely when FEV1 is low; and, post-bronchodilator increase in FEV1 > 12% and 400 mL from baseline consistent with marked reversibility is compatible with ACOS.[3]

It was said that ACOS is not a single dis-

ease but rather includes patients with different phenotypes and shares features of both asthma and COPD. There is a wide agreement that patients with features of asthma and COPD have more frequent exacerbations, with poor quality of life, more rapid decline in lung function and high mortality; thus, the importance of the identification of patients with ACOS should be emphasized.[8]

METHODS

This was a single-center cross-sectional study that included newly diagnosed patients and patients on follow-up visit who have been previously diagnosed to have asthma or COPD in the outpatient department of the University of the Philippines-Philippine General Hospital Section of Pulmonary Medicine from December 2015 until the computed sample size of 54 COPD patients and 53 asthma patients was reached. This sample size assumed an ACOS prevalence of 20 ± 10% with 90% level of confidence.

For those with asthma, the following patients were included: all patients 30 years old and above who were diagnosed to have bronchial asthma, either confirmed by spirometry or clinically diagnosed, including those with presumptive tuberculosis on chest x-ray and were determined to be sputum smear negative. Among those with COPD, the following patients were included: all patients 30 years old and above who were diagnosed to have COPD, either confirmed by spirometry or clinically diagnosed, including those with presumptive TB on chest x-ray and were determined to be sputum smear negative. Those with concomitant congestive heart failure, recent myocardial infarction, recent eye or abdominal surgery, pregnant, those who are mentally incapacitated who will not be able to follow instructions to perform spirometry, and those who were sputum smear positive and/or TB bronchiectasis were excluded.

Informed consent was solicited by the primary or sub-investigator and a thorough history and physical examination was performed on the day of study inclusion. A chest x-ray was performed and spirometry was done if there were no suspicious densities suggestive of pulmonary tuberculosis (PTB). On patients with suspicious densities on chest x-ray suggestive of PTB, two sputum specimens for examination was taken one hour apart. Spirometry was done on patients with negative sputum examination.

A syndromic diagnosis of airways disease was done using Box 5-2b found in the ACOS consensus-based document.[6] Patients were classified as: "more likely to be asthma" or "more likely to be COPD" if 3 or more boxes were checked for either asthma or COPD respectively. Patient were classified as "diagnosis of ACOS should be considered" if there were similar numbers of checked boxes in each column. If a patient was diagnosed to have ACOS, his or her attending physician was notified as more close follow-up is needed in patients with ACOS.

Specifically, a diagnosis of ACOS was considered if a patient had the following features: usually age ≥ 40 but may have had symptoms in childhood or early adulthood; respiratory symptoms including exertional dyspnea which are persistent but may have prominent variability; airflow limitation not fully reversible but often with current or historical variability; persistent airflow limitation; frequently a history of doctor-diagnosed asthma (current or previous), allergies, and a family history of asthma, and/or noxious exposures; symptoms are partly but significantly reduced by treatment which usually progress and treatment needs are high; chest x-ray similar to COPD; exacerbations may be more common than in COPD but are reduced by treatment; and, comorbidities are reduced by treatment and can contribute to impairment.[3]

Spirometric variables that that were used to support the diagnosis of ACOS were as follows: (1) normal FEV1/FVC pre- or post-bronchodilator (BD) not compatible with ACOS unless with other evidence of chronic airflow limitation; (2) post-BD FEV1/FVC < 0.7 usually present; (3) FEV1 ≥ 80% predicted compatible with diagnosis of mild ACOS: (4) FEV1 < 80% predicted as an indicator

of severity of airflow limitation and risk of future events such as mortality and exacerbations; (5) post-BD increase in FEV1 >12% and 200 mL from baseline suggestive of reversible airflow limitation common and more likely when FEV1 is low and ACOS should be considered; and, (6) post-BD increase in FEV1 >12% and 400 mL from baseline suggestive of marked reversibility as compatible with ACOS.

RESULTS AND DISCUSSION

Of the 53 asthma patients and 54 COPD patients who were included, four and five patients, respectively, were lost to follow up. Hence, they were not able to complete the pulmonary function test and was thus excluded from the study. Forty-nine patients with asthma and 49 patients with COPD were included in the statistical analysis.

Out of the 49 patients with asthma, 36 patients were identified to have purely asthma and 13 patients had ACOS (Table 1). On the other hand, 40 COPD patients had purely COPD and 9 patients were found to have ACOS. Among ACOS patients, there were more asthma patients (59.09%) compared to COPD patients (40.91%).

The demographic profile of patients are shown in Table 2.

As to age, asthma patients had a mean age of 56.42 years old and was more variable (SD 11.74 years); while COPD patients had a mean age of 66.63 $\pm$ 9.53 years. There were no patients with ACOS below 40 years of age and only one patient younger than 50 years old. ACOS patients had a mean age of 65.32 $\pm$ 8.58 years.

There were more male patients identified to have chronic disease of the airways. However, majority of asthma patients were females (69.4%) while majority of COPD (92.5%) and ACOS (63.64%) patients were males.

Only 33.67% of patients had history of previous PTB infection regardless of treatment status. Of note, 47.5% of COPD patients and 40.91% of ACOS patients had previous PTB infection, while only 5% of asthma patients had previous PTB. Previous PTB infection has not been implicated to increase risk of development of ACOS but it has been found that it increases the overall prevalence of airflow obstruction.[9]

Only five patients (13.9%) with asthma smoked or were previous smokers. In contrast, 97.5% of COPD and 62.2% of ACOS patients smoked or were previous smokers. Asthma patients had a mean smoking history of 4.72 $\pm$ 14.67 pack-years; COPD patients, a mean of 50.60 $\pm$ 30.28 pack-years; and ACOS patients, a mean of 32.23 $\pm$ 37.65 pack-years.

The prevalence of ACOS in this study was 22.45% (Table 3), which is similar to the worldwide average of 22% (p=0.545). Although the exact prevalence of ACOS among asthma patients has not yet been studied, it was noted that the prevalence of ACOS in the asthma group was higher (26.53%) as compared to the COPD group (18.37%, Table 4).

As expected, the prevalence of ACOS increased with increasing age and was noted to be highest in those aged 50-59 years old and was not present in patients less than 40 years old.

CONCLUSION

There is still debate as to the existence of Asthma-COPD Overlap Syndrome and to date it is still not defined. It was noted in this study that there were more asthma patients noted to have

Table 1. **Patients with Chronic Disease of the Airways**

	Pure		ACOS		Total	
	Number	%	Number	%	Number	%
Asthma	36	47.37	13	59.09	49	50.00
COPD	40	52.63	9	40.91	49	50.00
Total	76	100.00	22	100.00	98	100.00

Table 2. **Demographic Profile of Patients**

	Asthma		COPD		ACOS		Total	
Number of Cases	36	100	40	100	22	100	98	100
Age (years)	n	%	n	%	n	%	N	%
30-39	3	8.33	0	0.00	0	0.00	3	3.06
40-49	7	19.44	2	5.00	1	4.55	10	10.20
50-59	10	27.78	7	17.50	5	22.73	22	22.45
60-69	11	30.56	14	35.00	10	45.45	35	35.71
70-79	4	11.11	14	35.00	5	22.73	23	23.47
80 and above	1	2.78	3	7.50	1	4.55	5	5.10
Mean +/- SD	56.42 ± 11.74		66.63 ± 9.53		65.32 ± 8.58			
Sex								
Male	11	30.56	37	92.5	14	63.64	62	63.27
Female	25	69.44	3	7.5	8	36.36	36	36.73
Previous PTB								
Yes	5	13.89	19	47.5	9	40.91	33	33.67
No	31	86.11	21	52.5	13	59.09	65	66.33
Cigarette Smoking (pack years)								
None	31	86.11	1	2.50	6	27.27	38	38.78
<10	1	2.78	0	0.00	3	13.64	4	4.08
10-20	1	2.78	6	15.00	0	0.00	7	7.14
21-30	0	0.00	4	10.00	4	18.18	8	8.16
31-40	1	2.78	7	17.50	1	4.55	9	9.18
41-50	1	2.78	6	15.00	5	22.73	12	12.24
>50	1	2.78	16	40.00	3	13.64	20	20.41
Mean +/- SD	4.72 ± 14.67		50.60 ± 30.28		32.23 ± 37.65			

Table 3. **Prevalence of ACOS**

	Prevalence	z-Test	p-Value*
This study	0.2245	0.606	0.545
Worldwide average	0.2200		

*z-Test on Proportion ($p < 0.05$)

Table 4. Prevalence of ACOS among Asthma and COPD Patients

	Prevalence of ACOS
Asthma Group	0.2653
COPD Group	0.1837

Table 5. Prevalence of ACOS according to Age Group

	Prevalence of ACOS
Age (years)	
30-39	0.0000
40-49	0.0102
50-59	0.0510
60-69	0.1020
70-79	0.0510
80 and above	0.0102

ACOS which may represent a severe form of asthma in adults.[5] These patients should be identified and more closely followed up as they are more difficult to treat and have more frequent exacerbations.

This study showed that the prevalence of ACOS is our setting is similar to the worldwide prevalence, but a study with a larger population may be done to validate these findings.

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PROSPECTIVE COHORT STUDY

Clinical Correlation of the Radiologic Findings and Pulmonary Function of Patients with Bronchiectasis: a Lung Center of the Philippines Experience

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ABSTRACT

Objective: To describe the clinical characteristics and evaluate the high-resolution computed tomography (HRCT) findings of patients with bronchiectasis in correlation with their pulmonary function test (PFT) and their functional capacity

Methodology: This prospective study was conducted on stable patients with bronchiectasis diagnosed by HRCT at the Lung Center of the Philippines outpatient department from April 2014 through September 2014. Pulmonary function test and HRCT scores were taken, and dyspnea was assessed using the modified Borg scale (MBS).

Results: Fifty-eight patients were evaluated. Majority (75.9%) were female, mean age was 50.9 years, and most were non-smokers (87.9%). Fifty percent presented with mixed types of bronchiectasis. Post-tuberculosis infection was the most common etiology (94.8%). PFT results showed mostly probable restrictive type. FVC, FEV1 and MBS score were significantly correlated to CT score, bronchial dilatation, bronchial wall thickening, and number of bronchiectatic segments ($p<0.001$). No significant correlation was found between the number of bullae ($p=0.190$) and emphysematous segments ($p=0.718$).

Conclusion: Patients with cystic and mixed types of bronchiectasis, high CT score, bronchial dilatation, bronchial thickening and a higher number of bronchiectatic segments have more functional impairment. CT score is a predictor of FVC, FEV1 and dyspnea.

Keywords: bronchiectasis, HRCT score, pulmonary function

INTRODUCTION

Bronchiectasis is defined as a localized permanent abnormal dilatation of an airway,[1,2] characterized by airflow obstruction, with symptoms including cough, sputum production, wheeze, dyspnea and decreased exercise tolerance. Most patients with bronchiectasis have an obstructive pulmonary function defect, although mixed-obstructive-restrictive or restrictive patterns of lung function can be found in a minority of patients.[3] A local study of bronchiectasis patients founf that the most common finding on spirometry was an obstructive ventilatory pattern.[4] The severity of airflow was related to the extent of bronchiectatic segments, as demonstrated on high-resolution computed tomography (HRCT).[2] Extensive bronchiectatic changes result in a reduction in vital capacity leading to a restrictive defect, whereas productive sputum causes obstruction by mucosal thickening and sputum retention. However, the mechanism of airway obstruction is

not certain. Previous studies have found it might be associated with the collapse of large airways at expiration, the retention of endobronchial secretion, bronchial wall thickening, sputum proteases, obliterative bronchitis, airway hyper-reactivity or accompanying asthma, and emphysema.[1,3] The causes of dyspnea and reduced exercise capacity are multifactorial—these include altered pulmonary mechanics, inefficient gas exchange, decreased muscle mass and confounding psychological morbidity, all of which lead to a progressive detraining effect. Koulouris et al demonstrated that the presence of tidal expiratory flow limitation in patients with bronchiectasis related to an increase in dyspnea and a reduced tolerance for exercise.[5]

Currently, HRCT of the chest is a confirmatory test for bronchiectasis and is commonly used to grade bronchiectatic severity and extent.[2] The computed tomography (CT) scoring system modified from the one described by Bhalla et al[6] is used to quantify the severity and extent of bronchiectasis. CT scoring consists of the following parameters: bronchial dilatation, peribronchial wall thickening, number of bronchiectatic segments, number of bulla and number of emphysematous segments.[2]

Several studies have demonstrated the correlation between HRCT score and forced expiratory volume in 1 second (FEV_1) and the extent of physiological impairment.[3,7,8] In a retrospective study, Lee et al found that patients with cystic bronchiectasis had higher CT scores, more dilated lumen, and lower forced vital capacity (FVC), FEV_1, and FEV_1/FVC than patients with cylindrical bronchiectasis.[2] They also found that CT score is the most important predictor of lung function.

One study found that dyspnea perception, FEV_1, and the daily amount of produced mucus independently affected the health status of bronchiectasis patients. Psychological depression was related to exercise performance and perception of dyspnea was related to exercise capacity.[9] There is little published data concerning the assessment of physiologic status with respect to the radiologic degree of bronchiectasis and the exercise capacity of patients.[2] We have found no published data correlating the severity of bronchiectasis with the functional status of patients as determined by their dyspnea score.

This study aims to describe the clinical characteristics of bronchiectasis patients and correlate the extent and severity of their bronchiectasis on HRCT with their pulmonary function test (PFT) and functional capacity.

METHODS

This prospective study was conducted at the general outpatient department (OPD) of the Lung Center of the Philippines (LCP) from April 2014 through September 2014. The recruited patients were 18 years old and above; with on-and-off chronic cough for 3 months or more, sputum production and easy fatigability; radiographic evidence of bronchiectasis on chest radiograph using the criteria of Gudbjerg et al (increased pulmonary markings, honeycomb-like structures, atelectasis and pleural changes)[10] or HRCT scan of the chest (bronchial wall dilatation and wall thickening)[17] done ≤6 months prior; clinically stable disease with no history of change in the medications or oxygen supplementation within 1 month; and no signs of acute exacerbation. Returning patients with previous records and new patients with available chest radiographs or CT scan with a diagnosis of bronchiectasis were included. Plain HRCT of the chest was done for those with chest X-rays only or whose chest CT scans had been done >6 months prior.

Excluded from the study were patients with exacerbation of bronchiectasis (increased sputum production, increased cough, increased dyspnea, change in the color of the sputum, changes in chest sounds, radiographic changes consistent with a new pulmonary process and presence of fever); patients with features of active pulmonary tuberculosis (TB) on thoracic imaging (chest radiography showing heterogeneous consolidation involving apical and posterior segment of upper

lobes and superior segment of lower lobes, often with cystic or cavitary changes, with nodular and fibrotic infiltrates, or CT scan showing tree-in-bud sign, patchy or lobular areas of consolidation and cavitation, and microscopy showing sputum acid-fast bacilli [AFB] smear or TB culture positive); current smokers or those who have smoked ≥10 years; pregnant women; patients with cystic fibrosis; and those with a history of hemoptysis within the past 2 weeks. Informed consent was collected from the participants. The study protocols were approved by the hospital's Ethics Review Committee.

Patients had their PFT and plain HRCT of the chest done either on the day of recruitment or within a week from consultation. Single-visit protocol was used to characterize the clinical and radiologic phenotypes of bronchiectasis, where physical features and radiographic patterns were assessed. Functional capacity was assessed by evaluating FEV_1 and FVC results on PFT and by using the modified Borg's dyspnea scoring. This study had no natural history of disease course follow-up.

PFT (simple spirometry without postbronchodilator test) was performed in compliance with American Thoracic Society (ATS)/European Respiratory Society (ERS) standards, using the Viasys Vmax Encore 22. The degree of ventilatory impairment was based on Morris-Polgar classification. FVC, FEV_1, and FEV_1/FVC ratio were measured and indicated as percentage values in accordance with the age, sex and height of the patients.

HRCT of the chest was done using multidetector CT scanner Hitachi Pronto. All images were obtained with the patient in supine position, in full inspiration and without contrast medium. CT images were evaluated and CT scoring was done by 2 in-house radiologists. Bronchiectasis was categorized as "cylindrical" (tubular) when the bronchial lumen had a smooth tubular outline; "varicose" when the lumen had a variable diameter producing a beaded appearance; and "cystic" (saccular) when the dilated bronchi had the appearance of rings or clusters of cysts.

The extent of bronchiectasis, severity of bronchial dilatation, bronchial wall thickness (BWT), presence of mucus plugging in large and small airways, and decrease in parenchymal attenuation were scored separately for each lung lobe according to the modified Bhalla system: extent of bronchiectasis (0=none, 1=one or partial bronchopulmonary segment involved, 2=two or more bronchopulmonary segments involved, 3=generalized cystic bronchiectasis); severity of bronchial dilatation (0=normal, 1=less than twice the diameter of the adjacent pulmonary artery, 2=more than twice the diameter of adjacent pulmonary artery); severity of bronchial wall thickening (0=normal, 1=0.5 times the diameter of the adjacent pulmonary artery, 2=0.5 to 1.0 times the diameter of the adjacent pulmonary artery, 3=at least 1.0 times the diameter of the adjacent pulmonary artery); presence of mucus plugging in large airways (0=none, 1=present); presence of mucus plugging in small airways (0=none, 1=present); and extent of decreased attenuation (0=normal, 1=at most 50% of lobar volume, 2=more than50% of lobar volume).[1,3]

The functional status of the patients was assessed by grading their dyspnea severity through the modified Borg scale (MBS), written in English, with a Filipino translation. The scale was shown to the patients, who were then asked to point to the number on the scale that corresponded with their degree of dyspnea.

We analyzed the data based on distribution, demographic profile, patient features, PFT parameters, HRCT results and score, and grade of dyspnea using the SPSS statistical software for Windows. Scores were expressed as means, standard deviations or medians with ranges. Associations between PFT result, HRCT score and functional status were determined using Spearman's rank correlation. Chi-squared test was used to evaluate the association between categorical variables.

RESULTS

Fifty-eight patients with diagnosed bronchiectasis, confirmed by HRCT of the chest, were included in the study. Females made up the majority (76%). The mean age was 50.9±12.1 years; range was 38 to 63. Fifty-one (88%) were non-smokers. Twenty-six percent had tubular (cylindrical) bronchiectasis; 24%, cystic (saccular); and 50%, mixed. The underlying etiology for all was post-infection: 95% post TB infection and 5% post recurrent pneumonia. The mean FVC was 46% of the predicted value; FEV_1, 53%; and FEV_1/FVC ratio, 80% (Table 1).

Cough (86%) and easy fatigability (71%) were the most common complaints. Twenty (35%) of the patients had increased sputum production, and 13% had dyspnea, usually during exertion. The common findings on physical examination were crackles/rhonchi (12%). Three percent had decreased breath sounds, wheezes and clubbing (Table 2).

Table 1. Clinical Profile of Stable Bronchiectasis Patients (N=58)

Parameter	n (%)
Age, y*	50.9±2.1
Sex	
Male	14 (24.1)
Female	44 (75.9)
Smoking history	
Ex-smoker	7 (12.1)
Non-smoker	51 (87.9)
Etiology of bronchiectasis	
Childhood disease	0 (0.0)
Tuberculosis	55 (94.8)
Pneumonia	3 (5.2)
Types of bronchiectasis	
Tubular/cylindrical	15 (25.9)
Cystic/saccular	14 (24.1)
Mixed (tubular and cystic)	29 (50.0)
Varicose	0 (0.0)
Lung function parameter*	
FVC % predicted	45.9±17.8
FEV_1 % predicted	53.3±17.2
FEV_1/FVC	80.3±9.2

*Mean ± standard deviation.
FEV = forced expiratory volume in 1 second; FVC = forced vital capacity.

The most common radiologic finding of bronchiectasis was multilobar (76%); the most commonly involved lobes, the right upper (67%) and the left upper (50%) (Table 3).

The mean bronchial dilatation of the tubular group (1.2) was significantly lower than that of both the cystic (2.1) and the mixed groups (2.0) (p=0.004). Tubular-type bronchiectasis also displayed the least wall-thickening patterns (p=0.045) on chest CT scan. There was significant difference between the mean extent of bronchiectasis of the tubular group (1.3) compared to the cystic (1.9) and mixed groups (1.9) (p=0.027) (Table 4).

There were no significant differences between tubular, cystic and mixed bronchiectasis in terms of FVC% predicted, FEV1% predicted and FEV1/FVC (Table 5). No significant differences were found among the 3 groups in terms of bronchial dilatation (0.121), bronchial wall thickening (0.538), extent of bronchiectasis (0.051), number of bullae (0.730) and number of emphysematous segments (0.264) (Table 6).

The radiologic severity according to ventilatory impairment showed no significant difference (p=0.078), suggesting that the distribution of radiologic severity according to lung impairment was similar among normal, restrictive and mixed types of ventilatory defect (Table 7).

Probable restrictive type of ventilatory pattern was detected in most of our patients (tubular, 73%; cystic, 93%; and mixed type, 83%). No obstructive ventilatory pattern was observed in this study.

FVC and FEV_1 demonstrated significant difference in all HRCT scores in an inversely related fashion, per negative Pearson's correlation coefficient (Figure 1). The FEV_1/FVC ratio was

Table 2. Symptoms and Signs of Bronchiectasis

Symptom/Sign	n (%)
Cough	50 (86.2)
Increased sputum	20 (34.5)
Dyspnea	13 (22.4)
Easy fatigability	41 (70.7)
Blood-streaked sputum	0 (0.0)
Chest pain	3 (5.2)
Crackles	7 (12.1)
Rhonchi	7 (12.1)
Decreased breath sounds	2 (3.4)
Wheezes	2 (3.4)
Clubbing	2 (3.4)

not significantly associated with HRCT scores (Table 8).

MBS score was significantly correlated to total CT score, bronchial dilatation, bronchial wall thickening and number of bronchiectatic segments. There was no significant correlation between dyspnea score, number of bullae (p=0.190) and emphysematous segments (p=0.718) (Table 9). There was a positive correlation (r=0.261) between the CT score and the MBS (Figure 2).

FEV_1 and CT score were significantly dependent (p=0.007). A mild CT score tended to have higher FEV_1 (FEV_1 ≥80% predicted), while a moderate-to-severe CT score tended to have lower FEV_1 (<79% predicted) (Table 10).

FVC and CT score were significantly dependent (p=0.01). Moreover, mild CT scores tended to have higher FVCs, while those with a moderate-to-severe CT scores tended to have lower FVCs (FVC <80% predicted) (Table 11).

DISCUSSION

Bronchiectasis is generally an anatomic abnormality resulting from many different factors. It is defined pathologically as an irreversible dilatation of bronchi usually related to airway infection.[2] It is typically characterized by chronic productive cough, easy fatigability, dyspnea, rhonchi/crackles, and occasionally wheezes, as were seen in our patients. Our study showed that there are more females with bronchiectasis than males; this data is consistent with the findings of previous studies.[2,3,4,13] We had more females than males in our study, perhaps because we excluded patients who were at risk for chronic obstructive pulmonary disorder (COPD), ie, current smokers and those with 10 years' smoking history, who were more commonly males.

According to literature, in 30% to 74% of patients with bronchiectasis, etiology could not be determined, but post-infection has been regarded as the most common cause.[14] We came up with a similar finding, specifically noting tuberculosis infection as a significant factor in the history of almost all of our patients, like in the local prospective study done by Ramos et al.[4] Our study showed that bronchiectasis involvement was multilobar in majority, like in the study done by Habesoglu et al[13]; however, unlike them who found the right and left lower lobes as the most common location, we found the right and left upper lobes as the most commonly involved. This involvement of the upper lobes of the lungs was consistent among our participants, the majority of whom developed bronchiectasis post tuberculosis infection, which often involves the apical lobes.

Table 3. Radiologic Distribution of Bronchiectasis Based on HRCT Findings

Localization	n (%)
Multilobar	44 (75.9)
Single lobe	8 (13.8)
Right upper lobe	39 (67.2)
Left upper lobe	29 (50.0)
Right middle lobe	27 (46.6)
Lingula	2 (3.4)
Right lower lobe	13 (22.4)
Left lower lobe	21 (36.2)

HRCT=high-resolution computed tomography.
Note: Frequency of each lobe involvement was calculated separately.

Table 4. CT Scores According to Type of Bronchiectasis

Bhalla's CT Score	Tubular (n=15)		Cystic (n=14)		Mixed (n=29)		P-value
	n (%)	Mean±SD	n (%)	Mean±SD	n (%)	Mean±SD	
Bronchial dilatation							
0	1 (6.7)	1.2±0.7*	0 (0.0)	2.1±0.8**	0 (0.0)	2.0±0.9**	0.004
1	11 (73.3)		4 (28.6)		10 (34.5)		
2	2 (13.3)		5 (35.7)		8 (27.6)		
3	1 (6.7)		5 (35.7)		11 (37.9)		
Bronchial wall thickening							
0	0 (0.0)	1.2±0.6**	0 (0.0)	1.7±0.7	1 (3.4)	1.8±0.9**	0.045
1	13 (86.7)		6 (42.9)		11 (37.9)		
2	1 (6.7)		6 (42.9)		9 (31.0)		
3	1 (6.7)		2 (14.3)		8 (27.6)		
Extent of bronchiectasis							
0	0 (0.0)	1.3±0.5*	0 (0.0)	1.9±0.9**	0 (0.0)	1.9±0.8**	0.027
1	11 (73.3)		6 (42.9)		11 (37.9)		
2	4 (26.7)		3 (21.4)		10 (34.5)		
3	0 (0.0)		5 (35.7)		8 (27.6)		
Number of bullae							
0	10 (66.7)	0.3±0.5	8 (57.1)	0.6±0.9	16 (55.2)	0.6±0.8	0.482
1	5 (33.3)		4 (28.6)		10 (34.5)		
2	0 (0.0)		1 (7.1)		2 (6.9)		
3	0 (0.0)		1 (7.1)		1 (3.4)		
Number of emphysematous segments							
0	9 (60.0)	0.4±0.5	5 (35.7)	0.8±0.7	14 (48.3)	0.6±0.7	0.275
1	6 (40.0)		7 (50.0)		12 (41.4)		
2	0 (0.0)		2 (14.3)		3 (10.3)		
3	0 (0.0)		0 (0.0)		0 (0.0)		

CT=computed tomography.
*Mixed tubular and cystic type of bronchiectasis.
**Mixed obstructive and restrictive ventilatory defect.

We scored morphologic changes of the lungs using the CT scoring system developed by Bhalla et al.[6] As a consequence of airway infection, there was structural destruction of lung tissues followed by functional deterioration.[2] The degree of anatomical change that can be assessed radiographically may reflect pulmonary functional limitation. We correlated the CT scores, types of bronchiectasis, pulmonary functional status and dyspnea perception of patients in our study. In contrast to previous studies, which reported obstructive pulmonary defect in the majority of bronchiectasis patients,[2,13] our study showed that most of our patients had probable restrictive type of ventilatory defect, and a few had mixed obstructive/restrictive ventilatory defect, which is uncommon.[14,15] However, pulmonary function parameters may still be normal in minimal degree of bronchiectasis,[2] which was observed in some of our patients. However, Lee et al have reported that most of their patients had mixed type of ventilatory defect, followed by obstructive defect.[2]

Table 5. Pulmonary Function Test Results According to Type of Bronchiectasis (Mean ± SD)

	Tubular/ Cylindrical (n=15)	Cystic/Saccular (n=14)	Mixed* (n=29)	P-value
Lung function parameter				
FVC % predicted	47.8±17.1	50.1±22.2	43.0±15.7	0.428
FEV_1 % predicted	45.9±17.8	54.4±19.4	50.0±17.3	0.287
FEV_1/FVC	79.7±6.7	85.4±4.8	78.2±11.1	0.054
Impairment of lung function				
Normal	2±13.3	1±7.1	1±3.4	0.456
Restrictive type	11±73.3	13±92.9	24±82.8	
Mixed type**	2±13.3	0±0.0	4±13.8	

FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity; SD=standard deviation.
*Mixed tubular and cystic type of bronchiectasis.
**Mixed obstructive and restrictive ventilatory defect.

The likely reason for this finding may be because we excluded patients who were at risk of COPD, specifically, current smokers and those with significant smoking history ≥10 years. We have noted that COPD and asthma were the coexisting diseases or comorbidities of the patients in other studies.[2,4,13,16] Nicotra et al found that obstructive lung disease was common in bronchiectatic patients who were cigarette smokers, while Lynch et al reported that airway obstruction was seen more in cylindric type of bronchiectasis, which was associated with a greater number of current and previous smokers.[12] In most of our patients, chest CT scan findings showed fibrosis.

Habesoglu et al found a strong inverse correlation between the extent of bronchiectasis, the degree of bronchial dilatation, BWT, decrease of attenuation in lung parenchyma, and PFT parameters in patients with pure bronchiectasis,[1] but the extent of bronchiectasis and the decrease in the attenuation in the lung parenchyma were the main determinants of the reduction of FVC and FEV_1; this suggests that morphologic changes in patients with pure bronchiectasis could lead to both restrictive and obstructive functional impairment.[1]

Sheehan et al[8] stated that the mucus load of airways varies over time, and this could be a reason for some fluctuation in pulmonary function. Reports have suggested that the obstructive component of bronchiectasis is caused by a combination of structural damage to the airways, secretions in the airways, bronchiolitis, bronchial hyperreactivity,[12] obliterative bronchitis accompanied by bronchiectasis,[1] bronchial wall thickening, and decreased attenuation of the lung parenchyma.[8] Habesoglu et al found that the degree of bronchial dilatation was the main independent variable associated with a decrease in FEV_1/FVC ratio. Lee et al reported that the degree of bronchial dilatation correlated with airway obstruction.[2] Roberts et al suggested that the increase in the degree of bronchial dilatation correlated with the amount of airway obstruction at lower levels.[17] In parallel, the increase in airway obstruction can be associated with morphologic changes in small airways, which cannot be radiologically demonstrated with HRCT.[1]

Roberts et al found that decreased attenuation of the lung parenchyma on the expi-

Table 6. CT scores According to Type of Ventilatory Defect

Bhalla's CT Parameters	Normal (n=4)		Restrictive (n=48)		Mixed (n=6)		P-value
	n (%)	Mean±SD	n (%)	Mean±SD	n (%)	Mean±SD	
Bronchial dilatation							
0	1 (25)	1±0.8	0 (0)	1.9±0.8	0 (0)	1.7±1.0	0.121
1	2 (50)		19 (39.6)		4 (66.7)		
2	1 (25)		14 (29.2)		0 (0)		
3	0 (0)		15 (31.3)		2 (33.3)		
Bronchial wall thickening							
0	0 (0)	1.3±0.5	1 (2.1)	1.7±0.8	0 (0)	1.5±0.8	0.538
1	3 (75)		23 (47.9)		4 (66.7)		
2	1 (25)		14 (29.2)		1 (16.7)		
3	0 (0)		10 (20.8)		1 (16.7)		
Extent of bronchiectasis							
0	0 (0)	1.0±0.0	0 (0)	1.9±0.8	0 (0)	1.3±0.5	0.051
1	4 (100)		20 (41.7)		4 (66.7)		
2	0 (0)		15 (31.3)		2 (33.3)		
3	0 (0)		13 (27.1)		0 (0)		
Number of bullae							
0	3 (75)	0.3±0.5	28 (58.3)	0.6±0.8	3 (50.0)	0.5±0.8	0.73
1	1 (25)		15 (31.3)		3 (50.0)		
2	0 (0)		3 (6.3)		0 (0)		
3	0 (0)		2 (4.2)		0 (0)		
Number of emphysematous segments							
0	3 (75)	0.3±0.5	21 (43.8)	0.7±0.7	4 (66.7)	0.3±0.5	0.264
1	1 (25)		22 (45.8)		2 (33.3)		
2	0 (0)		5 (10.4)		0 (0)		
3	0 (0)		0 (0)		0 (0)		

Table 7. Radiologic Severity According to Ventilatory Impairment

Radiologic Severity	Normal (n=4)		Restrictive (n=48)		Mixed (n=6)		P-value
	n	%	n	%	n	%	
Normal	0	0	0	0	0	0.0	0.078
Mild	4	100	19	40	3	50	
Moderate	0	0	26	54	3	50	
Severe	0	0	3	6	0	0.0	

*Radiologic severity based on HRCT score: normal=0, mild=1 to 10, moderate=11 to 21, severe=22 to 31.

Figure 1. FEV_1 vs CT score (left) shows inverse correlation (r=–0.625), and FVC vs CT score (right) shows inverse relationship (r=–0.609)

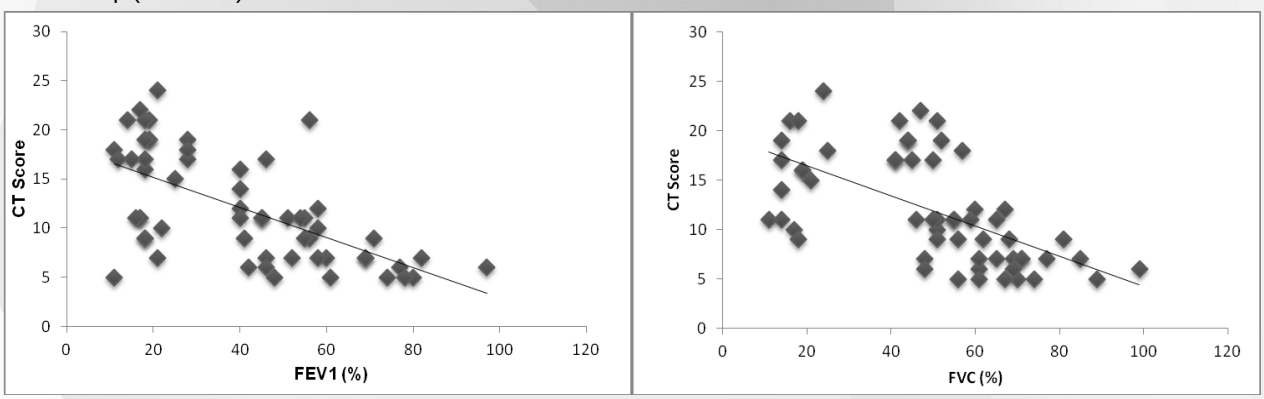


Table 8. Correlation Between HRCT Scores and Lung Function Parameters

	FVC		FEV_1		FEV_1/FVC	
	Pearson r	P-value	Pearson r	P-value	Pearson r	P-value
HRCT score	-0.609	<0.001	-0.625	<0.001	0.210	0.114
Bronchial dilatation	-0.664	<0.001	-0.512	<0.001	0.252	0.056
Bronchial wall thickening	-0.507	<0.001	-0.571	<0.001	0.170	0.202
No. of bronchiectatic segments	-0.570	<0.001	-0.516	<0.001	0.193	0.148
No. of bullae	-0.473	<0.001	-0.522	<0.001	0.129	0.333
No. of emphysematous segments	-0.185	0.165	-0.376	0.004	0.154	0.248

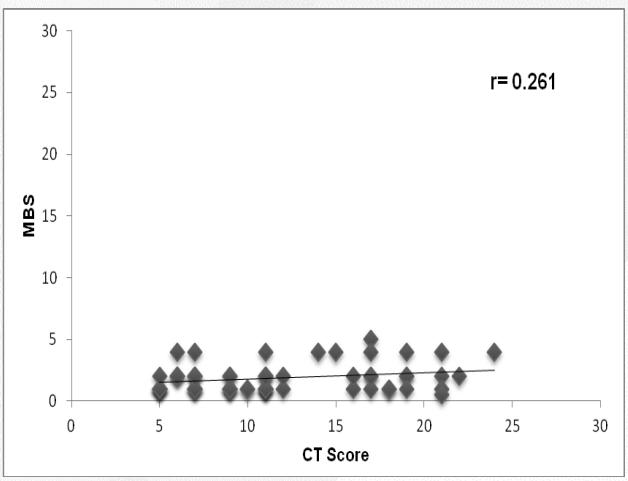
HRCT=high-resolution computed tomography; FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity.

Table 9. Correlation Between CT Score and Functional Status of Patients Using Modified Borg Scale (MBS)

	MBS Score	
	Pearson r	P-value*
CT score	0.261	0.048
Bronchial dilatation	0.334	0.010
Bronchial wall thickening	0.273	0.038
No of bronchiectatic segments	0.260	0.049
No. of bulla	0.175	0.190
No. of emphysematous segments	0.048	0.718

ratory CT scan was a major determinant of airflow obstruction. In bronchiectasis, this phenomenon represents inflammatory or obliterative bronchiolitis, which is an integral histologic feature. Obliterative bronchiolitis is believed to be a key early event in the pathogenesis of bronchiectasis in cystic fibrosis, and others have argued that obliteration of peripheral bronchi and bronchioles results from the spread of chronic infection from bronchiectatic airways.[17] Thus, bronchial wall thickening in small airways is a pathophysiologic event in airflow obstruction.

Figure 2. Relationship Between CT Score and Dyspnea Score



CT=high-resolution computed tomography; MBS=modified Borg scale.

Although restrictive lung impairment is a feature of previous studies of bronchiectasis and was a significant finding in our patients, we found no satisfactory explanation for this finding. Possible mechanisms for lung restriction include atelectasis, pleural disease, and parenchymal scarring and peribronchial fibrosis that accompany bronchiectasis secondary to previous infection, particularly, tuberculosis,[1,17] Evolution of peri-bronchial inflammation to fibrotic disease might account for a restrictive functional element and might also lessen gas trapping by a traction effect on partially obstructed airways.[17]

Among the different types of bronchiectasis, the cystic and mixed types showed more bronchial dilatation and bronchial wall thickening than the tubular type. This may reflect more pronounced distortion of the lung architecture and airways inflammation. However, there was no difference in terms of the number of bullae and emphysematous segments both in the cystic and mixed (cystic and tubular) types of bronchiectasis. In other studies, patients with cystic bronchiectasis also showed a decrease in the individual parameters of lung function compared to patients with cylindrical bronchiectasis.[2,12]

We found no significant differences in type of bronchiectasis in relation to the FEV_1, FVC and FEV_1/FVC ratio. In contrast, Alzeer et al[7] and Lynch et al[12] found FVC and FEV_1 to be significantly lower in cystic patients than in cylindrical patients.

We observed that the radiologic severity of bronchiectasis is the same in all types of lung impairment. The FVC% and FEV_1% predicted were significantly correlated to CT scores: bronchial dilatation, bronchial wall thickening, and the number of bronchiectatic segments. However, there was no significant difference with FEV_1/FVC ratio. FVC and HRCT scores were inversely related to each other. CT score includes severity, extent and associated findings in bronchiectasis; it reflects functional changes.

There was significant correlation between

Table 10. Correlation Between Severity of Bronchiectasis (CT Score) and FEV_1

CT Score	FEV_1 (% predicted)				P-value
	≥80%	50–79%	30–49%	<30%	
0 (normal)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.007
1–10 (mild)	3 (100)	13 (72.2)	5 (41.7)	5 (20.0)	
11–20 (moderate)	0 (0.0)	4 (22.2)	7 (58.3)	15 (60.0)	
21–30 (severe)	0 (0.0)	1 (5.6)	0 (0.0)	5 (20.0)	

CT=computed tomography; FEV_1=forced expiratory volume in 1 second.

Table 11. Correlation Between Severity of Bronchiectasis (CT Score) and FVC

Total CT Score	FVC (% predicted)				P-value
	≥80%	50–79%	30–49%	<30%	
0 (normal)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.010
1–10 (mild)	4 (100.0)	18 (60.0)	2 (20.0)	2 (14.3)	
11–20 (moderate)	0 (0.0)	11 (36.7)	6 (60.0)	9 (64.3)	
21–30 (severe)	0 (0.0)	1 (3.3)	2 (20.0)	3 (21.4)	

CT=computed tomography; FVC=forced vital capacity.

the dyspnea score (MBS score) and the total CT score, bronchial dilatation, bronchial wall thickening and the number of bronchiectatic segments. A higher CT score would correlate to a higher MBS; thus, CT score could be a predictor of dyspnea.

CONCLUSION

We conclude that radiologic findings such as cystic and mixed (tubular and cystic) type, high CT score, bronchial dilatation, bronchial thickening and the number of bronchiectatic segments were highly relevant to functional impairment in our patients with stable bronchiectasis. CT score appeared to be the most important predictor of FVC and FEV_1.

As a prospective investigation of stable bronchiectasis patients, our study was limited in that it did not measure total lung capacity through helium dilution or body plethysmograph to confirm restrictive pulmonary impairment. In addition, the CT scans were interpreted by different in-house radiologists who were unaware of the clinical conditions of the patients, and 2 different in-house radiologists did the CT scoring.

We recommend further studies to verify these clinical, functional and radiologic relationships in a bigger population. Investigators could do complete lung volume studies using body pletysmograph. Future studies could also correlate CT scan with long-term outcome and find its role in acute exacerbations.

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RETROSPECTIVE STUDY

Prevalence and Characteristics of the Three Clinical Phenotypes of COPD at Lung Center of the Philippines

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ABSTRACT

Objectives: To determine the prevalence and analyze the most relevant clinical characteristics of chronic obstructive pulmonary disease (COPD) in patients seen at a tertiary hospital's COPD outpatient clinic

Methods: This retrospective study stratified the characteristics of COPD into three phenotypes (ie, chronic bronchitis, emphysematous and COPD asthma) based on imaging tests, pulmonary functions and reported symptoms.

Results: Out of 165 patients, 60% were chronic bronchitic (phenotype 1); 27%, emphysematous (phenotype 2); and 13% showed mixed characteristics with asthma (phenotype 3) (p=0.09). There was no significant difference in level of smoking among the groups. Type 2 patients showed lower forced expiratory volume in one second (FEV_1) compared to types 1 and 3 (p<0.001). No significant differences were observed in the proportion of patients who experienced any exacerbations in the past.

Conclusions: In a general population of COPD patients, three patient profiles can be seen in clinical practice. Most fall under the chronic bronchitis or emphysematous phenotype. Emphysematous patients normally show worse pulmonary functions than the other two groups, with no differences in exacerbations and use of hospital health care resources.

Keywords: COPD, phenotype, clinical phenotypes

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a preventable and treatable disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with the lungs' abnormal inflammatory response to noxious particles or gasses, primarily caused by cigarette smoking. COPD is a leading cause of morbidity and mortality worldwide and results in an economic and social burden that is both substantial and increasing.[1] Current clinical guidelines define COPD by the presence of chronic, almost irreversible, airflow obstruction, confirmed by spirometry, with a ratio of post-bronchodilator forced expiratory volume in 1 sec to forced vital capacity (FEV_1/FVC) <70 in the absence of a defined pathology, such as bronchiectasis or tuberculosis, to otherwise explain the airflow obstruction.[2] The main problem with these guidelines is that they ponder too much on the value of forced spirometry in the diagnosis and assessment of the severity of COPD, thereby preventing the adequate assessment of the "various faces of the disease".[3] It is now widely accepted that COPD is a complex syndrome with numerous pulmonary and extra-pulmonary components.[4]

Since the Ciba symposium in 1959, COPD has been considered an overlap between chronic

bronchitis, emphysema and subtypes of asthma associated with chronic airflow limitation.[5] This was first represented in a non-proportional Venn diagram by Snider.[2] In the 1960s, Burrows[6] further defined the emphysematous phenotype to differentiate it from the bronchitic phenotype. Since then, various observational studies have confirmed the existence of groups of patients with peculiar characteristics such as the presence of emphysema in imaging techniques and a decrease in the diffusion test, low sputum production, low body mass index (BMI), normal arterial blood gases and greater dyspnea; chronic bronchitis with no evidence of emphysema in chest x-rays and with normal diffusing capacities; and patients with characteristics similar to bronchial asthma, which have generally been excluded from clinical trials but actually constitute a phenotype with greater concentration of eosinophils in their secretions and bronchial mucosa.[3]

As a result of these studies, there is consensus that FEV_1 by itself does not adequately describe the complexity of COPD and cannot be used in isolation for the optimal diagnosis, assessment and management of the disease. A clear alternative has not yet been defined, but identification and subsequent grouping of key elements of the COPD syndrome into clinically significant subgroups can guide therapy more effectively.[4] In recent years, the term "COPD phenotype" has been used to refer to the clinical types of patients with COPD. The term "phenotype" is defined as a single disease attribute or a combination of attributes that describe differences between individuals with COPD as they relate to clinically meaningful outcomes.[4] These recent pieces of information on different phenotypes of COPD indicate that we are not justified in continuing to assume that a classification based exclusively on spirometric criteria is a good classification.[7]

Recognizing the different phenotypes within COPD is important in understanding the underlying disease processes. Each phenotype may have a different pathophysiology, and the identification of biological mechanisms specific to some phenotypes may lead to the development of biomarkers aimed at the diagnosis of phenotypes and the identification of candidates to specific and more targeted treatments. It is, therefore, from the clinical point of view, possible to identify thee different COPD phenotypes, the assessment of which could facilitate a better understanding and management of the disease.[8]

The objective of this study is to determine the prevalence of each phenotype in a population of COPD patients seen at a tertiary hospital's COPD outpatient clinic and to analyze the most relevant clinical characteristics in each of the three described COPD phenotypes.

METHODS

This is a retrospective, descriptive study performed at a tertiary hospital COPD outpatient clinic. Charts were included for reviewed if the patient was aged ≥40 years, consulted at the clinic from January 2013 through December 2013, had a >10 pack-year index (PYI) smoking history, and was diagnosed with COPD according to Global Initiative for Chronic Obstructive Pulmonary Disease 2014 criteria (post-bronchodilator FEV_1/FVC <0.70). Charts were excluded if the patient had a current diagnosis of asthma, bronchiectasis or pulmonary tuberculosis.

A sample size of 165 was computed based on the report of a local study, that the estimated prevalence of COPD in the Philippines was around 12.5% to 13.8% and an alpha of 0.05.

Demographics, BMI, comorbidities, smoking status, exacerbations and hospitalizations, treatment, dyspnea score in daily living and results from pulmonary function tests/chest radiography/chest CT scan were collected. Patients were then categorized into different subgroups according to the following criteria[3,7]:

- **Phenotype 1. Chronic Bronchitis** - cough and sputum production on most days for at

3 months per year, for ≥2 years; absence of pulmonary emphysema, demonstrated through imaging technique (ie, CT scan or thorax radiography); and absence of asthma antecedents.

- **Phenotype 2: Emphysema** - pulmonary emphysema proved by CT scan, or diffusion test with transfer factor for carbon monoxide/alveolar volume (TLCO/VA) values inferior to 80% and thorax radiography suggesting emphysema.
- **Phenotype 3. Asthma overlap** - personal history or physician diagnosis of asthma before the age of 40; and absence of pulmonary emphysema demonstrated through imaging techniques, CT scan or thorax radiography.

Descriptive analysis was performed on all the variables: absolute and relative frequencies for qualitative variables, mean with standard deviation for continuous variables.

Pearson's chi-squared test was used to compare independent samples for quantitative variables; ANOVA for qualitative variables. Tukey's honest significant difference (HSD) was used for analysis between groups. In all statistical tests performed, the level of statistical significance was set at <0.05. SPSS Statistics v. 17.0 statistical package was used.

RESULTS

Out of the 400 charts reviewed, 180 met the inclusion criteria and 165 were randomly selected to be analyzed in the study. Of the 165 included patients, 60% (n=98) presented as chronic bronchitic (type 1); 27% (n=45) were emphysematous (type 2); and the remaining showed mixed characteristics with asthma (type 3). The proportion of male patients was significantly higher in type 1 and type 2; the proportions of females was significantly higher in type 3 (p=0.009). No significant differences were noted in smoking level, age, BMI, and level of dyspnea. The emphysematous group showed lower FEV_1 than the chronic bronchitic group (p<0.001). FVC and FEV_1/FVC were also significantly lower in type 2 than in type 3. The mean height in type 2 was significantly higher than in type 3 (163.0 cm vs 157.5 cm; p<0.05) (Table 1).

The proportions of patients with any exacerbation in the past year were the same for the three groups (34%, 33%, 52%; p=0.234). There was no significant difference among the three groups in proportion of patients with only one exacerbation (p=0.282) and with two or more (p=0.767). No significant differences were observed in the numbers of visits to the emergency room (p=0.333), hospital admittances (p=0.487), and ICU admittances (p=0.405) (Table 2).

Common comorbidities observed in the study group were hypertension, diabetes mellitus, cardiovascular disease and cerebrovascular diseases. There were no noted significant differences among the three groups in terms of these observed comorbidities (Table 3).

Long-acting beta-agonist (LABA) plus inhaled corticosteroid (ICS) was the most frequently used medication (92%), followed by doxofylline, and then tiotropium, excluding the use of the short-acting bronchodilator salbutamol, which was mainly used as rescue medication (Table 4). There were no significant differences in the use of LABA+ICS and salbutamol among the three groups. Doxofylline use was significantly higher in the emphysema group (p<0.001). Among the medications used for the cardiovascular sphere, statins were most frequently used in the chronic bronchitic group (p=0.003) (Table 4).

DISCUSSION

The results of this study show that, for an equal degree of smoking, three patient profiles can be identified in clinical practice: Patients with pulmonary emphysema, phenotype 1, show

Table 1. Baseline characteristics of included patients according to COPD phenotype

	Chronic Bronchitis (n=97)	Emphysema (n=44)	Asthma Overlap (n=21)	p-value
Age	66.8±8.9	68.1±8.6	67.2±9.5	0.682
Height	160.9 ±6.6	163±6.1	157.5±8.1	0.009*
BMI	21.6±5.9	20.8±5.4	19.8±5.0	0.343
FEV_1 (% predicted)	53.5±19.0	39.9±16.1	45.0±19.3	<0.001**
FVC (% predicted)	72.6±17.4	64.8±19.0	67.9±12.6	0.040**
FEV_1/FVC	51.8±13.2	45.6±13.1	45.4±12.3	0.018**
Dyspnea (mMRC)				
0	28.6	28.9	31.8	0.978
1	53.1	48.9	50.0	
2	15.3	15.6	13.6	
3	3.1	6.7	4.5	
4	0.0	0.0	0.0	
Smoking	37.2±24.3	37.6±16.0	25.8±24.7	0.090
Gender				
Male	90 (92.8%)	41 (93.2%)	15 (71.4%)	0.009
Female	7 (7.2%)	3 (6.8%)	6 (28.6%)	

*Significant difference between types 2 and 3.
**Significant difference between types 1 and 2.
mMRC=Modified Medical Research Council Dyspnea Scale.

Table 2. Exacerbation frequency in the past year

	Chronic Bronchitis	Emphysema	Asthma Overlap	p-value
Exacerbations, %	0.5	0.4	0.7	0.479
Patient with any exacerbations, %	34.1	33.0	52.4	0.234
1 exacerbation	25.0	26.8	42.9	0.282
≥2 exacerbations	9.1	6.2	9.5	0.767
Visits to the emergency due to exacerbation, %	0.45	0.40	0.67	0.333
Hospital admittances due to exacerbation, %	0.3	0.2	0.4	0.487
ICU admittances due to exacerbation, %	0.022	0.04	0.10	0.405

Table 3. Comorbidities per COPD phenotype

	Chronic Bronchitis	Emphysema	Asthma Overlap	p-value
Hypertension, %	44.3	29.5	52.4	0.140
Diabetes mellitus, %	5.2	4.5	4.8	0.987
Cardiovascular disease, %	2.1	2.3	0	0.793
Cerebrovascular accident, %	1.0	0	0	0.999

Table 4. Cardiorespiratory medications per COPD phenotype

	Chronic Bronchitis	Emphysema	Asthma Overlap	p-value
Respiratory medications				
LABA+ICS	93	93	91	0.960
Salbutamol	60	60	73	0.581
Tiotropium	36	32	41	0.609
Doxofylline	36	79	64	0.000
Comorbidities medications				
Calcium channel blocker	13	24	14	0.302
Statins	22	4	9	0.003
Angiotensin receptor blocker	16	19	27	0.446
Anticoagulants	4	7	5	0.796
Anti-diabetics	2	4	9	0.400

ICS=inhaled corticosteroid; LABA=long-acting beta-agonist..

worse pulmonary functions and are associated with greater mean height. The chronic bronchitic group, phenotype 2, has better pulmonary function. The third group, phenotype 3, is not large in general population of COPD and is more prevalent among women. The prevalence in this group may vary notably when diagnostic criteria are modified.[9]

The term COPD phenotype is used as a characteristic of the disease, establishing difference in clinical relevance, but it still generates discrepancy of criteria within the scientific community.[10] This is important because previous studies confirm that for the same FEV_1, COPD patients can be very different in terms of clinical, functional, imaging, and evolution course point of view. The ECLIPSE study recently demonstrated that these differences may also extend to exacerbations and FEV_1 deterioration.[11] Approaches to phenotype identification in COPD have been very varied. Some studies try to identify all the possible phenotype features and establish groups after performing statistical analysis. But in most of these studies, most of the phenotype characteristics lack clinical meaning and their relevance has not been established. On the other hand, using predefined clinical phenotypes for COPD in clinical practice is very easy—they are based on theories that are solid,

and they represent groups of patients with clinical characteristics differentiated regardless of their functional stage.[12]

Garcia-Aymerich et al have identified three types of patients by means of cluster analysis: group 1 represented a greater functional severity and worse clinical situation; group 2, less overall respiratory impairment; and group 3, lower functional deterioration, like group 2 but with greater obesity prevalence, cardiovascular disorder, diabetes and systemic inflammation.[13] That study's results are consistent with our study in that, for equal degree of smoking, they also identified a group showing worse lung function than others.

In a separate study, Izquerdo-Alonzo et al recruited patients from different pulmonary outpatient services and used the same criteria as our study to stratify patients into subgroups. They found that the emphysema group showed lower BMI, worse pulmonary function and a greater degree of dyspnea; in the chronic bronchitic group, greater concentration of comorbidity and high BMI; and in the third group, greater prevalence among women.[3] Their data are consistent with our results in that the emphysematous group showed worse pulmonary function and the asthma overlap showed greater prevalence in women and the lowest proportion among the three groups.

The asthma overlap group was the predominant COPD phenotype in the study of Marsh et al—they represented more than 50% of the study population.[7] Conversely, this overlap group was not seen by Garcia-Aymerich et al; patients who had certain characteristics with asthma could have been excluded from their study. This could also be the same reason why the asthma overlap group comprised the lowest proportion of patients in our study, because patients with post-bronchodilator characteristics of asthma were not enrolled in the COPD clinic.

Increased reversibility is one of the key differential aspects of the overlap-asthma COPD phenotype. Welte et al observed frequent significant reversibility in COPD patients. Recently, by consensus, a group of experts established the diagnosis of an overlap phenotype[14]: the patient must meet three major criteria or two major and two minor among the following: **Major criteria:** very positive bronchodilator response (>400ml and >15% in FEV_1), sputum eosinophilia or previous diagnosis of asthma; and **minor criteria:** increased total serum IgE, previous history of atopy or positive bronchodilator test (>200ml and >12%) on at least 2 occasions.[15]

Previous literature suggests that part of phenotypic heterogeneity in COPD is due to divergent distribution of bronchial airway (chronic bronchitis) and parenchymal disease (emphysema). Another characterization has been Type A (Pink Puffer) and Type B (Blue Bloater) COPD, clinico-pathophysiologic syndromes that clustered together and were thought to represent points on a continuum representing different pathophysiology. Subsequently, certain authors considered this classification obsolete and of poor clinical usefulness, promoting a uniform vision of COPD classified based on FEV_1 values. After the publication of the Global Initiative for Obstructive Lung Disease (GOLD) in 2001, key aspects in the disease's heterogeneity gave priority to the simplicity of spirometric values. But as stated earlier, focusing solely on FEV_1 poses a barrier in dealing with the disease, because FEV_1 does not adequately reflect all the multiple clinical and systemic manifestations of the disease.[16]

As seen in this study, despite differences in the clinical characteristics of patients, the amount of exacerbation was similar in the three groups. Acute exacerbation of COPD is currently defined as "a sustained worsening of the patient's condition, from the stable state and beyond normal day-to-day variations, that is acute in onset and necessitates a change in regular medication in a patient with underlying COPD."[17] But the numeric assessment of exacerbation has limited value, because there are

important limitations in this current definition of COPD exacerbation. The general description poses numerous operational challenges for use in the clinical phenotyping. It remains unclear whether these changes are quantitative or if there is a qualitative element.[4] The study also does not allow for the identification of the characteristics of all exacerbations. Numerous data associate the presence of chronic bronchitis with greater exacerbation. The absence of differences in the study may be, at the very least, conditioned by a greater efficiency of the treatment in those patients with a greater risk of exacerbations.[3] Also, the patient-recorded increases in symptoms that appear to be exacerbations outnumber those that cause them to present for medical attention.[4] These findings pose different phenotypes of exacerbation, the treatment and prevention of which should be individualized according to the baseline characteristics of each patient.[18]

Patients with COPD often present with comorbid diseases. Crisafulli et al found that metabolic (systemic hypertension, diabetes and/or dyslipidemia) and heart disease (chronic heart failure and/or coronary heart disease) were the most frequently reported comorbid combinations among the diseases associated with COPD.[19] This was also observed in our study. In another study by Mannino et al, the presence of respiratory impairment, as determined using both lung function measurement and the presence of respiratory symptoms, was associated with a higher risk of having comorbid hypertension, cardiovascular disease and diabetes.[20] The reason for this association was unclear but it was theorized that systemic inflammation, chronic infections, shared risk factors or undefined factors may contribute to the development of comorbid conditions, and these disorders can be seen as manifestations of COPD or vice versa. The presence of many of these comorbidities appears to have deleterious effects on several outcomes in COPD.[18] Izquerdo et al have reported that the chronic bronchitis group showed a greater concentration of comorbidity and cardiovascular risk factors.[3] This finding was further supported by Hassan et al, who also found that the chronic bronchitis group showed a greater concentration of comorbidity.[21] However, our study did not show significant differences among the three groups in terms of these comorbidities.

Whether treatment of comorbid conditions alters the natural history of COPD, or whether treatment of COPD is altered by the presence of a concomitant comorbidity, awaits further study.[4] Currently, only smoking cessation and long-term oxygen therapy in patients with resting hypoxemia while awake clearly alter prognosis for survival or decline in lung function.[22,23] Mancini et al found that statins, ace-converting enzyme inhibitors and angiotensin-receptor blockers reduced both the cardiovascular and pulmonary outcomes of COPD patients.[24] This may be due to mitigation of pulmonary injury by the statins and drugs affecting angiotensin II.[25,26] Dobler et al found statins may have beneficial effects by reducing all-cause mortality, deaths from COPD, respiratory-related urgent care, COPD exacerbations and lung function decline; and by improving exercise capacity.[27] Soyseth et al hypothesized that statins might improve all-cause disease mortality in COPD because many COPD patients probably have unrecognized ischemic disease.[28] However, Keddissi et al associated the use of statins with an attenuated decline in lung function and a lower incidence of respiratory-related emergency room visits and/or hospitalization in COPD, which imply that statins may have a direct disease-modifying effect on COPD.[29] In our study, statin use is significantly different among the three groups, with the chronic bronchitic group predominantly using this drug. The question of whether this group's use of statin could have contributed to the observed better pulmonary function and relatively less number of hospitalizations compared to the other two groups needs further investigation and follow-up.

One salient feature noted in this study is that despite the significant differences in their airflow limitation, the three groups did not show significant differences in numbers of exacerbation and hospitalizations. One possibility is that patients in the emphysematous group, who have the worst pulmonary function, might be poor perceivers of dyspnea. This hypothesis is well established in asthma but has not been formally explored in COPD.[30] Also worth noting is that the chronic bronchitic and asthma overlap groups are, on the average, 4 cm shorter than the emphysematous group, and the previous two groups show better pulmonary function. The shorter height in the asthma overlap group is attributable to the fact that most subjects were women. Kjensil et al have noted that lung functions were overestimated in COPD patients with relatively modest height reductions, and height reduction depends on the number and severity of vertebral deformities.[31] Patients that were included in the study may be followed up to further evaluate for any co-existing vertebral deformities.

The prescription pattern observed is not surprising as current clinical current guidelines recommend that pharmacological treatment should be used mainly on FEV_1 values and on symptoms. But such an approach may no longer be correct, based on recent experience in the development of roflumilast, the first drug developed specifically for the treatment of COPD associated with chronic bronchitis. Clinical trials have shown that, among patients with chronic bronchitis–associated COPD and a history of exacerbations, roflumilast improves lung function and reduces the frequency of exacerbations that require medical interventions.[32] This shows that identification of a patient's profile allows greater benefit, as the drug is administered to the most adequate patient and withheld from those who are unlikely to benefit from it. This can be a key in the development of new drugs that may be effective in certain groups of patients but may look inefficacious when a nontargeted COPD population is analyzed.[3]

The main limitation of this study is that it is retrospective and used cluster analysis to group patients according to key variables. The clinical relevance of these data would still require longitudinal validation to determine how such clustered subjects differ with respect to important clinical outcomes. Also the criteria established to define the groups may seem arbitrary. Lastly, the population comes from the pulmonary outpatient clinic; therefore, the results may not necessarily be extrapolated to the general population.

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RETROSPECTIVE STUDY

Clinical Profile and Outcome of Lung Cancer Patients with Pneumonia Admitted at Lung Center of the Philippines: A 5-year Retrospective Study

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ABSTRACT

Objective: To determine the clinical profile and outcome of lung cancer patients with pneumonia admitted at a tertiary hospital over a 5-year period.

Methodology: This was a retrospective cohort study that included 312 lung cancer patients admitted due to a tertiary hospital for pneumonia from January 1, 2009 to December 31, 2013. Study data were extracted from patient records and analyzed through descriptive statistics. Correlation between patient outcomes and patient characteristics were also statistically analyzed.

Results: In total, 312 lung cancer patients admitted due to pneumonia were included. Age ranged from 29 to 86 years, with a mean age of 61.23 years. Majority of patients were male (68.6%), had non-small cell adenocarcinoma (88.5%), and stage IV/extensive disease (78.2%). Almost half (45.3%) of patients opted supportive treatment. Around a third (32.7%) had *Candida* spp as the predominant organism grown in sputum culture. Overall, 74% patients were discharged improved while 26% died. Clinical stage and patient age were found to be significantly associated with patients outcome ($p<0.05$). All deaths occurred in patients with stage IV/extensive disease.

Conclusion: Pneumonia is life-threatening in lung cancer patients. It can shorten survival especially those with advanced age and cancer stage, in which mortality is high. These two factors are reliable predictors of mortality that can be used to prognosticate patients.

INTRODUCTION

The main causes of death in patients with lung cancer are local progression of the disease, metastases to remote organs and respiratory infections, particularly pneumonia.[1] Pneumonia is considered as a secondary cause of death, which is caused not only by the progression of the disease but also by the applied treatment negatively influencing the immunity of patients.[2] In a study done by Zieba etal (2003) in Poland, pneumonia was diagnosed in 58.5% as the secondary cause of death among lung cancer patients.[3]

Severe pulmonary infections in lung cancer patients may develop due to local or systemic immunological disorders, primarily affecting cellular immunity.[4,5] This can be compounded by an impaired cough reflex, which may take place against the background of applied treatment or as a result of neoplastic metastases to the brain.[6] Moreover, metastases to bone marrow may lead to leukopenia and anemia.[4,7,8] Studies would show that the main causes of pneumonia were atelectasis and dysfunction of phagocytes and lymphocytes, especially in non-small cell lung cancer (NSCLC).[4]

Another group of factors predisposing to the occurrence of the respiratory system infection

includes those related to the radical and palliative treatment of lung cancer. Most anti-neoplastic drugs have a suppressive effect on the function of the immune system.[9] By the suppressive influence on the cellular immunity, they contribute to the increase of susceptibility to infections.[10] The syndrome produced by radiotherapy depends on the size of irradiated area and the amount of a total dose. Developing inflammatory changes in lungs may be responsible for the occurrence of respiratory failure and death, especially if complicated by respiratory system infection.[7,11,12]

This study aimed to investigate the clinical profile and outcome of lung cancer patients with pneumonia admitted at a tertiary hospital in the Philippines over a 5-year period, and to identify patient characteristics that could prognosticate outcomes.

METHODS

This was a retrospective cohort study that included lung cancer patients, treated or untreated, with pneumonia admitted at a tertiary hospital in the Philippines from January 1, 2009 to December 31, 2013. Patients admitted for reasons other than pneumonia, those who did not undergo culture and sensitivity testing on admission, and those who died due to conditions other than pneumonia, were all excluded.

Data were collected retrospectively from patient records. For those who fulfilled the inclusion/exclusion criteria, patient demographic data, cancer type, clinical stage, treatment modalities received, microbiologic data and patient outcomes during hospital stay were collected, summarized and analyzed statistically.

Data were presented as means and standard deviations (SD) or frequencies and percentages, as appropriate. Cramers V and Chi-Square tests were employed to establish statistical correlation between clinical variables and patient outcome. A p-value of less than 0.05 was considered statistically significant.

Institutional review and approval from the Department of Pulmonary Medicine was acquired for this study.

RESULTS

In total, 312 lung cancer patients who were admitted from January 1, 2009 to December 31, 2013 secondary to pneumonia were included in our study. Demographic characteristics of these patients are reflected in the Table. The age range is from 29 to 86 years old with a mean age of 61.23 years. Majority of patients were males with a total rate of 68.6% while 31.4% were females as shown in the table.

Most patients had NSCLC (Table 1). Adenocarcinoma predominated the histologic type in 88.5% of cases. Squamous non-small cell carcinoma was seen in 3.8% of patients while the

Table 1. Characteristics of included patients

Characteristic	Value (n=312)	
Age (mean)	61.23 ± 11.87 years	
	Frequency	**%**
Gender		
Female	98	31.4%
Male	214	68.6%
Type of cancer		
Non-small cell carcinoma		
Adenocarcinoma	276	88.5%
Squamous	12	3.8%
Small cell carcinoma	24	7.7%
Cancer Stage		
Stage I	0	0
Stage II	4	1.3%
Stage III	64	20.5%
Stage IV/extensive	244	78.2%
Treatment		
Surgical resection + chemotherapy	13	4.1%
Radiation Therapy + chemotherapy	30	9.6%
Chemotherapy	128	41.0%
Supportive treatment	141	45.3%

Table 2. Organisms isolated in blood culture

Organism	N	Percent
Coagulase negative *Staphylococcus*	6	6.5%
No growth	87	93.5%
Total	93	100.0

remaining 7.7% had small cell carcinoma.

On admission, 78.2% had stage IV/ extensive lung cancer (patients with small cell-extensive disease was categorized as stage IV) and 20.5 % had stage III. Most patients opted for supportive treatment (45.3%) or chemotherapy (41%).

Table 2 shows the organisms isolated in blood culture of patients included in the study. Out of the 312 patients, only 93 had blood culture. Coagulase-negative *Staphylococcus* was isolated in 6.5% of patients while the rest (93.5%) had no growth. In sputum culture, *Candida* spp (32.7%) was the predominant organism while 23.4% of the specimen had no growth. Other common organisms isolated from sputum culture include *Moraxellla catarrhalis* (9.0%), alpha-hemolytic streptococci (8.3%), *Pseudomonas aeruginosa* (8.0%), coagulase-negative staphylococci (6.4%) and *Acinetobacter baumanii* (6.1%).

The outcome of patients during hospitalization is shown in Table 3 and Figure 1. In total, 74% were discharged improved while 26% died. Cancer stage was found to be correlated with outcomes ($p<0.001$). No mortality was noted in patients with stage II and III lung cancer; all 81 patients who died had stage IV/extensive disease.

Advancing age was also correlated with poorer patient outcomes ($p=0.025$) (Table 4). However, the correlation of outcomes with gender or cancer treatment modality was not statistically significant (Table 5 and 6, respectively).

DISCUSSION

To our knowledge, this is the first local study to examine pneumonia in lung cancer patients. Our retrospective study indicates that pneumonia among lung cancer patients is indeed life threatening mainly because of their underlying condition. Based on the data gathered, majority of these patients are males (68.6%) with a mean age of 61.23 years.

Male predominance is consistent with several studies worldwide in which lung cancer is considered as the most common cancer in this group secondary to high incidence of smoking.[13] In terms of age, lung cancer peaks in persons between 60-80 years old and becoming common among those below 40 years old according to latest statistics.[1] Therefore, the demographic profile of lung cancer patients with pneumonia gathered from our study still reflects the demography of lung cancer patients in general.

This study also revealed that greater number of patients had adenocarcinoma (88.5%), compared to other histologic types like small cell carcinoma (7.7%) and squamous cell carcinoma

Table 3. Organisms isolated in sputum culture

Organism	N	%
Candida spp.	102	32.7
No growth	73	23.4
Moraxella catarrhalis	28	9
Alpha-hemolytic streptococcus	26	8.3
Pseudomonas aeruginosa	25	8
Coagulase-negative staphyloccocus	20	6.4
Acinetobacter baumanii	19	6.1
Enterobacter aerogenes	9	2.9
Staphyloccoccus aureus	5	1.6
Stenotrophonas maltophila	3	1
Pantoea agglomerans	2	0.6
Total	312	100

Table 4. Cramer's V: Relationship of Cancer stage and outcome

Cancer stage	OUTCOME		Total	Value	P-value
	Improved	expired			
Stage II	4	0	4	0.313	<0.001
Stage III	64	0	64		
Stage IV/ extensive	163	81(33.2%)	244		
Total	231	81	312		

Table 5. Cramer's V: Relationship of patient's age and outcome

Age (years)	OUTCOME		Total	Value	P-value
	Improved	Died			
29-47	31	8 (20.5%)	39	0.153	0.025
48-66	132	40 (23.2%)	172		
67-86	68	33 (32.6%)	101		
Total	231	81	312		

Table 6. Chi-square: Relationship of Gender and Outcome

Gender	OUTCOME		Total	Value	df	2-sided P-value
	Improved	Died				
Female	77	21	98	1.203	1	0.273
Male	154	60	214			
Total	231	81	312			

Table 7. Chi -Square: Relationship of cancer treatment modalities and outcome

Treatment modalities	OUTCOME		Total	Value	df	2-sided P-value
	Improved	Died				
Supportive treatment	107	34	141	3.364	2	0.067
Chemotherapy	90	38	128			
Radiotherapy + Chemotherapy	21	9	30			
Surgery + Chemotherapy	13	0	13			
Total	231	81	312			

(3.8%). This finding is contrary to what many investigators have noted that patients with squamous cell lung cancer tend to contract pneumonia more readily than patients with cancer of other histopathological types.[12] However, the predominance of adenocarcinoma in this study is not reflective of those lung cancer patients who acquired pneumonia but rather based on the fact that adenocarcinoma is the most common cancer worldwide.[13]

With regards to clinical stage, most patients in our review had stage IV/extensive lung cancer (78.4%) while the rest had stage III (20.5%), and stage II (1.3%). Majority opted supportive treatment (45.3%) while others received chemotherapy (41%), concurrent radiation therapy and chemotherapy (9.6%), and for patients with early stage lung cancer, surgical resection plus adjuvant chemotherapy (4.1%) were offered. Their underlying condition, location of metastasis and the treatment received were contributory to the degree of immunosuppression leading to the development of several infections particularly pneumonia based on several studies.[4,5]

Our study also demonstrated that *Candida* sp. (32.7%) was the predominant organism grown in sputum cultures of these patients. Other isolates include *Moraxella catarrhalis* (9.0%) alpha-hemolytic streptococcus (8.3%), *P. aeruginosa* (8.0%), coagulase-negative staphylococcus (6.4%), *A. baumanii* (6.1%), *Enterobacter aerogenes* (2.9%), *S. aureus* (1.6%), *Stenotrophomonas maltophila* (1%) and *Pantoea agglomerans* (0.6%). Data also revealed that significant number of patients had no growth (23.4%) in their sputum as well as in blood culture (93.5%). Coagulase-negative staphylococcus was isolated in blood culture of the remaining patients (6.5%). A study done by Zeiba in Poland showed that *Streptococcus* and *Proteus* species as well as *Mycobacterium tuberculosis* were the predominant organisms isolated in this group of patients. Putinati et al indicated Gram-negative rods (usually *Haemophilus* at 45.2%) as the most frequent cause. *S. aureus* (33.3%), *Pneumocystis carinii* and *Chlamydia trachomatis* (16.7%) as well as Gram-negative cocci (4.8%.) were also seen in this group of patients.[9] Japanese investigations, on the other hand, noted frequent involvement of *S. aureus*, *Enterococcus faecalis*, and various Gram-negative organisms such as *Pseudomonas*, *Acinetobacter*, *Enterobacter*, and *Klebsiella* species on lung cancer patients who had pneumonia.[14] Variability of results gathered from different countries may depend on the setting as well as the predominant organism in that particular area.[15]

According to a local study done by Handog and Dayrit in 2005 at the Research Institute of Tropical Medicine, the warm tropical climate in our country and its interplay with age, occupation, genetic susceptibilities and immune responsiveness contribute to the high prevalence of fungal infections among Filipinos.[16] In their paper, it was also noted that although fungal culture yield is low, *Candida sp*. is the most common isolate obtained predominantly from specimens taken from the oral mucosa and nails. This opportunistic organism may become pathologic once the immune system is impaired, as in the case of patients with lung cancer.

This study reported that 74% of patients recovered from pneumonia. All deaths occurred in those with stage IV/extensive disease ($p<0.001$). Likewise, a significant relationship between age and outcome was also established, ($p=0.025$) in which increasing age parallels with increasing mortality. Therefore, these factors can be used to prognosticate lung cancer patients with pneumonia. However, gender and cancer treatment modalities did not significantly correlate with patient outcomes.

This study was limited in the variables examined in relation to patient outcomes. Future studies may provide more in-depth analysis into functional status, presenting signs and symptoms, co-morbidities and duration. Treatment for pneumonia should also be explored in further

studies. Nonetheless, the high clinical response rate suggests that prompt diagnosis and treatment of pneumonia may yield high clinical success rates. Additionally, the prevalence of *Candida* sp. indicates that physicians should have a high index of suspicion for Candida pneumonia in these patients, and should consider anti-fungal coverage when necessary.

CONCLUSION

Pneumonia is common among lung cancer patients, and this study demonstrated that pneumonia can be life-threatening in these patients, especially in those with stage IV disease (33.2%). Advanced age was also correlated with increased mortality. Thus, age and cancer stage can be used to prognosticate patients. Prompt identification and immediate proper management are also necessary to lessen morbidity and mortality.

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