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Remember not to forget

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

"Remember how we forgot?"
- Shane L. Koyczan, "Remembrance Year"

There is a understandable premium clinicians place on diagnostic tests and tools which are not only simple, but speedy as well. Health care has become increasingly more expensive, and in many instances when urgent care is required, time is of the essence, especially since every day spent waiting for a test result means additional cost to care.

However, our articles in this issue describe situations wherein diagnostic testing, although considerably costly, is worth both the expense and the wait. The case reports on Primary Ciliary Dyskinesia (PCD) and Good Syndrome demonstrate the value of complete diagnostic testing, despite the attendant costs, since it clinches the diagnosis for rare and less common conditions, especially because these patients may present with signs and symptoms which may be often associated with more endemic illness.

The 16-year-old patient with PCD presented with hemoptysis, and already underwent two treatment courses for pulmonary tuberculosis, and was only considered for the diagnosis upon review of his childhood history. The 50 year-old patient with Good Syndrome was also frequently diagnosed with pulmonary infections, and it was only after a more extensive review of her medical background allowed her medical team to consider the syndrome. Both of these patients were able to clinch their rare diagnoses through complete albeit expensive diagnostic testing. However, none of these investigative testing would have been pursued if the attending physicians did not recognize the possibility of the less common diagnoses. Furthermore, if costly testing such as CT scans, bronchoscopy, and immunological work-up were not done, then these patients would have ended up misdiagnosed.

On the other hand, the other articles in this issue remind us that there are simple and less costly ways of evaluating patients. Despite the fact that sputum AFB testing is slowly being replaced by the Gene Xpert MTB/Rif Assay as the go-to initial test to diagnose pulmonary tuberculosis, it still remains valuable when cost of work-up is restrictive. Likewise, this article from Bascara et al reminds us that a third sputum AFB smear can still be helpful, in the same way that Sario and Gonong have demonstrated that the testing characteristics of Gene Xpert MTB/Rif Assay do not necessarily outperform histopathology and culture in diagnosing tuberculous pleural effusion.

Moreover, the use of checklists and questionnaires in augmenting medical history taking has proven to be helpful tools in evaluating patients either in-hospital or in an outpatient setting. In addition, these tools aid clinicians ensure that all significant patient medical data are

captured, especially in urgent and critical care situations where quick decision-making is required despite limited patient history-taking. Eventually, questionnaires and checklists also allow for more focused diagnostic testing, such as sleep testing for patients screened for likely obstructive sleep apnea (OSA), which become even more valuable since the screening tool recommended by Macaraig and Gappi is homegrown and tailored for Filipinos.

In the same way, algorithms such as the one presented by Castillo and Cabrera is a tool similar to a checklist in that it directs the clinician to the next diagnostic and/or therapeutic step/s. Being a pre-operative algorithm, the Lung Center of the Philippines (LCP) Risk Assessment tool was initially designed to evaluate patients with lung cancer, but this study demonstrates that it easily evaluates for non-neoplastic cases as well.

Essentially, this issue reminds us that some diagnostic tests such as sputum AFB testing, histopathology and culture remain relevant despite the fact that there are more updated and sophisticated tests available nowadays. Also, remembering less common medical conditions comes in handy in the approach to patients with potentially rare syndromes or illnesses. It is definitely difficult to imagine how many patients have been – and continue to be – misdiagnosed with pulmonary tuberculosis for such manifestations as cough, hemoptysis and bronchiectasis.

Checklists and questionnaires as diagnostic screening tools, as well as algorithms as means to direct therapeutic approaches, help clinicians remember necessary aspects in medical history taking, and steps in moving patient care forward. Nevertheless, local versions of these tools come few and far between and so to develop those tailor-fit for Filipinos will prove to be extremely valuable contributions to patient care.

In the end, let this PJCD issue help us remember not to forget the basic essentials in the diagnosis of TB, which continue to play significant roles especially among the cost-conscious, or not to forget the less common diagnostic possibilities which can mimic more endemic medical conditions.

Indeed, let it not be said that, in the diagnostic and therapeutic approach to our patients' illness, we did not remember certain key aspects that can direct (or redirect) patient care. Let us, therefore, always make a conscious effort to remember not to forget.

CASE REPORT

A Case Report on Primary Ciliary Dyskinesia in a 16-Year-Old Male With Bronchiectasis, Normal Situs, and Sperm Immotility

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ABSTRACT

Primary ciliary dyskinesia (PCD) is a rare genetic disorder of the motile cilia. The common manifestations are recurrent infection of the upper and lower respiratory tract due to impaired mucociliary clearance, leading to development of bronchiectasis with predilection to the middle and bilateral lower lobe, situs abnormalities in 50% of cases, and infertility due to poor motility of spermatozoa flagella in males and poor ciliary movement of the epithelial lining of the oviduct in females.

This paper reports a case of a 16-year-old male who came in with recurrent non-massive hemoptysis, secondary to bronchiectasis via chest CT scan. He presents with perennial rhinosinusitis and a history of neonatal pneumonia. Patient was worked up for congenital causes of bronchiectasis. Fiberoptic bronchoscopy revealed normal bronchial tree with suppurations and no obstruction, low fractional exhaled nitric oxide (FeNO) level (using chemiluminescence analyzer), and low sperm count with predominant non-motile population. The semen sample was sent for transmission electron microscopy (TEM) analysis, which revealed various ultrastructural defects such as missing central microtubules, microtubular disorganization and missing inner and outer dynein arms. These structural abnormalities in the spermatozoa flagella were associated with PCD.

Keywords: primary ciliary dyskinesia, bronchiectasis, FeNO, TEM, sperm immotility

INTRODUCTION

Bronchiectasis is the irreversible dilatation of the bronchial airway, developed from inflammation secondary to infection. Reid classified the types of bronchiectasis as cylindrical, cystic and varicose. It can be localized or diffuse in presentation and can be congenital or acquired. The more common of the two is the acquired type, which occurs after repeated bouts of airway infections, including post-tuberculous (TB) infection. Among the congenital causes, the most commonly reported are cystic fibrosis and primary ciliary dyskinesia (PCD).

Bronchiectasis is best assessed with the help of high-resolution computed tomography (HRCT), and its location in the bronchial tree can lead to the identification of its etiology. Bronchiectasis in the upper lobes is associated with post-TB infection and cystic fibrosis, while middle lobe and lower lobe predominance are associated with PCD.

PCD is a rare autosomal recessive genetic disorder of the motile cilia found in the all-ciliated epithelial lining and the spermatozoa flagellum with a 9+2 microtubular structure arrangement in the axoneme.[1] However, there are rare reports of an autosomal-dominant and X-linked transmission.[2] PCD is the general diagnostic nomenclature for all congenital ciliary disorders, including Kartagener syndrome (bronchiectasis, situs inversus, sinusitis), which occur in 70% of

patients with PCD.[3] PCD in general occurs in 1 of every 10,000 to 40,000 live births and is often misdiagnosed due to misinterpretation of signs and symptoms, such as the absence of laterality defects, and also because its diagnosis requires highly specialized diagnostics tools, such as high-speed video microscopy analysis for the evaluation of ciliary beat pattern and frequency and transmission electron microscopy (TEM) for the identification of ultrastructural defects on cross-sectional view of the ciliary structure.

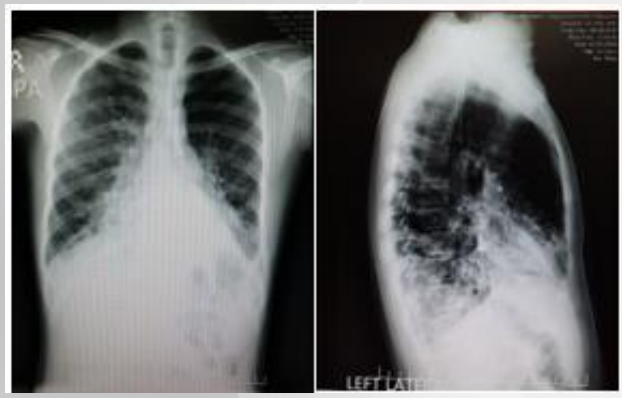
CASE REPORT

A 16-year-old male student from the province of Pampanga came to our institution due to recurrent hemoptysis.

Three years prior to admission, he had experienced massive hemoptysis with severe anemia and had been admitted at a local hospital. He required transfusion of three units of packed red blood cells and was worked up for pulmonary TB (PTB). Acid-fast bacilli (AFB) smears were both negative, but patient was treated as PTB clinically diagnosed and was started with category I TB treatment under direct observational treatment strategy (DOTS), which he completed in six months. There was no recurrence of hemoptysis until 14 months prior, with four episodes at one cup per episode. Patient was then referred to a tertiary hospital for further work-up and management. Upon transfer, a chest radiograph was done (Figure 1). Patient underwent fiberoptic bronchoscopy, and bleeding was identified at the superior segment of the left lower lobe. A Fogarty blockade was done. Bronchial aspirate during the procedure was also sent for cultures and came back negative for all, including TB. Cell block cytology found degenerated squames in a mixed inflammatory background.

A chest computed tomography (Figure 2) was done for work-up. It showed diffuse left lower lobe (LLL) volume loss, bronchiectatic changes/cavity formations within the atelectatic LLL, a compensatory hyperaeration of both upper

Figure 1. Chest radiograph, posteroanterior and left lateral views showing heterogenous opacities in both lungs with obscuration of the left hemidiaphragm and both sulci, suggesting pneumonia on top of TB with possible pleural effusion more on the left.

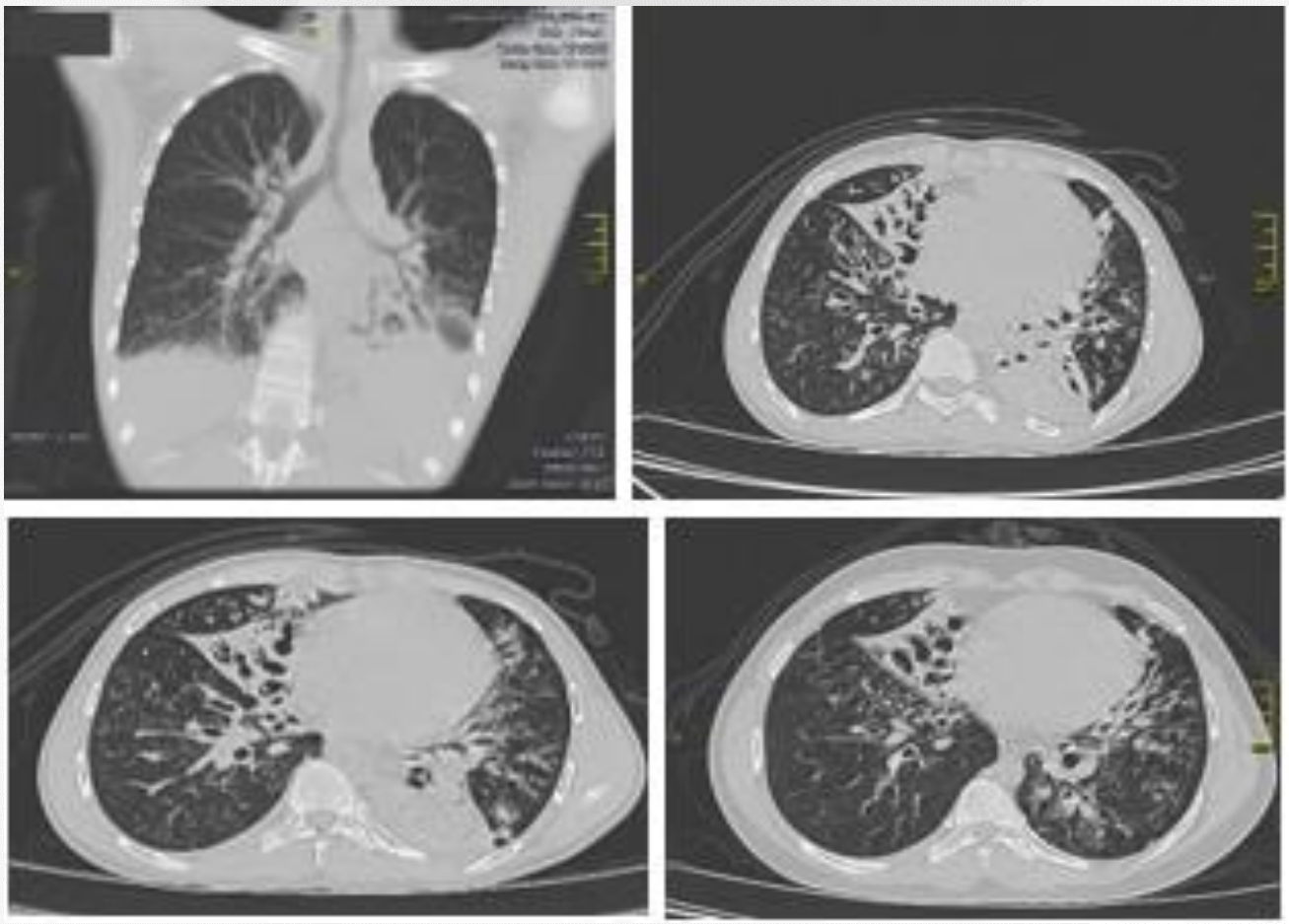


and right lower lung, and an atelectatic right middle lobe (RML) with tubulocystic bronchiectasis. Diffuse centrilobular nodules with tree-in-bud pattern were demonstrated in both lungs, predominantly in the right lower lobe. Patient was referred to pediatric service for co-management. Patient was then worked up for PTB relapse. TB Gene Xpert showed negative results, but patient was treated as PTB relapse and started on Category II anti-TB treatment under DOTS, which he completed in eight months as outpatient. Prior to discharge, patient had no recurrence of hemoptysis, and the Fogarty catheter was removed. Plans for possible left lower lobectomy was discussed with the relatives after two to three months of anti-TB treatment. Patient was asked to follow up.

Six months prior to admission, patient followed up as outpatient. A repeat scan was done, which showed significant clearing of the LLL opacities, but with chronic contraction of the LLL and RML. Severe tubulocystic bronchiectasis are unchanged (Figure 3).

Patient was referred to pulmonary service for further work-up. Impression at this time was post-infectious bronchiectasis vs congenital causes of bronchiectasis, and patient was admitted. Upon

Figure 2. Chest computed tomography 3 years prior to admission showing right-middle and left-lower-lobe bronchiectasis



further investigation of history, the patient was found to have had neonatal pneumonia that required his admission to the neonatal unit and a month-long stay in the hospital. He also had perennial rhinosinusitis without any identified triggers, productive cough with yellowish and whitish sputum but no hearing loss noted. Diabetes mellitus type II was identified from the maternal grandmother (family history came only from the maternal side due to the patient's estrangement from his father). Patient never smoked nor drank alcoholic beverages. There were no pertinent environmental exposures.

Upon admission, patient was ambulatory, well nourished and had a BMI of 23.43 kg/m^2. His vital signs where within normal range, and he had peripheral capillary oxygen saturation (SpO2) of 98% on room air. No clubbing or cyanosis was noted. Pertinent chest findings were crackles and end-inspiratory wheeze on the right middle lung field. The rest of the physical examination results were unremarkable.

A pulmonary function test was done to determine ventilatory impairment. It showed very severe obstructive ventilatory defect with severe air trapping and no significant bronchodilator response, as well as moderate reduction in diffusing capacity of the lungs for carbon monoxide (DLCO). A lung perfusion scan was also done to determine the extent of the disease

and to rule out vascular abnormalities and anomalous blood supply, such as pulmonary sequestration, as possible causes of the bronchiectasis; it showed that the differential contribution to total perfusion in the left and right lung were 23.9% and 76.1%, respectively, but there were no signs of any pulmonary sequestrations.

The patient underwent fiber optic bronchoscopy to evaluate for presence of obstructive lesions, congenital deformities such as tracheal dilatation, and any signs of granulomatous lesions, like in sarcoidosis, as possible causes of the bronchiectasis. On images at the level of the carina up to the bilateral lower lobes, there were purulent secretions but no tracheal dilations, nor any granulomatous lesions or obstructive lesions identified, except for a nodular lesion on the RB8, which revealed chronic inflammation and submucosal gland hyperplasia on histopathology (Figure 4). Bronchial washing and bronchial lavage were done, and specimens were sent for analysis, which showed predominance of neutrophils (73%) but no growth

Figure 3. Comparative chest CT scan 14 months prior (left) and 6 months prior (right) to admission

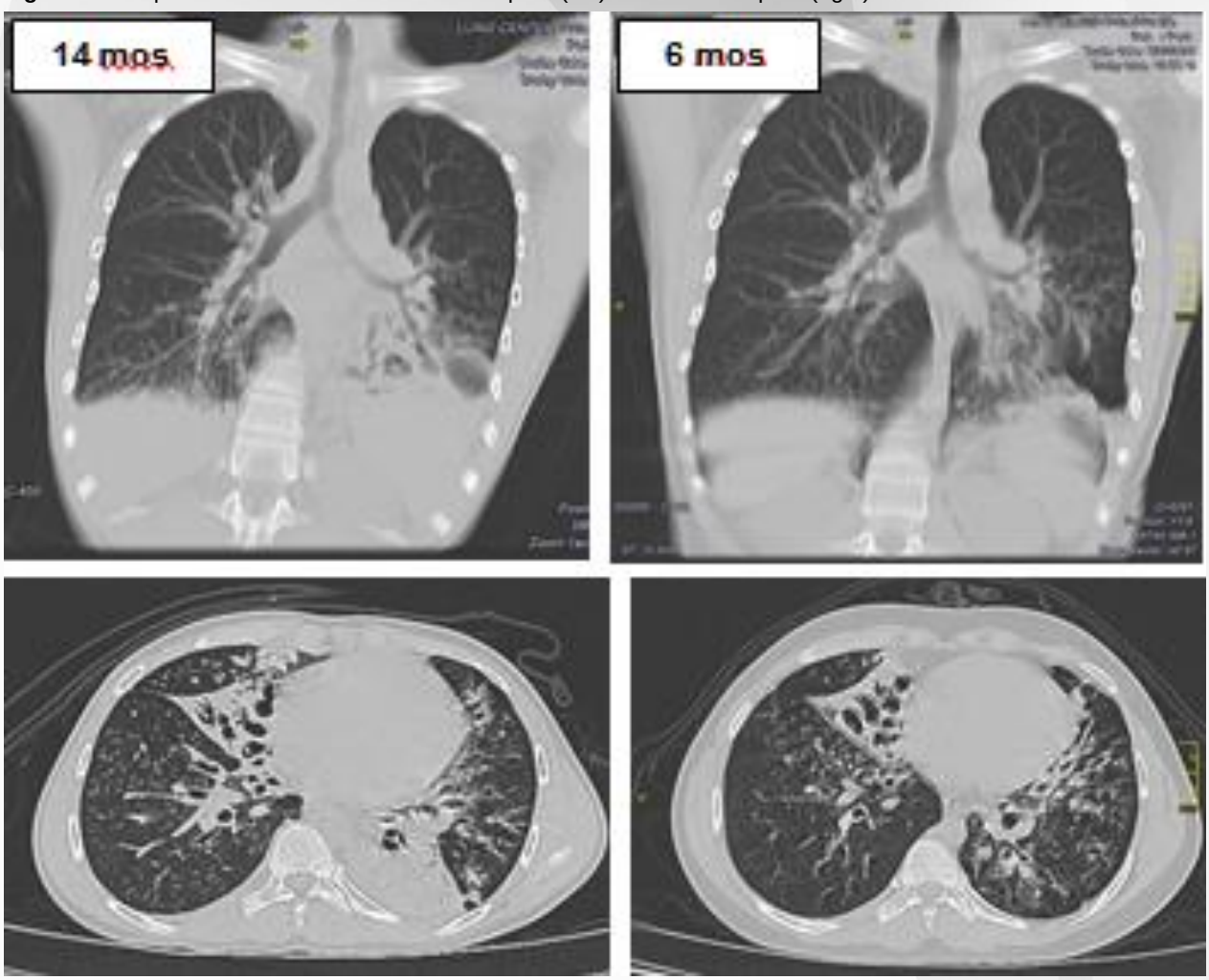
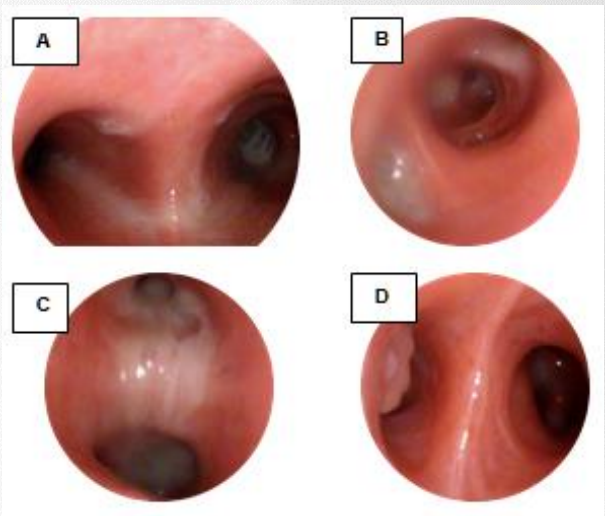


Figure 4. Fiberoptic bronchoscopy images: (A) level of the carina showing purulent secretions; (B) view from the bronchus intermedius; (C) view from LC2; and (D) nodular lesion on the orifice of RB8



on either culture study and also negative for acid-fast bacilli (AFB). Summarizing all pertinent findings and diagnostic tests results, we were highly considering at this point the diagnosis of PCD. Hence, additional tests were done.

Two-dimensional echocardiography was done to evaluate for presence of cardiac defect, and an ultrasound of the abdomen was done to identify any laterality defects; both tests revealed normal results. Then we proceeded with other diagnostics to confirm diagnosis of PCD. In lieu of the nasal nitric oxide test, we did a FeNO test using a chemiluminescence analyzer. It gave a low result of 4 parts per billion. The semen specimen was then sent for TEM analysis due to the high percentage of immotile population. This revealed 8+2 pattern with missing inner and dynein arms and missing central microtubular pairs (Figure 5), all of which are associated with PCD.

Patient and relatives were informed of the diagnosis and were advised to do regular follow-up with periodic chest imaging, lung function monitoring and sputum surveillance via culture. Airway clearance therapy for bronchiectasis and monitoring for extrapulmonary manifestations were emphasized. Further genetic testing and genogram on the relatives were also discussed.

DISCUSSION

PCD, a rare autosomal recessive genetic disorder of the motile cilia, encompasses all congenital ciliary disorders. A limited number of patients are identified with PCD because there are no specific manifestations pertaining to it, so studies regarding its epidemiology are few and usually involve both children and adult populations.

The cilia

The cilia, the main structure of concern in PCD, are hairlike attachments (approximately 200 per cell) found along epithelial surfaces such as the respiratory tract.[1] There are two types of cilia in a normal individual: motile and non-motile. Motile cilia with a wavelike pattern and a 9+2 microtubule structural arrangement are found in the ependymal lining of the brain ventricles, epithelial lining of the upper and lower respiratory tract, eustachian tube in the middle ear and oviducts, and have the same structural arrangement as the spermatozoa flagella. Motile cilia with the rotational motion and 9+0 arrangement are seen in the primary monocilia that established the left-right asymmetry during embryogenesis, where the placement of the apex of the heart, stomach and spleen are at the left side while the liver is predominantly at the right side. Non-motile cilia are mostly sensory in nature and are found in the eyes, ears, nose, bile duct and kidney tubules.[4]

The structure of the cilium is composed of the axoneme, or the body attached to the base, found on the epithelial lining. This axoneme is composed of different microtubular structures that

are important for producing the ciliary beat or movement. These microtubular structures are in a 9+2 arrangement best seen on cross-sectional view, composed of nine microtubular doublets arranged in the periphery of the axoneme and two central microtubular pairs. Attached to one of the microtubular pairs on the periphery are the dynein arms (outer and inner). These arms generate the ciliary beat at a frequency of 6 to 12 Hz by allowing the microtubules to slide against one another using adenosine triphosphate (ATP). While the cilia move, the axoneme structure is maintained by the radial spokes that connect the microtubular doublets on the periphery to the central microtubular pair, as well as the nexin links that connect each microtubular doublet to one another, seen in the diagram below. These structures provide the force and movement of the cilia. They move in a wavelike pattern that propels the surrounding fluid against the beating cilia or move the entire cell, like in the spermatozoa. The cilia move the cerebrospinal fluid within the brain ventricles, facilitate mucociliary clearance of the upper and lower respiratory tract, provide the undulating movement of the spermatozoa flagella and transport the ovum through the oviduct.

PCD genetics

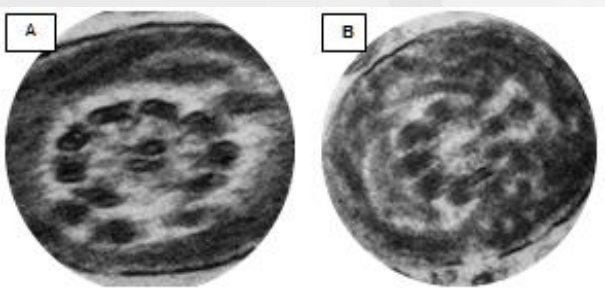
In PCD, there are more than 30 genetic mutations currently identified.[5] These mutations lead to the disrupted encoding of the proteins, for the assembly of the structural components of the axoneme of the cilium. Hence in PCD, all cilia may be affected. These genetic mutations occur in closed communities inherited from the carrier parent via autosomal recessive transmission. But reports of autosomal-dominant transmission and X-linked transmission occur on rare occasions. These genetic mutations are heterogenous; that shows variable phenotypical features. Therefore, there are no specific manifestations pathognomonic of PCD, but these genetic mutations that lead to the ultrastructural defects seen on the TEM of any ciliated structures cause immotility or inefficient function of the cilia.

Pathophysiology

Patients commonly present with otosinopulmonary diseases. The most common manifestations are chronic productive cough; otitis media; development of bronchiectasis due to poor mucociliary clearance causing repeated infections; microbial colonization followed by continuous inflammation and eventual destruction of the bronchial structures,[6] which leads to progressive airway obrstrction[7]; history of neonatal pneumonia due to poor clearance of amniotic fluid from the lungs upon birth; perennial sinusitis; and situs abnormalities in 50% of the patients, due to the poor leftward rotational movement of the primary monocilia during embryogenesis. Situs abnormalities like dextrocardia occur in Kartagener syndrome, which is 70% of all PCD-diagnosed patients. Other ciliary structures are also affected in PCD; therefore, PCD can present as hydrocephalus, due to stagnant flow of CSF, and infertility, due to poor motility of the spermatozoa flagellum and high incidence of ectopic pregnancies. Congenital cardiac defect is noted in 5% of cases; hence, the use of 2D echocardiogram.

Diagnosis of PCD is a tedious process, so

Figure 5. TEM results of the spermatozoa flagella: (A) 8+2 pattern with both inner dynein arms missing and (B) missing central microtubular pairs



good clinical history is important to identify clinical manifestations from the patient highly suspicious of PCD, like our patient, a young person who presented with massive hemoptysis at 14 years of age, with bronchiectasis on the right middle and lower lobes. In the Philippines, hemoptysis is one the common manifestations of PTB, so our patient was treated as PTB clinically diagnosed twice (negative AFB smear, TB Gene Xpert). But despite adequate treatment under DOTS, there was a note of progression of the bronchiectasis. The consideration of bronchiectasis as the main problem in this particular case led to the series of work-ups to rule out other etiologies of bronchiectasis aside from the post-TB infection most likely associated with our patient.

Differential diagnoses for PCD

Post-infectious bronchiectasis—TB, in particular—was ruled out because despite the reading of upper-lobe PTB findings on chest CT scan, the bronchiectasis was noted on the middle lobe and lower lobes[8] least likely to be affected by TB infection. Therefore, congenital causes of bronchiectasis were considered, due to the age of our patient. The most common identified cause of bronchiectasis in children is cystic fibrosis. This was an unlikely diagnosis for our patient because cystic fibrosis is associated more with the Caucasian population and is rare in the Asian race. Also, the affected lobes of bronchiectasis were in the upper lobes, in contrast to what was seen in our patient. Other causes, such as pulmonary sequestration, were ruled out through the results of the lung perfusion scan. Idiopathic or inflammatory causes such as sarcoidosis were ruled out due to the absence of granulomatous lesions from bronchoscopy. Autoimmune causes such as systemic lupus erythematous (SLE) were ruled out due to the patient's gender, age, and absence of systemic manifestations such as cutaneous lesions, photosensitivity and arthritis.

Inhalational causes were ruled out because our patient had no significant exposures to biomass fumes, inert gases and metals. This left PCD as the probable cause of the bronchiectasis, especially considering the history of neonatal pneumonia, perennial rhinosinusitis, and low sperm count with predominance of immotile population.

Diagnosis of PCD

In 2016, the European Respiratory Society (ERS) published a guideline on the diagnosis of PCD.[9] The main goal was to provide evidence-based recommendations on diagnostic tools for PCD. It focused on clinical presentation, use of nasal nitric oxide, evaluation of ciliary beat pattern and frequency using high-speed video microscopy analysis, identification of ultrastructural defects under TEM, genetic testing and use of immunofluorescence.

Patients with more than one of the following manifestations should undergo further testing for PCD: persistent wet cough, situs anomalies, congenital cardiac arrest, persistent rhinitis, chronic middle-ear disease with or without hearing loss, and history of term infants with neonatal upper and lower respiratory symptoms or neonatal intensive care admittance

Our patient had normal situs but had productive cough, a history of neonatal pneumonia and admission to the neonatal unit, and perennial rhinosinusitis.

The ERS, also recommended the use of the PCD Rule (PICADAR) diagnostic tool. The PICADAR was developed by Behan at al to help general practitioners identify which among their patients presenting with chronic productive cough have PCD.[10] This tool has seven significant predictors that lead to a maximum score of 14. Patients with scores ≥10 have >90% probability of having a PCD-positive diagnosis, while a score ≥5 suggests an 11.1% probability. We applied this to our patient and came up with a score of 7.

We compared this to the probability predictive curve from the derivation group in the study and found a 44.1% probability of a PCD-positive diagnosis. The PICADAR was developed from the data of a large heterogenous group, so it has only a weak recommendation. These findings prompted us to proceed with nitric oxide determination.

Nasal nitric oxide (nNO) has been proven to be a good screening tool for PCD. The ERS also recommended it to be part of the diagnostic work-up of patients for PCD. NO is produced from the interaction of the substrate L-arginine with inducible NO isoenzyme within the epithelial cells. It is an important signaling molecule present in the respiratory tract and other systems. It causes bronchodilation and vasodilatation in the respiratory tract in particular. Noone et al compared nNO levels of patients with confirmed PCD from those of the parents of PCD patients, normal controls and patients with cystic fibrosis. They found that patients with PCD had significantly lower levels of nNO than the normal controls and the patients with cystic fibrosis. They also noted that the nNO of the parents of the PCD patients who carried the genetic mutation also had significantly lower levels of nNO compared to the normal controls.[11] The reasons behind low nNO levels in PCD patients was explored by Walker et al, who proposed four hypotheses: (1) there is an increased breakdown of NO within the epithelial cells, trapped in the mucus layer or being used up by the denitrifying bacteria present in the mucus layer; (2) there is reduced biosynthesis of NO and its metabolites due to decreased expression of inducible nitric oxide synthase (iNOS) or low substrate levels of L-arginine; (3) there is a normal biosynthesis of NO trapped within the paranasal sinuses; and (4) there is hypoplasia and agenesis of the paranasal sinuses, so there is reduced production and storage capacity for NO.[12] However, in lieu of nNO, we used FeNO determination in our patient because it was the one available. Exhaled nitric oxide level determination has been standardized by the American Thoracic Society (ATS) for clinical use. The ATS uses ranges of FeNO in children (normal >20 and <35 ppb) and adults (normal >25 and <50 ppb) populations. A low FeNO implies a non-eosinophilic or no airway inflammation, including PCD, cystic fibrosis, and rhinosinusitis, while a high FeNO implies an uncontrolled or deteriorating eosinophilic airway inflammation seen in atopic asthma and eosinophilic bronchitis.[6] Our patient had a FeNO of 4 ppb, which supported PCD as our diagnosis.

The ERS recommended the use of high-speed video microscopy analysis (HSVA) to evaluate ciliary pattern and frequency, but this tool is only available in highly specialized centers. It can show the wavelike pattern seen in normal cilia and in the case of PCD.[13] It can show different patterns such as dyskinetic, asynchronous movement, immotile or circular movement. But there are patients with PCD who still present with normal ciliary beating and frequency but are nonetheless proven to have genetic mutation and ultrastructural defects on electron microscopy. Therefore, a normal HSVA cannot totally exclude PCD diagnosis. This specific test was not available in our institution, so we proceeded with another diagnostic tool.

TEM can clearly show the ultrastructural abnormalities within the axoneme of the cilium. It was previously considered the gold standard for PCD diagnosis. However, normal TEM findings among patients with clinical presentations suspicious for PCD cannot rule out PCD, because 30% of patient with identified genetic mutations can present with normal TEM. The most commonly identified ultrastructural defect is the absence of defect of the outer dynein arm, seen in 50% to 55% of cases, while the combined defect of both dynein

arms occurs in 10% to 15%.[1] Other ultrastructural defects associated with PCD are missing central microtubule pair, like the one presented in our patient; the absence or defect of the inner dynein arm; or a combination of defects of any components of the axoneme, such as inner dynein arm absence and microtubular disorganization or defect, which can present as different pattern arrangements, such as 8+2 (also seen in our patient) or 9+0. We were able to send out the semen specimen of our patient to another tertiary hospital for the sperm flagella TEM analysis, which revealed an 8+2 pattern with both dynein arms missing and missing central microtubule pairs on other flagella.

The ERS has not made any recommendation yet for the role of genetic testing and immunofluorescence in the diagnosis of PCD, because of the limited number of literature to answer the inclusion-criteria questions. However, these tests can be done to identify which particular genetic mutation is involved.[8] Also to be able to provide genetic counselling to relatives, to be able to identify whom among them have the same disorder, to be able to initiate monitoring strategies regarding pulmonary and extrapulmonary diseases.

A diagnostic algorithm (Appendix) adapted from Lobo et al[1] enabled us to diagnose our patient as PCD.

Management and monitoring

Once a diagnosis of PCD is made, the goals of each physician must focus on the identification and management of extrapulmonary manifestations that are not associated with other causes of bronchiectasis, otitis media, rhinosinusitis, cardiac defect and infertility. The recommended are standard therapy that must be given for acute episodes of otitis media and rhinosinusoidal diseases: scheduled audiology assessment to identify hearing loss among the patients and surgical interventions such as polypectomy for sinus drainage to prevent recurrent sinusitis. Infertility is one of the major concerns in patients with PCD. It must be part of the work-up among these patients, and assisted fertilization techniques may be given.

The most common pathology in PCD is bronchiectasis. However, at present, there are no randomized controlled trials regarding the management of PCD patients. It is empirically based on the management of bronchiectasis and involves airway clearance therapy, antibiotic use, oral anti-inflammatory agents, and surgical intervention if warranted. Airway clearance therapy is composed of different pulmonary rehabilitation exercises, which are highly recommended to improve quality of life and lung capacity, and mechanical cough assist, such as insufflator/exsufflator cough assist or lung flute. Antibiotics target the most common pathogens identified with bronchiectasis. In children, these are *Haemophilus influenza*, *Staphylococcus aureus* and *Streptococcus pneumoniae*, while in adults there is the predominance of *Pseudomonas aeruginosa*, other Gram-negative bacteria and non-TB mycobacteria. Use of inhaled antibiotics such as gentamicin has been proven to prevent exacerbation and improve lung function. Oral anti-inflammatories such as macrolide have proven benefits, but the patient must be worked up first for the presence of non-TB mycobacteria to prevent the development of resistance. Surgical interventions are not generally recommended, but if there is presence of localized severe bronchiectasis, lobectomy may be offered.[2]

Important also in the management of these patients is the regular follow-up or monitoring of the patients' status, especially with regard to their lung function and the extent of lung disease. It is recommended for severe cases that a spirometry test be done at least twice a year, sputum surveillance at least every 3 months and periodic

imaging using HRCT to monitor the extent of the lung disease.[2]

In summary, we have reported the case of a 16-year-old male initially presenting with bronchiectasis with predominance on the right middle and bilateral lower lobes and chronic productive cough. By the location of bronchiectasis and the smear and culture negative for TB, we were able to rule out post-TB infection bronchiectasis and lead our diagnostic work-up to the congenital causes of bronchiectasis, given the age of the patient. Other congenital causes of bronchiectasis were ruled out, the most common of which within the age group of our patient was cystic fibrosis, due to cystic fibrosis' low incidence among Asians and the location of bronchiectasis. The history of neonatal pneumonia and perennial rhinosinusitis led our diagnostic work-ups to the diagnosis of PCD. Despite no laterality defects identified, the very low FeNO level and various ultrastructural defects identified on the TEM of spermatozoa flagella confirmed the diagnosis of PCD.

It is important for physicians to consider PCD in patients presenting with unusual location of bronchiectasis, like in our case, to identify the clinical manifestations associated with PCD and to be aware of the different diagnostic tools available to support the diagnosis of PCD. It is also important to be able to identify and manage pulmonary and extrapulmonary diseases among these patients—these diseases include otitis media, rhinosinusitis, infertility and other ciliopathies that are not associated with other causes of bronchiectasis. Further studies on the genetics and management of patients with PCD are still in process.

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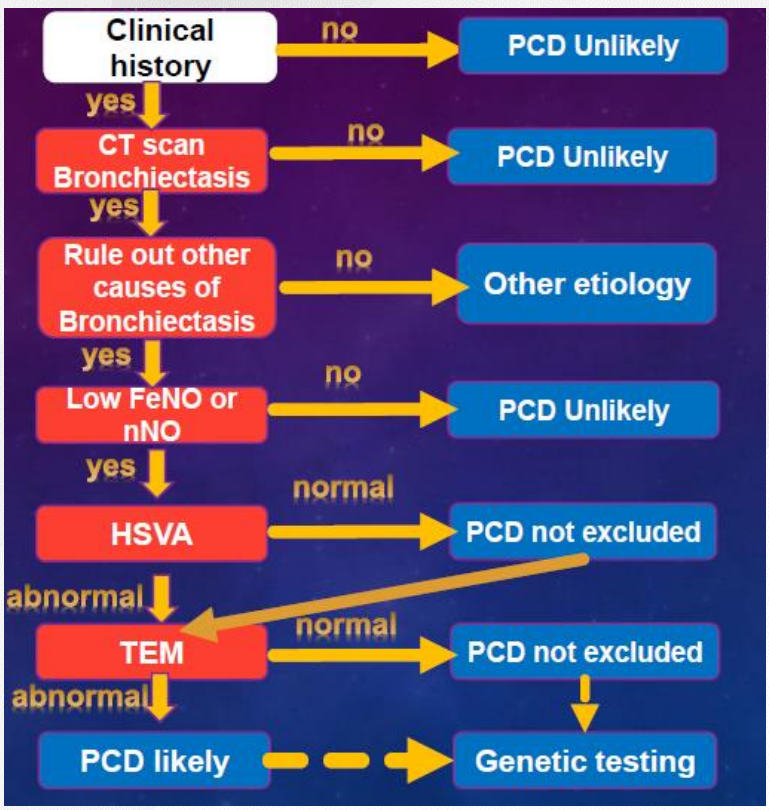
Appendix

Diagnostic algorithm for Primary Ciliary Dyskinesia



Adapted from Lobo LJ, Zariwala MA, Noone PG. Primary ciliary dyskinesia. QJM. 2014;107(9):691-699.

CASE REPORT

Good Syndrome: A Case Report

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ABSTRACT

Good syndrome, a rare cause of combined B-cell and T-cell immunodeficiency, occurs in 7% to 13% of patients with adult-onset hypogammaglobulinemia and in 6% to 11% of patients with thymoma. We report the case of a 50-year-old Filipino female who presented with chronic productive cough and had an extensive history of recurrent pneumonia and an incidental finding of oral candidiasis.

THE CASE

SD, a 50-year-old female, single, Filipino, from Caloocan City, came in with the chief complaint of cough. Seven months prior to admission, she had experienced productive cough with occasional whitish phlegm but no associated fever, weight loss or dyspnea. She was admitted at a provincial hospital, managed as a case of community-acquired pneumonia, given unrecalled intravenous antibiotics for a week and then was discharged improved with oral antibiotics. However, the recurrence of productive cough prompted the patient to medically consult again with two other private physicians, who gave her unrecalled antibiotics.

Three months prior to admission, due to productive cough, the patient went to Taiwan for general medical consult and work-up. Chest radiography showed infiltrates within the right lung. Chest CT scan suggested multiple intrathoracic masses. The esophagoduodenoscopy report indicated the presence of esophagitis and oral candidiasis. The patient was given fluconazole 100 mg/tab once a day for 14 days.

A week prior to admission, despite taking herbal supplements and antitussives, the patient experienced persistent and increasingly severe productive cough. This prompted her to seek consult at our institution and was, hence, admitted. Review of systems only revealed a decrease in patient's appetite. Past medical history revealed that a medical consult in 1985 had diagnosed her with an anterior chest mass on chest radiograph. The said mass was surgically removed. Histopathologic report revealed thymoma. There was no follow-up thereafter. In 1992, a medical consult due to persistent cough revealed via chest X-ray a recurrence of the anterior chest mass. Repeat surgical removal of the mass was done, and histopathologic report showed thymoma. Oncologic evaluation was advised, but the patient was lost to follow-up.

Between May 2012 and September 2014, the patient medically consulted several times due to on-and-off cough, treated with various unrecalled antibiotics. A succeeding chest CT scan revealed heterogeneously enhancing, well-defined mediastinal and pleural lesions in the right lower lung, with chest wall nodules and minimal pleural effusion in the right and fibrosis in the right upper lobe. No axillary lymph nodes were enlarged. There was an incidental finding of hepatic cysts. The patient was referred to an oncologist, and she underwent four cycles of neo-adjuvant chemotherapy. Surgical debulking was subsequently done because there was no change in the size of the mass. Histopathologic results showed thymoma, WHO type AB, with three unremarkable lymph nodes but no capsular inva-

sion. Follow-up plain chest CT scan revealed the disappearance of the anterior-right infrahilar-enhancing soft tissue density. The tumor did not recur. Pleural-based nodules in the right lung did not change. There was no evidence of enlarged lymph nodes or pleural or pericardial effusion.

The patient had received no previous blood transfusions, no anti-Koch's treatment, and had no known comorbidities. She claimed to be allergic to nystatin. Family history was unremarkable. She worked as an accountant and was a non-smoker, single, with no history of sexual contact. Recent travel history was in Taiwan in November 2015 for medical consultation.

Course on admission

Patient came in ambulatory, conscious, coherent, oriented to time and place and person and not in cardiorespiratory distress. Blood pressure was 110/80 mm Hg; cardiac rate, 81 bpm; respiratory rate, 20 cpm; temperature, 36.5° C; weight, 37.3 kg; oxygen saturation, 97% at room air. Significant physical examination noted whitish oral plaques in the posterior area of the tongue. Patient had no palpable cervical lymphadenopathies. She had symmetrical chest expansion and no retractions. The surgical incision scar over the right subchondral area and right anterior axillary line and anterior thorax was noted, with a palpable 4-by-4-cm firm and movable non-tender mass at the right mid-axillary line. There were crackles on the right lower lung field. Neurologic exam results were unremarkable.

Upon admission, the patient's chest radiography showed an elevated right hemidiaphragm with ill-defined infiltrates in the right lung, defined as pneumonia but Koch's infection in the right upper lobe could not be ruled out. A deformity was noted in her right seventh posterior rib with the presence of a sternotomy, surgical staple wires and a port catheter. Complete blood count suggested mild anemia (hemoglobin 100 g/L), thrombocytopenia (platelet 102,000/µL), and the presence of bands (15%) (white blood cells of $6.1x10^9$ cells/mm^3; segmenters of $61x10^9$ cells/mm^3; lymphocytes of 20 $x10^9$ cells/mm^3; monocytes of $4x10^9$ cells/mm^3). Empiric treatment for community-acquired pneumonia was started with piperacillin-tazobactam 4.5-g IV every 8 hours and azithromycin 500-mg tablet once a day. Chest CT scan showed interstitial pneumonia in the superior segment of the left lower lobe and a cavitary nodule in the superior segment of the right lower lobe; emphysematous lungs; fibrosis in the right apex and in both lower lobes; bronchiectatic changes in the right lower lobe; no enlarged mediastinal lymph nodes and no pleural effusion. Sputum culture growth was *Candida* spp; *Mycobacterium tuberculosis* (MTB) culture was negative.

Esophagogastroduodenoscopy showed whitish plaques on the tongue, in the oral cavity and in the esophagus, consistent with oral candidiasis. Fluconazole was started at 100-mg tablet twice a day. Enzyme-linked immunosorbent assay (ELISA) for HIV was non-reactive.

The primary immunodeficiency panel showed low results: lymphocytes, 430 (13.7%); monocytes, 289 (9.2%); granulocytes, 2,421 (77.1%); total leukocytes, 3,140 (100%).

Confirmatory flow cytometry with T-cell markers revealed low counts of both B and T lymphocytes: CD3 pan T-lymphocytes, 389; CD4 T helper cells, 114; CD8 T suppressor, 290; CD4:CD8 T helper/T suppressor, 0.39; CD16+56 natural killer (NK) cells, 34; CD20 pan B-cells (B1), 5; CD19 B-cells:pre-B cells, 10; serum IgG, 64.9; serum IgA, 27.4; serum IgM, 15.2; total serum IgE <5.00; complement C3, 138. Direct and indirect Coombs tests came back negative.

IVIG therapy was initiated thereafter. This improved the patient's clinical symptoms, and she was subsequently discharged. Follow-up chest CT scan plain, done one week after discharge, showed interval regression of the interstitial infiltrates in the superior segment of the left lower lobe, with interval decrease in the size of the previously noted cavitary lesion in the superior segment of the right lower lobe.

One month after discharge, there was complete

resolution of the patient's cough, and repeat plain chest CT scan further showed interval clearing of the interstitial densities in the superior segment of the left lower lobe. Patient was maintained on IVIG therapy.

DISCUSSION

The triad of thymoma, hypogamma-globulinemia and a concomitant immuno-deficiency state (clinically apparent as recurrent pulmonary infection)is classically defined as Good syndrome. This disorder was first characterized in 1955 by Robert Alan Good, a pioneer in the field of immunodeficiency diseases, who recognized the crucial role played by the thymus in the development of the immune system.[1]

Good syndrome is a rare cause of combined B-cell and T-cell immunodeficiency. It occurs in 7% to 13% of patients with adult-onset hypogammaglobulinemia and in 6% to 11% of patients with thymoma.[2] Good syndrome usually manifests in the fourth or fifth decade of life, without preference for either sex. The immunodeficiency may precede or follow the diagnosis of thymoma. Although the cause and pathogenesis of this disorder are unknown, its main characteristics are hypogammaglobulinemia, a low B-cell count or the absence of B cells, CD4+ T-cell lymphopenia and reduced serum levels of IgG, IgA and IgM.[3] Because their cell-mediated immunity is compromised, individuals with Good syndrome are susceptible to bacterial and opportunistic infection, which are part of the disease's clinical characteristics. Systemic fungal infection is not a common feature of Good syndrome. However, mucocutaneous candidiasis has been diagnosed in 24% of cases.[3]

The diagnosis of Good syndrome should be considered in patients presenting with recurrent airway infections and an anterior mediastinal mass.[4] Immunological workup, including T-cell subsets, B cells and quantitative immunoglobulins, should be considered part of the routine diagnostic evaluation in patients with a thymoma and recurrent infections.[5]

Treatment of Good syndrome involves resection of the thymoma, IVIG replacement to maintain adequate immunoglobulin values, and antibiotic treatment if necessary.[6] Therapy with IVIG can reduce the risk of infection, excessive antibiotic administration, hospitalization and the development of pulmonary damage. In contrast to other paraneoplastic disorders associated with thymoma (ie, pure red cell aplasia or myasthenia gravis), Good syndrome is not influenced by thymectomy. It is also important to note that Good syndrome may progress even after thymectomy and corticosteroid treatment.

Mortality among Good syndrome patients is usually due to infection, autoimmune disease, or hematological complications. So far, Good syndrome has only been studied retrospectively in case reports and small retrospective case series. Therefore, the course of the disease is not well understood. A recent study showed a Kaplan-Meier survival analysis indicating 5-year survival for approximately 82% and 10-year survival for 68%, with a median survival of 14 years.[7] Thus, early recognition and treatment with antibiotics or immunoglobulin replacement can change the natural course of this rare condition and have been proven effective in keeping patients symptom-free.

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RETROSPECTIVE STUDY

Yield Pattern of Three-sputum Smears in the Case Detection of Pulmonary Tuberculosis in a Tertiary Hospital

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ABSTRACT

Background: Sputum smear microscopy remains the cornerstone of pulmonary tuberculosis (PTB) case detection. However, its utility is limited by poor sensitivity. In 2007, the World Health Organization (WHO) reduced the minimum number of sputum smear specimens needed to be examined for PTB diagnosis, from three to two, owing to the low incremental yield in the third sputum smear specimen. However, differing yield patterns of sputum smears across studies in different countries have been noted, with significant diagnostic yield in the third sputum smear and higher positivity rates when utilizing three-sputum smear specimens in high-prevalence areas. The utility of a third sputum smear cannot be underestimated in a high-burden-of-disease setting and an increasing-risk population such as found in the Philippines.

Methodology: This was a hospital-based retrospective, cross-sectional chart review study conducted from 2012 to 2014. It included 893 presumptive PTB patients aged ≥18 years, with no prior history of PTB, who were subjected to three-sputum smear microscopy examinations. The pattern of positive smears, the incremental yield of each sputum smear, and the positivity rate of two-smear combinations were analyzed.

Results: Of the 893 three-sputum-smear combinations analyzed, 20.8% had at least a single positive smear. The first smear was positive in 17.6%; 20.4% in the second smear and 20.0% in the third smear. Majority of cases were detected in the first smear; 3.1% more patients were diagnosed with the second smear and the incremental yield from the third smear was minimal (0.2%). However, of those that had only two positive smears, two-sputum positivity was highest in those with positive second and third smear (2.8%).

Conclusion: A three-sputum smear specimen in the case detection of PTB has a non-negligible diagnostic yield. Furthermore, a significantly higher rate of two-smear positivity is observed for PTB suspects from whom three specimens were collected, compared to those with fewer.

INTRODUCTION

The prevalence of pulmonary tuberculosis (PTB) in the Philippines is 500 cases per 100,000 members of the population.[1] It is generally estimated that up to 20 contacts may be infected by each acid-fast bacilli (AFB)–positive case before the index case is diagnosed.[2] The current data still equate to a high burden of disease in our setting. Early diagnosis and timely treatment are principles of PTB control, leading to reduction in illness, death and spread of PTB.[3]

Sputum smear microscopy remains the cornerstone of case detection in high-burden, resource-poor settings, owing to its relatively low complexity, low cost and high specificity.[3] Poor sensitivity, however, remains a significant problem. Consequently, the optimization of smear microscopy techniques to improve sensiti-

vity and the development of new diagnostic tools are still areas of active investigation.[3] The examination of three-sputum specimens for PTB diagnosis became routine following studies that showed three specimens collected over two days identified the highest number of patients while requiring the least number of visits.[3] Over time, there have been arguments as to the number of sputum specimens that needed to be collected, assessing the specimens' benefit and adequacy for diagnosis and aiming to reduce expenses in the diagnosis of PTB.

In 2007, the World Health Organization (WHO) revised the minimum number of sputum smear specimens that needed to be examined for PTB diagnosis, reducing it from three to two in settings where a well-functioning external quality assurance (EQA) scheme exists. This revision was due to a low incremental yield—between 2% and 5%—in the third sputum smear specimen, based on the meta-analysis by Mase et al, done on 37 eligible studies.[3] However, the authors' conclusions had limitations to their generalizability. Furthermore, studies in different countries have noted differing yield patterns of sputum smears. There are findings (notably in high-burden-of-disease areas) of significant diagnostic yield in the third sputum smear and an increasing smear positivity rate in the succeeding sputum smear specimens.[4-7] In addition, as stipulated in the seventh edition of the Canadian Tuberculosis Standards, at least three-sputum smears should still be collected because the yield of the third sputum specimen may be significant, as high as 5% to 10%.[8] Therefore, the utility of a third sputum smear cannot be underestimated in a high-burden-of-disease setting and in increasing-risk populations (e.g., multi-drug–resistant tuberculosis– and human immunodeficiency virus–infected individuals) such as those found in the Philippines.

This study aimed to determine the yield pattern of three-sputum smear specimens in the case detection of PTB in a tertiary hospital from 2012 to 201, including the three-sputum smear positivity and incremental-yield patterns in our locale, and to correlate these with the current Department of Health (DOH) recommendation. This will assist clinicians in improving the case detection process.

METHODOLOGY

This was a retrospective, cross-sectional chart review study conducted at a tertiary hospital that included patients with presumptive PTB enrolled at the private-public mix directly observed treatment short course (DOTS) of the hospital, aged 18 years or above, with no prior history of PTB and who underwent three-sputum smear microscopy examinations. Only patients from 2012 to 2014 were included. Those who did not meet all criteria were excluded.

We retrieved the individual sputum smear microscopy results of all included patients, and encoded in MS Excel 2013 spreadsheets. The positive yield rates of three specimens for each patient were computed and plotted using the time-series graph. Change rates and cumulative true positive were estimated. To test whether the rates were significant, z-test of difference in proportions was used. IBM SPSS version 21 was used as statistical software.

RESULTS

Out of 1,048 patients, 893 patients met the inclusion criteria while 155 were excluded (77 submitted only two-sputum smear specimens and 78 had a previous history of PTB). Of the 893 three-sputum-smear combinations analyzed, 187 (20.8%) had at least a single positive smear (Table 1). The first smear was positive in 17.6%; 20.4% in the second smear and 20.0% in the third smear. Of those that had only two positive smears, two-sputum positivity was highest in those with positive second and third smear. Finally, the two-sputum combination that gave the highest overall positivity rate was the combination of positive second and third smears.

Table 1. Pattern of Sputum Smear Positivity in Three-sputum Smear Specimens

Pattern of Smear Positivity	Positive (N=893)	%	p-value
Any smear positive	187	20.8	<0.001
First	157	17.6	0.048
Second	182	20.4	<0.001
Third	179	20.0	<0.001
All 3 smears positive	149	16.7	<0.001
Only 2 smears positive	32	3.6	<0.001
Positive-positive-negative	4	0.4	<0.001
Positive-negative-positive	3	0.3	<0.001
Negative-positive-positive	25	2.8	<0.001
Patients diagnosed using a two-sputum smear-positive combination			
Positive smear 1 and 2 (positive-positive-any)	153	17.1%	
Positive smear 1 and 3 (positive-any-positive)	152	17.0%	
Positive smear 2 and 3 (any-positive-positive)	174	19.5%	

Table 2. Incremental Yield of Positive Smears from Three-sputum Collections

Incremental Yield Pattern	Smear Positive (N=893)	Incremental yield (%)
Positive identified on first smear (positive first smear)	157	17.6%
Positive identified on second smear (negative first smear, positive second smear)	28	3.1%
Positive identified on third smear (positive third smear only)	2	0.2%

Table 2 shows the incremental yield of positive smears from three-sputum collections (i.e., the additional number of smear-positive patients diagnosed with the additional smear). While majority of cases were detected in the first smear (18%), 3% more patients were diagnosed with the second smear and the incremental yield from the third smear was minimal (0.22%).

DISCUSSION

The DOH, in its 2014 update on the manual of procedures (MOP) for case detection and handling of PTB, advocated the use of two sputum smear specimens instead of the routine three. This was adapted from the WHO recommendation, which was largely based on a systematic review of 37 studies (18 prospective, 19 retrospective), which demonstrated that an average of 85.8% of cases are detected with the first specimen, an incremental yield of 11.9% with the second specimen and an insignificant incremental yield of 3.1% with the third specimen.[3,9] However, the same meta-analysis highlighted limitations such as the heterogeneity in study design, population and methodology, which potentially introduce significant variability

in findings and thus affect their generalizability.[3]

The meta-analysis recognized the issue on accuracy of results, stemming from the absence of blinding in most studies and the absence of assessment of positive sputum smear specificity.[3] The recommendation was that before national TB programs consider changing the examination procedure to only two sputum smear specimens, a functional EQA program and an internationally standardized approach should be established, both to strengthen the country-specific evidence base and to allow comparisons to be made among studies.[3] Publication bias may have caused important and relevant data to be missed, because older studies and some non-English publications were excluded from the review.[3] In addition, the Centre for Reviews and Dissemination (CRD), upon reviewing the meta-analysis, noted that there were no data provided on the differences in results across studies, so it was not certain whether average values reflected the findings of all studies. The quality of the included studies also appeared poor, which weakened the evidence base.[10] With the study appearing to have limited evidence from generally poor-quality and heterogeneous studies, a more cautious conclusion should be considered.[10]

Differing yield patterns of sputum smears have been observed across studies in different countries, and there are findings (notably in high-burden-of-disease areas) of a significant diagnostic yield increase with the third sputum smear. Descriptive studies by Saleem et al and Van Deun et al noted incremental yields from 7.9% to 9.8% in the third sputum smear.[7,11] Similar studies conducted in Nairobi and Zambia showed contributions of 8% and 7.9%, respectively, from the third sputum smear.[12,13] A re-analysis of data from a study involving 42 laboratories in four high-burden countries showed the incremental yield of the third smear reaching 7.4%.[14] A retrospective study by Kisa et al noted that the detection of *Mycobacterium tuberculosis* was directly proportional to the number of specimens collected and that obtaining at least three specimens increased smear positivity and consequent sensitivity.[5] Furthermore, studies have documented a higher yield involving the third sputum smear with two-smear positive combinations in a three-sputum collection. Hamid et al noted a 6.8% yield from the first and third samples and an 8.2% yield from the second and third samples, compared to only 1.4% from the first and second samples among two smear positive cases.[15] Similarly, Saleem et al identified around 1.9% yield from the first and third samples and a 2.2% yield from the second and third samples, compared to 1.8% detection from the first and second samples among two smear positive cases.[7]

The study shows that the first two sputum smear examinations of a three-sputum smear specimen can detect majority of cases, with the third smear adding only a minimal incremental yield. This is consistent with the meta-analysis findings of Mase et al and other studies.[3,15] However, it is noted that the smear positivity rate increases in the succeeding sputum smear specimens, and this study found a comparable positivity rate of the second (20.4%) and third (20%) smears. This data is consistent with the findings of Kisa et al and the existing national guidelines for tuberculosis control, which recommend a three-sputum smear specimen for the evaluation of PTB suspects.[5,7] In addition, a review of sputum smears noted a significant difference of 7% smear positivity for PTB suspects from whom three specimens were collected, compared to those with fewer collected specimens.[7] This implies the non-negligible utility of the third sputum smear specimen.

Using two smear positive combinations, we noted a significantly higher rate of smear positivity (2.8%) with the second and third specimens compared to other two smear positive combinations. This is consistent with the findings of Saleem et al and Hamid et al, wherein smear positivity was higher with the second and third specimens (2.2% and 8.2%) than the first and second (1.8% and 1.4%) and the first and third

(1.9% and 3.8%) combinations.[7,15] In a similar analysis by Hamid et al, the yield was higher with the first and third smears (6.8%), compared to the first and second (4.4%) and the second and third smears (2.4%)[15]; nevertheless, these findings support the bearing of the third sputum smear specimen. These data suggest that the third smear contributes to a higher positivity rate.

Although recent findings show high rates of detection with the first and second sputum smears, the general limitation is the overall variable sensitivity of sputum smear microscopy in PTB case finding. Variations in results could be related to the probability that the detection of AFB is directly related to the concentration of bacilli in the sputum.[7] In this study, smear positivity was notably varied among some of the sputum specimens submitted by the same PTB suspect. In two cases where only the third sputum smear was positive, the bacilli load was surprisingly high (3+). Furthermore, the studies used as basis for related literature (especially those done in high-burden areas) had an established expanded EQA program that ensured smear quality, thereby eliminating erroneous results.[7,15] Conversely, the Philippines has yet to establish a fully functional expanded EQA program nationwide. In our locality with a high burden of disease and emerging multi-drug–resistant tuberculosis, it would be wise to reconsider the minimal yet additive diagnostic information of the third sputum smear rather than miss an opportunity to treat a possible infectious PTB case.

CONCLUSION AND RECOMMENDATIONS

A three-sputum smear specimen in the case detection of PTB shows a non-negligible diagnostic yield in the succeeding specimens. Furthermore, a significantly higher rate of two-smear positivity is observed for PTB suspects from whom three specimens were collected, compared to those with fewer. In a setting where the establishment of an expanded EQA program nationwide is still an ongoing process, the utility of a third sputum smear cannot be underestimated in a high-burden-of-disease setting and an increasing-risk population (e.g., multi-drug–resistant TB patients and people living with human immunodeficiency virus) such as in the Philippines.

This study was conducted in a local hospital with a limited number of samples. A wider scale of sputum specimens for evaluation is recommended to increase the sample size. Although inter-reader variability was addressed by employing DOTS-accredited medical technologists, the analysis of specimens by an EQA program will ensure acceptability and reproducibility of results. In addition, the retrospective methodology of the study precluded the availability of a number of patient data and specimen results. A prospective study will address these inadequacies.

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RETROSPECTIVE STUDY

Validity Study of Gene Xpert MTB/RIF Assay in the Diagnosis of Tuberculous Pleural Effusion among Adult Patients at the Lung Center of the Philippines

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ABSTRACT

Introduction: Tuberculous pleural effusion (TPE) can be difficult to diagnose. Existing tests to confirm the disease are limited in accuracy and time to diagnosis, and also require costly invasive procedures. The objective of this study is to determine the accuracy of Gene Xpert MTB/RIF assays in the diagnosis of TPE among adult patients at the Lung Center of the Philippines (LCP).

Methodology: This was a cross-sectional analytical study done among 60 patients with unilateral pleural effusion seen at LCP from October 2014 to September 2016. Thoracentesis, closed tube thoracostomy or video-assisted thoracoscopic surgery (VATS) with pleural biopsy was done. The specimens were sent for histology and *Mycobacterium tuberculosis* (MTB) culture, and Gene Xpert results were collected for data analysis.

Results: Of 60 participants, 26 (43.3%) had definite TPE. The diagnostic accuracy of this test was compared to MTB culture, histology and composite reference standard. Gene Xpert in relation to MTB culture showed sensitivity and specificity of 100% and 94.34%, respectively. In relation to histopathology, its sensitivity was 14.29% and its specificity was 82.05%. In relation to the composite reference standard, sensitivity was 30.77% and specificity was 94.12%.

Conclusion: The Gene Xpert MTB/RIF assay has poor sensitivity; therefore, it is not a good routine diagnostic tool for the diagnosis of TPE even in high-burden settings such as our country. On the other hand, with its high specificity, it can forestall further invasive procedures in some patients with TPE.

Keywords: *tuberculous pleural effusion, Gene Xpert MTB/RIF assay*

INTRODUCTION

Tuberculosis (TB) is predominantly a respiratory disease, affecting the lungs in about 80% of cases. About 30% of TB cases involve an extrapulmonary site, occurring with or without concomitant lung involvement. TB can affect virtually any organ, although peripheral lymph nodes and pleural space are the most common extrapulmonary sites.[1] In many areas of the world, TB remains the most common cause of pleural effusions in the absence of demonstrable pulmonary disease.[2]

Tuberculous pleural effusion (TPE) is thought to result from the rupture of a subpleural caseous focus in the lung, into the pleural space;[2] its diagnosis can be difficult because of the low positivity of the various diagnostic tests, since TPE usually contains a low number of *Mycobacterium* bacilli, and the diagnostic sensitivity of pleural fluid cultures is relatively

low, at 30% to 50%. Conventional diagnostic tests for TPE include microscopic examination of the pleural fluid for acid-fast bacilli (AFB); mycobacterial culture of pleural fluid, sputum or pleural tissue; and histopathological examination of pleural tissue. These tests have recognized limitations for clinical use when used alone, but in combination, they have been recognized as the best reference standard for evaluation of the accuracy of novel tests.

As mentioned, existing diagnostic modalities to confirm the diagnosis of this specific extrapulmonary tuberculosis (EPTB) are limited in accuracy and time to diagnosis, and they often require invasive procedures that are too costly for most of the patients in our setting.

Gene Xpert MTB/RIF assays have high accuracy and do not only have a high sensitivity and specificity in smear-positive pulmonary tuberculosis (PTB) (98% and 98%, respectively) but are also considered a reasonable diagnostic tool in smear-negative PTB (sensitivity and specificity at 67% and 99%, respectively).[3] This test has been proven to improve the diagnosis of PTB with accuracy and results that are released in less than two hours. However, the varying levels of accuracy of this test in the diagnosis of EPTB—specifically, TPE—has been reported from small pilot studies abroad. However, a South African study by Friedrich et al demonstrated a sensitivity of 25% and specificity of 100% on 20 samples of confirmed pleural TB patients.[4] Currently, no studies on this topic had been done in the Philippines. Therefore, involving subjects from our local setting was needed, to improve our local practice as pulmonologists in diagnosing TPE.

This paper aims to determine the accuracy of Gene Xpert MTB/RIF assays in the diagnosis of TPE among adult patients at the Lung Center of the Philippines (LCP).

METHODOLOGY

This cross-sectional analytic study included male or female patients ≥18 years old; with chest radiography finding consistent with unilateral pleural effusion; who underwent thoracentesis with pleural biopsy, closed tube thoracostomy with pleural biopsy or VATS with pleural biopsy; and who were seen at LCP from October 2014 to September 2016. Excluded were patients who were diagnosed with malignancy, had recurrent pleural effusion, were previously treated with anti-TB regimen or had parenchymal lesions consistent with PTB.

Either thoracentesis with pleural biopsy, closed tube thoracostomy with pleural biopsy or VATS biopsy was done. The biopsy specimens were sent for histology, part of the pleural fluid was sent for MTB culture and sensitivity, and 10 mL of pleural fluid was collected and submitted for Gene Xpert testing. Results were collected for data analysis.

Patient participation was voluntary. The process and methods were explained to each patient by the investigators. Written informed consent was taken from all the patients. Aspects of the research were fully explained, and the participants were given enough time to ask questions. Questions from the participants were answered until the participants were fully satisfied. Confidentiality was assured. No monetary compensation was given. The participants were given copies of the informed consent with contact numbers of the principal investigator.

The demographic characteristics, presenting signs and symptoms, and procedures done on patients who were diagnosed with TPE and those who were not, based on the composite reference standard, were compared using chi-square test for dichotomous variables, while Student's t-test and the Wilcoxon rank sum test were used for continuous normally distributed and non-normally distributed variables, respectively.

Sensitivity, specificity, positive predictive value, negative predictive value and likelihood ratios for Gene Xpert were calculated using MTB culture, histology and the composite reference standard.[4]

RESULTS

Of the 60 participants, 26 (43.3%) had definite TPE based on the positive composite reference standard which includes sputum AFB, MTB culture and histopathology. Mean age was 37.2 years. Majority were males (84.6%). The most common clinical manifestation was cough (80.8%), followed by dyspnea (61.5%), fever (46.2%), chest/back pain (42.3%), weight loss (30.8%), sputum production (26.9%), hemoptysis and others (e.g., loss of appetite, dizziness) (11.5%) and tiredness (3.8%). These manifestations were mostly presented at more than two weeks' duration.

There was a significant difference on the mean age of patients (p=0.030) and the duration of presenting signs and symptoms (p=0.011) between the two groups. It was noted that those who were positive for TPE were younger (37. 2 years) than those who were negative (47.8 years), and the duration of presenting signs and symptoms was mostly longer than two weeks in the former (96.2%) as compared to the latter (70.6%). Eleven (42.3%) patients who were positive for TPE underwent VATS with pleural biopsy, while 8 (30.6%) underwent thoracentesis with pleural biopsy (PB) and 7 (26.9%) had closed tube thoracostomy (CTT) with PB.

To determine the accuracy of Gene Xpert MTB/RIF assay for diagnosing TPE, the results of this test was compared to MTB culture, histology and composite reference standard.

Gene Xpert was performed on 60 patients and TPE was detected on 10: seven were true positives and three were false positives. The rest were true negatives (Table 2).

Table 1. Included Patients with or without TPE based on the Composite Reference Standard

Demographic Characteristic	Positive (%) n=26	Negative (%) n=34	p-value
Age, years (mean)	37.2±15.48	47.8±21.50	0.03*
Sex			0.942
Male	22 (84.6)	29 (85.3)	
Female	4 (15.4)	5 (14.7)	
Signs and symptoms			
Cough	21 (80.8)	23 (67.6)	0.255
Sputum production	7 (26.9)	16 (47.1)	0.112
Hemoptysis	3 (11.5)	1 (2.9)	0.186
Fever	12 (46.2)	8 (23.5)	0.065
Weight loss	8 (30.8)	8 (23.5)	0.530
Tiredness	1 (3.8)	6 (17.6)	0.099
Chest/back pain	11 (42.3)	11 (32.4)	0.428
Dyspnea	16 (61.5)	20 (58.8)	0.832
Others	3 (11.5)	3 (8.8)	0.365
Duration			0.011*
<2 weeks	1 (3.8)	10 (29.4)	
>2 weeks	25 (96.2)	24 (70.6)	
Procedure			
Thoracentesis/PB	8 (30.6)	21 (61.8)	0.017*
CTT/PB	7 (26.9)	10 (29.4)	0.834
VATS/PB	11 (42.3)	3 (8.8)	0.002*

TPE, tuberculous pleural effusion; CTT, closed tube thoracostomy; PB, pleural biopsy; VATS, video-assisted thoracoscopic surgery.
*Significant.

To determine the accuracy of Gene Xpert MTB/RIF assay for diagnosing TPE, the results of this test was compared to MTB culture, histology and composite reference standard.

Gene Xpert was performed on 60 patients and TPE was detected on 10 subjects: seven were true positives and three were false positives. The rest were true negatives, with no false negatives (Table 2).

The sensitivity (95% CI) and specificity were 100% and 94.34%, respectively. The positive predictive value was 70%, and the negative predictive value was 100% (Table 3).

Gene Xpert detected TPE on 10 of 60 patients: three were true positives and seven were false positives. Eighteen were false negatives and 32 were true negatives (Table 4).

Sensitivity and specificity were 14.29% and 82.05%, respectively. The positive predictive value was 30%, and the negative predictive value was 64% (Table 5).

Compared to the composite reference standard, which includes sputum AFB smear, MTB culture and histopathology, Gene Xpert detected TPE on 10 of 60 patients: eight were true positives and two were false positives. Eighteen

Table 2. Performance Outcome for Gene Xpert MTB/RIF Assay in Relation to MTB Culture

	MTB Culture (+)	MTB Culture (–)
Gene Xpert (+)	7	3
Gene Xpert (–)	0	50

MTB, *Mycobacterium tuberculosis*; RIF, rifampicin.

Table 3. Validity/Accuracy of Gene Xpert in Diagnosing TPE in Relation to MTB Culture

Diagnostic Parameter	Point Estimate	95% CI
Sensitivity	100.00	59.04–100.00
Specificity	94.34	84.34–98.82
Positive predictive value negative	70.00	34.75–93.33
Negative predictive value	100.00	92.89–100.00
Positive likelihood ratio	17.67	5.89–53.03
Negative likelihood ratio	0.00	–

TPE, tuberculous pleural effusion; MTB, *Mycobacterium tuberculosis;* CI, confidence interval.

Table 4. Comparison of Gene Xpert Result with Histopathology

	Histopathology (+)	Histopathology (–)
Gene Xpert (+)	3	7
Gene Xpert (–)	18	32

Table 5. Validity/Accuracy of Gene Xpert in Predicting TPE in Relation to Histopathology

Diagnostic Parameter	Point Estimate	95% CI
Sensitivity	14.29	3.05–36.34
Specificity	82.05	66.47–92.46
Positive predictive value	30.00	6.67–65.25
Negative predictive value	64.00	49.19–77.08
Positive likelihood ratio	0.80	0.23–2.76
Negative likelihood ratio	1.04	0.83–1.31

TPE, tuberculous pleural effusion; CI, confidence interval.

were false negatives and 32 were true negatives (Table 6).

Sensitivity and specificity were 30.77% and 94.12%, respectively. The positive predictive value was 80%, and the negative predictive value was 64% (Table 7).

Table 4. Comparison of Gene Xpert Result with CRS

	CRS (+)	CRS (–)
Gene Xpert (+)	8	2
Gene Xpert (–)	18	32

CRS, composite reference standard, which includes sputum smear, culture and histopathology.

Table 7. Validity/Accuracy of Gene Xpert in Predicting TPE in Relation to CRS

Diagnostic Parameter	Point Estimate	95% CI
Sensitivity	14.29	3.05–36.34
Specificity	82.05	66.47–92.46
Positive predictive value	30.00	6.67–65.25
Negative predictive value	64.00	49.19–77.08
Positive likelihood ratio	0.80	0.23–2.76
Negative likelihood ratio	1.04	0.83–1.31

TPE, tuberculous pleural effusion; CRS, composite reference standard, which includes sputum smear, culture and histopathology; CI, confidence interval.

DISCUSSION

The Gene Xpert MTB/RIF assay has proven to be a promising breakthrough in the diagnosis of PTB and was even included in the recently updated clinical practice guidelines for the diagnosis, treatment, prevention and control of TB as one of the modalities for bacteriologically confirming PTB among patients who were sputum-smear negative. However, limited data have been published about the performance of Gene Xpert on pleural fluid in high burden settings such as the Philippines.

In a systematic review, Sehgal et al investigated the role of Xpert MTB/RIF in the diagnosis of TPE and found the pooled sensitivities and specificities of Xpert MTB/RIF to be 51.4% and 98.6%, respectively, with culture used as a reference standard.[3] By contrast our study found higher sensitivity but relatively the same specificity, i.e., 100% and 94.34% respectively. These findings are contradictory to a South Africa study that stated the reason for the high sensitivity found in previous studies was due to the low burden of disease in the settings where the studies were done, as well as the fact that these only reported a handful of patients with TPE.[5] We attribute these findings to the standard technique used and the better experience of handlers in processing the specimen for Gene Xpert study at our center.

Furthermore, as shown in Table 2, the diagnostic accuracy of Gene Xpert is comparable to MTB culture. Thus, Gene Xpert is a better option than culture, considering its ability to detect MTB in pleural effusion and provide information about rifampicin susceptibility within 2 hours.

In response to the recommendation of one meta-analysis done in India to use histopathology as a reference standard[3]: the sensitivity and specificity of Xpert MTB/RIF in this study were 14.29% and 82.05%, respectively—lower than the previously mentioned results. Nevertheless, Xpert MTB/RIF assay demonstrated low sensitivity but high specificity as a diagnostic tool.

The pooled sensitivities and specificities of Xpert MTB/RIF were 22.7% and 99.8%, respectively, with composite reference standard (CRS) used as the benchmark in a meta-analysis

by Sehgal et al.[3] In comparison, this study showed a sensitivity of 30.77% and a specificity of 94.12%. Gene Xpert MTB/RIF assay consistently showed low sensitivity but excellent specificity in the diagnosis of TPE.

In clinical practice, the ideal initial test used in the diagnosis of TPE is the pleural fluid adenosine deaminase level. However, due to the limited accessibility of this test, clinicians still rely on the clinical signs and symptoms; conventional diagnostic tests such as microscopic examination of the pleural fluid for AFB; mycobacterial culture of pleural fluid, sputum or pleural tissue; and histopathological examination of pleural tissue. Although the Gene Xpert MTB/RIF assay is currently being utilized in many TB-endemic countries,[6] this study has demonstrated that its sensitivity is largely suboptimal for extra-pulmonary specimen.[7,8] Therefore, it is not practical to use Gene Xpert as an initial diagnostic tool for TPE, considering its cost. Affordability, availability and cost-effectiveness remain important considerations in resource-poor TB-endemic countries. However, due to its high specificity, this test can be utilized for further investigation in patients with undiagnosed pleural effusion.

One limitation of this study was that is was conducted only among Service patients of LCP. The investigators recommend the continuation of this study on a bigger sample size, to further strengthen the data. It is also recommended that future studies evaluate the potential impact of response to treatment of TPE patients who were given an anti-TB regimen.

CONCLUSION

The Gene Xpert MTB/RIF assay has poor sensitivity, so it is not a good routine diagnostic tool for the diagnosis of TPE, even in high-burden settings such as our country. On the other hand, with its high specificity, it can forestall further invasive procedures in some patients with TPE.

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RETROSPECTIVE STUDY

Diagnostic Accuracy of Berlin, Flemons Sleep Apnea Clinical Score and St. Luke's Medical Center–Obstructive Sleep Apnea Clinical Score Questionnaires for Screening Obstructive Sleep Apnea in Filipino Patients

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ABSTRACT

Introduction: Although considered the gold standard for diagnosing obstructive sleep apnea (OSA), the polysomnogram (PSG) is time consuming, labor intensive and can be costly. Hence, a simple but accurate screening tool to identify patients with high risk for OSA should be established for Filipinos.

Methods: Records of all adult Filipino patients referred to the Comprehensive Sleep Disorders Center of St. Luke's Medical Center (SLMC)–Quezon City for overnight PSG from January 2011 to June 2015 were reviewed. Subjects were excluded if they were known OSA patients, had incompletely filled questionnaires, or were unable to tolerate a sleep study. OSA was screened using the Berlin sleep score, the Flemons sleep apnea clinical score and the SLMC–obstructive sleep apnea clinical score (OSACS). Results were compared to their overnight PSG results.

Results: SLMC-OSACS showed higher sensitivity (87%) and overall accuracy (84%) in predicting OSA. It showed higher overall accuracy (63%) and sensitivity (77%) in predicting mild OSA (63% and 77%, respectively) and moderate OSA (66% and 80%). In predicting severe OSA, it also had higher overall accuracy (86%) and sensitivity (90%), while specificity showed almost similar estimates in all of the three screening tools.

Conclusion: SLMC-OSACS showed higher sensitivity and higher overall accuracy in predicting OSA at different risk levels. Therefore, SLMC-OSACS is recommended as a screening tool for OSA for Filipinos.

INTRODUCTION

Obstructive sleep apnea (OSA) is a chronic condition characterized by frequent episodes of upper airway collapse during sleep. It consists of decreased airflow due to repetitive complete or partial obstruction of the upper airway, associated with progressive respiratory efforts` to overcome the obstruction.[1,2] These obstructive respiratory events are typically associated with cortical microarousals and oxygen desaturation, leading to sleep fragmentation and increased sympathetic neural activity.[2] Its effect on nocturnal sleep quality and the ensuing daytime fatigue and sleepiness is widely acknowledged.

OSA syndrome is first suspected on clinical grounds based on a typical history. Patients complain of non-restoring sleep, daytime fatigue and sleepiness, sometimes even sleep attacks. Classic signs and symptoms that indicate a patient may be at risk for OSA include obesity, snoring, witnessed apnea during sleep, apparent arousals during sleep, wake-time somnolence and

fatigue despite apparently adequate sleep.[3]

Apnea is defined as the complete cessation of airflow for at least 10 seconds. Hypopnea is defined as a reduction in airflow, followed by an arousal from sleep or a decrease in oxyhemoglobin saturation. Commonly used definitions of hypopnea require a 25% or 50% reduction in oronasal airflow associated with either a reduction in oxyhemoglobin saturation or an arousal from sleep.[1]

The apnea-hypopnea index (AHI) is often used to quantify the severity of OSA. The AHI is a measure of the number of apneas and hypopneas per hour of sleep. By consensus, mild sleep apnea is an AHI of 5 to 15 events per hour, moderate OSA is 15 to 30 events per hour, and severe OSA is >30 events per hour.[4]

The prevalence rates of OSA have been estimated in the range of 2% to 10% worldwide, and the risk factors for OSA include advanced age, male sex, obesity, family history, craniofacial abnormalities, smoking, alcohol consumption, neck circumference, sedative use, health illiteracy and Indian or Chinese ethnicity.[5,6]

There is accumulating evidence that OSA is being considered as an independent risk factor for hypertension, glucose intolerance/diabetes mellitus, cardiovascular diseases and stroke, leading to increased cardiometabolic morbidity and mortality.[6]

OSA is present in 2% of women and 4% of men living in Western communities.[5] It affects an estimated 20% of all Americans.[3] South Asians have a significantly higher prevalence of OSA compared to white Europeans (85% vs. 66%, p=0.017).[7]

The American Thoracic Society and the American Academy of Sleep Medicine recommend supervised polysomnography (PSG) in the sleep laboratory for two nights for the diagnosis of OSA and the initiation of continuous positive airway pressure (CPAP).[8]

Although considered a gold standard in OSA diagnosis, the PSG is not without its limitations. PSG requires an overnight stay in a sleep laboratory staffed with qualified personnel that can collect and interpret complex physiologic data. The process is time consuming, labor intensive, and can be costly.[1]

Early detection of OSA will mean prevention of its various serious consequences. Therefore, a simple but accurate screening tool should be established for Filipinos to stratify patients based on their clinical symptoms, physical examinations, and risk factors, and to identify both patients at high risk and in urgent need of PSG and further treatment, and also patients at low risk and who may not need PSG.

The primary objective of this study is to compare the diagnostic accuracies of OSA screening tools—namely, Berlin, Flemons sleep apnea clinical score (SACS) and the SLMC–obstructive sleep apnea clinical score (OSACS) questionnaires—among Filipino patients.

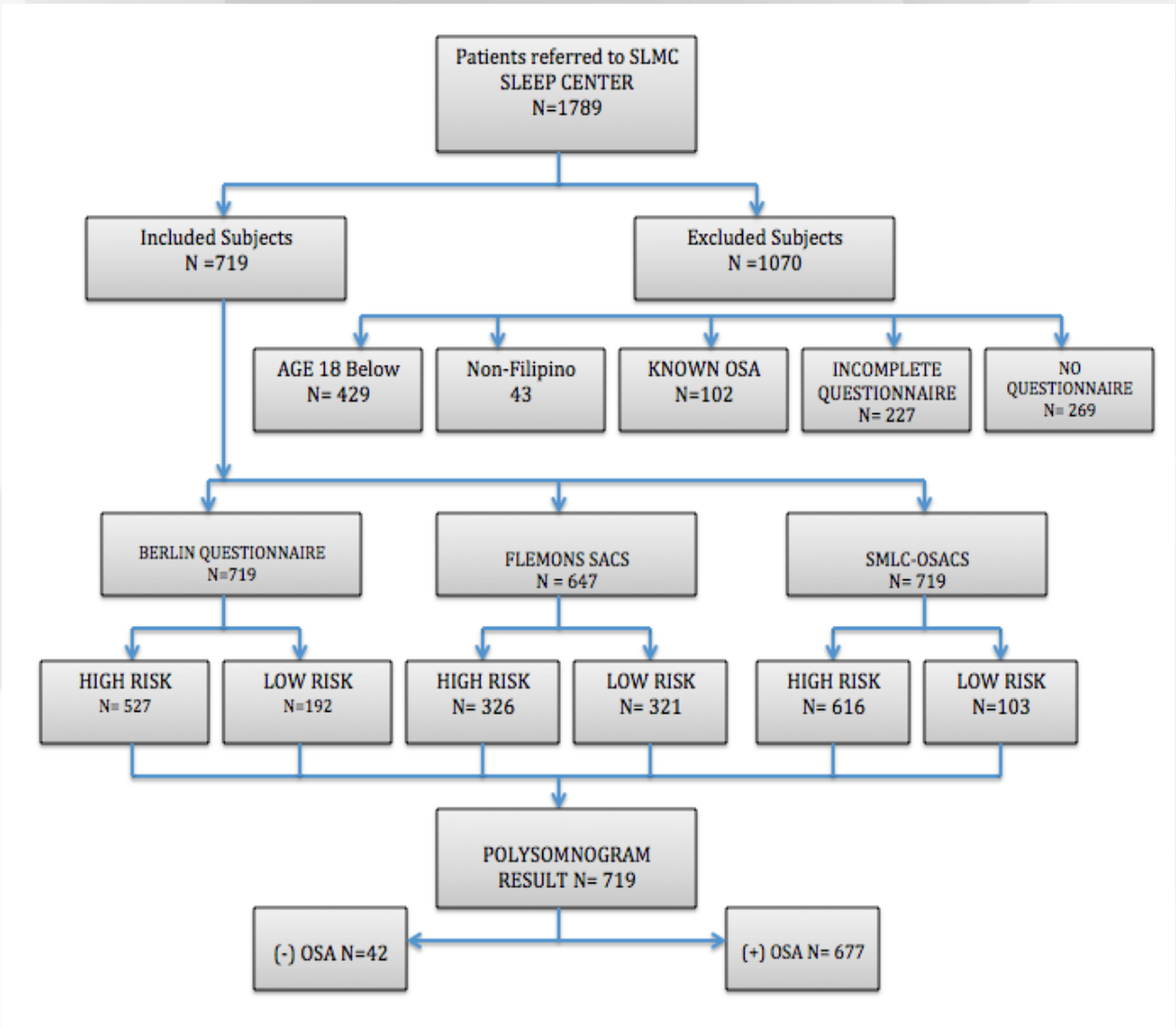
METHODS

This descriptive cross-sectional study compared the predictive probabilities for OSA of different sleep questionnaires, namely, Berlin questionnaire, Flemons SACS and the SLMC-OSACS utilized in the Comprehensive Sleep Disorders Center of SLMC–Quezon City. The study was done from January 2011 to June 2015. Results were compared with the gold standard, PSG.

This study retrieved and reviewed 719 cases. Anthropometric measures including body weight, height, body mass index (BMI) and neck circumference were documented for all patients. The study included adults (≥18 years old) of Filipino nationality. Patients were excluded if they were <18 years old, had known OSA, did not complete their questionnaires, could not tolerate a sleep study or were not Filipinos.

The Berlin questionnaire has 11 questions grouped in three categories. The first category comprises five questions concerning snoring, witnessed apneas and the frequency of such events. The second comprises four questions addressing daytime sleepiness, with a sub-question

Figure 1. Patient Selection Process



FLEMONS SACS, Flemons sleep apnea clinical score; OSA, obstructive sleep apnea; SLMC-OSACS, St. Luke's Medical Center–Obstructive Sleep Apnea Clinical Score.

about drowsy driving. The third comprises two questions concerning history of high blood pressure (>140/90 mmHg) and BMI >30 kg/m^2. Categories 1 and 2 are considered positive if there are two positive responses in each category, while category 3 is considered positive if there is a self-report of high blood pressure or BMI >30 kg/m^2.

Study patients are scored as high risk if scores are positive for two or more of the three categories.[9]

The Flemons SACS predictors of sleep apnea include neck circumference, hypertension, habitual snoring and bed partner reports of nocturnal gasping/choking respirations. Probabi-

lity of sleep apnea is considered high if SACS is ≥15.[9]

The SLMC-OSACS comprises three independent variables: snoring affecting others, BMI and bothersome daytime sleepiness (Appendix). A validation study in 2003 for the best cut-off value for the clinical score found that a cut-off value ≥8 showed 84% sensitivity, 92% specificity, 8% false positive rate and LR of 14. A lower cut-off value of ≥5 revealed 100% sensitivity, 92% specificity, 8% false positive rate and LR of 12.5.[10]

Diagnostic PSG was performed using SomnoStar z4 or the Viasys Nicolet One machine, including pulse oximeter to check for desaturation; electroencephalogram (EEG) leads (eight on the head, two on the eyes, two on the chin); electrocardiogram (ECG) leads (two on the chest, one on each leg); transducer; thermistor on the nose to note for apnea/hypopnea; and respiratory bands on the chest and stomach. During actual PSG, the following data were obtained: respiratory effort by thoraco-abdominal excursion, respiratory inductive plethysmography and oronasal airflow pressure, oxygen saturation and sleep architectural data. The actual sleep study lasted for seven to eight hours.

The minimum computed sample size of 120 was based on the findings of published literatures wherein the Berlin, SACS, and OSA questionnaires yielded accuracies (sensitivity and specificity) of 80% and above, assuming that the tools would yield a clinically acceptable accuracy of 80%, with precisions +/-7.2% estimated at confidence index (CI) 95%. The sample size of 120 was considered sufficient to validate the diagnostic accuracies of the three tools.

Patients' profiles were described using mean values, standard deviations, frequencies, and percentages. These data were encoded in MS Excel 2013. In comparing profiles with mean values as indicators and grouped by OSA status, one-way ANOVA was used; for testing associations among categorical data, we used the chi-squared test of independence with appropriate matrices and the 2x2 Fisher's exact test. The accuracies of the three tools were estimated in terms of sensitivity, specificity, positive likelihood ratio (LR+), negative likelihood ratio (LR–), positive predictive value (PPV), negative predictive value (NPV) and overall accuracy. Any associated p-values less than 0.05 alpha were considered significant. IBM SPSS v.21 and NCSS PASS 2000 were used as statistical software.

RESULTS

A total of 719 patients were included in the study (Figure 1). The overall mean age was 45 years, and 72% were males. Older age was associated with increasing severity of OSA. Among those without OSA, mean age was 39 years; among those with severe OSA, mean age was 46 years ($p<0.001$). Most of the patients with normal results (62%) were females; most of the males were in the affected group ($p<0.001$). Fifty percent of patients with no OSA had ideal BMI. Among those with severe OSA, 38% were obese and 12% were severely obese ($p<0.001$). Those with larger neck circumferences had moderate to severe OSA, compared with those with normal size ($p<0.001$). Patients with high risk of OSA were 73% using the Berlin tool, 45.3% using Flemons SACS, and 86% by SLMC-OSACS (Table 1).

In predicting OSA, SLMC-OSACS score showed higher sensitivity (87%) than Berlin (74%) and Flemons (52%). In terms of specificity, Flemons showed the highest estimate (73%). Flemons also yielded the highest LR+ (1.92), followed by SLMC-OSACS (1.30). All tools yielded high PPV. In terms of overall accuracy, SLMC-OSACS ranked first (84%), followed by Berlin (71%) (Table 2).

SLMC-OSACS had the highest overall accuracy (63%) in predicting mild OSA. It was followed by the Berlin tool (56%). Sensitivity was also highest in SLMC-OSACS (77%), while specificity was equal between Flemons and Berlin. In predicting moderate OSA, SLMC-OSACS had the highest accuracy (66%) and sensitivity (80%), while Flemons and Berlin had similar specificity

Table 7. Radiologic Severity According to Ventilatory Impairment

	With OSA				P-value Normal vs OSA levels	P-value Normal vs All OSA
	Mild (%) n=91	Moderate (%) n=100	Severe (%) n=486	Normal (%) n=42		
Age (years)*	45.81 ± 11.52	44.54 ± 12.98	46.13 ± 11.35	38.81 ± 12.78	<0.001	<0.001
Sex (n, %)						
Females	41 (45.1)	35 (35)	99 (20.4)	26 (61.9)	<0.001	<0.001
Males	50 (54.9)	65 (65)	387 (79.6)	16 (38.1)		
BMI (kg/m^2)*	27.57 ± 5.38	29.28 ± 6.08	31.19 ± 6.59	26.34 ± 5.22		
Ideal (n, %)	35 (38.5)	27 (27)	80 (16.5)	21 (50.0)		
Underweight (n, %)	1 (1.1)	1 (1)	2 (0.4)	1 (2.4)	<0.001	<0.001
Overweight (n, %)	30 (33.0)	41 (41)	164 (33.7)	9 (21.4)		
Morbidly obese (n, %)	21 (23.1)	25 (25)	183 (37.7)	9 (21.4)		
Severely obese (n, %)	4 (4.4)	6 (6)	57 (11.7)	2 (4.8)		
Neck circumference, cm*	38.73 ± 4.13	40.27 ± 3.81	42.04 ± 7.56	38.25 ± 6.13	<0.001	0.008
Berlin score*	1.85 ± 0.88	1.83 ± 0.79	2.03 ± 0.76	1.83 ± 0.85	<0.001	0.295
Low risk	31 (34.1)	31 (31)	117 (24.1)	13 (31.0)	0.026	0.341
High risk	60 (65.9)	69 (69)	369 (75.9)	29 (69.0)		
Flemons SACS*	12.84 ± 9.08	17.29 ± 18.53	24.54 ± 20.63	9.62 ± 8.53	<0.001	<0.001
Low risk	54 (59.3)	57 (57)	183 (37.7)	27 (64.3)	<0.001	0.003
High risk	28 (30.8)	38 (38)	250 (51.4)	10 (23.8)		
SLMC-OSACS*	6.12 ± 2.25	6.26 ± 2.33	7.08 ± 1.97	5.76 ± 2.53	<0.001	0.002
Low risk	21 (23.1)	20 (20)	48 (9.9)	14 (33.3)	<0.001	<0.001
High risk	70 (76.9)	80 (80)	438 (90.1)	28 (66.7)		

BMI, body mass index; OSA, obstructive sleep apnea; OSACS, obstructive sleep apnea clinical score; SACS, sleep apnea clinical score; SLMC, St. Luke's Medical Center.
*Mean ± standard deviation.

indices. In predicting severe OSA, SLMC-OSACS yielded the highest overall accuracy (86%), followed by Berlin (72%). SLMC-OSACS generated the highest sensitivity (90%), followed by Berlin (76%). Specificity was similar in all three tools (Table 3).

DISCUSSION

This study compared three sleep questionnaires—Berlin, Flemons SACS and SLMC-OSACS—for their predictive probabilities for OSA. The questionnaires were tested within the same population, and scores were evaluated against the results of PSG as the gold standard for OSA diagnosis. The cut-off values used in this study were those previously published.[4,9,12]

The Berlin questionnaire is a validated instrument used to identify individuals at risk for OSA in primary and some non-primary care settings.[10] The Berlin has shown 95% sensitivity in predicting moderate-to-severe OSA (95.48%) and severe OSA (97.3%) but has demonstrated a very low specificity for OSA patients (25%), moderate-to-severe OSA patients (7.41%) and severe OSA patients (10.71%).[9]

Flemons SACS is a relatively simple model that can generate a sleep apnea score the sensitivity and specificity of which, at various levels, have been calculated and summarized as LRs. SACS <5 had LR of 0.25 (95% CI: 0.15 to 0.42) and a corresponding post-test probability of 17%, while a score >15 had LR of 5.17 (95% CI: 2.54 to 10.51) and a post-test probability of 81%. These LRs can simply and accurately determine the probability of a patient having sleep apnea.[4]

SLMC-OSACS is a devised prediction rule for the Filipino Asian population that was reported by Cua et al in 2000. The model provided a sensitivity of 71%, a specificity of 77% and a PPV of 83% in predicting a priori probability of having OSA, with a score ≥8 as the best cuff-off. In 2003, a validation study by Cua

Table 2: Diagnostic Accuracies of Berlin, Flemons SACS, and SLMC-OSACS Questionnaires in Predicting OSA in General*

Accuracy	SLMC-OSACS	Flemons SACS	Berlin
Sensitivity, %	87	52	74
Specificity, %	33	73	31
LR+	1.30	1.92	1.07
LR–	0.40	0.66	0.85
PPV, %	96	97	94
NPV, %	13	8	7
Overall accuracy, %	84	53	71

LR, likelihood ratio; NPV, negative predictive value; OSA, obstructive sleep apnea; OSACS, obstructive sleep apnea clinical score; PPV, positive predictive value; SACS, sleep apnea clinical score; SLMC, St. Luke's Medical Center.

*Predicting OSA using low-high risk scores.

Table 3: Diagnostic Accuracies of Berlin, FSACS, and SLMC-OSACS Questionnaires in Predicting the Severity of OSA

Accuracy	Predicting Mild OSA			Predicting Moderate OSA			Predicting Severe OSA		
	SLMC-OSACS	FSACS	Berlin	SLMC-OSACS	FSACS	Berlin	SLMC-OSACS	FSACS	Berlin
Sensitivity, %	77	41	56	80	40	58	90	69	76
Specificity, %	33	55	55	33	73	73	33	31	31
LR+	1.15	0.906	1.242	1.2	1.480	2.136	1.35	0.999	1.100
LR–	0.69	1.077	0.800	0.6	0.822	0.579	0.3	1.002	0.778
PPV, %	71	68	93	74	79	96	94	70	93
NPV,%	40	28	10	41	32	13	23	30	10
Overall accuracy, %	63	45	56	66	49	59	86	58	72

FSACS, Flemons sleep apnea clinical score; LR, likelihood ratio; NPV, negative predictive value; OSA, obstructive sleep apnea; OSACS, obstructive sleep apnea clinical score; PPV, positive predictive value; SLMC, St. Luke's Medical Center.

et al revealed the clinical score ≥8 as the best cut-off value, with an overall accuracy of 89%, sensitivity of 84%, specificity of 92%, false rate of 8%, and LR of 14. This validation study revealed a lower cut-off value ≥5 with sensitivity of 100%, specificity of 92%, false positive rate 8%, and LR of 12.5.[10] A study on the prevalence and association of OSA risk in Filipino patients with diabetes has been conducted using SLMC-OSACS. Twenty-one percent had high OSA risk, with 14% having estimated true OSA prevalence.[11]

In our study, Flemons demonstrated higher specificity (73%), while SLMC-OSACS showed higher sensitivity (87%). In overall performance, Flemons demonstrated higher likelihood that a patient would have OSA, implying that patients who attained the risk cut-off score in Flemons were 1.92 times more likely to have OSA.

In terms of having higher overall accuracy for OSA by demonstrating higher rates of true positive plus true negative among the total population assessed, SLMC-OSACS showed a higher estimate (84%).

As a whole, in predicting mild, moderate and severe OSA, SLMC-OSACS yielded consistently higher sensitivity estimates, followed by Berlin. This trend was also noted in the overall accuracies for both SLMC-OSACS and Berlin tools. Meanwhile, SLMC-OSACS showed consistently lower specificity than the other tools. Lastly, LR+ was higher in mild and severe OSA by SLMC-OSACS, and the trend of higher estimates was followed by Berlin.

OSA is considered to be a long-standing illness, and with its associated complications, it can bring economic burden to society. Referrals to sleep physicians or experts for further investigations and diagnostic evaluations may prevent adverse health outcomes. Hence, screening tools that may be used—especially in areas with limited resources—in order to identify patients who may need further work-up for OSA must be mandated. In addition, screening tools may also be used in formulating health care

diagnostic work-up and treatment.

An ideal diagnostic test for a general population should have a relatively high specificity to minimize false positives, but it should have sufficient sensitivity. Conversely, an ideal diagnostic test for a population with a high pre-test probability of disease should have higher sensitivity while maintaining high specificity.[2]

Given that SLMC-OSACS demonstrated higher sensitivity and overall accuracy in predicting OSA, physicians can identify patients who are at high risk for OSA and who need urgent evaluation and treatment.

In the general population, moderately severe OSA is present in 11.4% of men and 4.7% of women.[12] In a related study, using an AHI cut-off point of ≥5 events, 204 patients (87%) were found to have OSA. Using an AHI cut-off point of ≥15 events, 177 (76%) had moderate-to-severe OSA, while using an AHI cut-off point of ≥30 events showed 148 (63%) to have severe OSA.[9] Evidence suggests that a large proportion of individuals with OSA remain undiagnosed.

The presence and severity of OSA must be determined before initiating treatment. In the published guidelines by the Adult Obstructive Sleep Apnea Task Force of the American Academy of Sleep Medicine, treatment options should be discussed with patients who have AHI ≥5 plus symptoms of OSA, as well as those with AHI ≥15 that is moderate OSA.[13] Since SLMC-OSACS yielded consistently higher sensitivity estimates for mild, moderate and severe OSA and higher LR+ in mild and severe OSA, it can be used to predict patients most likely to be treated. Since PSG is expensive and not readily available, there is a need to improve access to diagnostic and effective treatment strategies for patients with OSA. Of particular interest is the utility of portable monitoring and empiric auto-CPAP treatment for patients who have a high pre-test clinical probability for at least moderate or severe OSA and who do not have co-existing cardiopulmonary conditions complicating OSA.[2] Home unattended PSG is a viable option for evaluating patients with moderate-to-high clinical suspicion for sleep-disordered breathing. Nevertheless, patients with failed or equivocal home studies and those with negative studies but persistent symptoms should undergo standard PSG.[6]

In addition, there are ethnic differences in prevalence and severity of OSA. In one study, despite the overall lower average BMI in the Asian population compared to Western societies, the prevalence of OSA syndrome in Asians was found to be similar that of Caucasian population. This could be attributed to differences in craniofacial features between Asian and Caucasian patients, such as an inferiorly positioned hyoid bone, enlarged soft palate and reduced upper airway width at the soft palate.[1,2] Therefore, any screening tool utilized should first be validated in the population where the tool will be used.

In this study, the target population was patients presenting to the sleep clinic with sleep disorders as evaluated clinically by referring physicians. This might present a potential bias in the evaluation of the strengths of the different questionnaires in identifying patients at risk for OSA, because OSA is highly prevalent in patients with a history of sleep disorders. It is therefore recommended that screening tools be used in general population in a clinical setting, to identify high-risk patients.

CONCLUSION

With the increasing burden of OSA complications, screening tools are important for identifying patients who may need further work-up. Screening tools must be simple and easy to use, and the variables applied must be from similar ethnic populations. SLMC-OSACS showed higher sensitivity, higher overall accuracy for OSA and higher sensitivity for predicting mild, moderate, and severe OSA. Therefore, SLMC-OSACS is the recommended screening tool for OSA among Filipinos.

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Appendix

St. Luke's Medical Center–Obstructive Sleep Apnea Clinical Score (SLMC-OSACS) Questionnaire

Body mass index (BMI)		
Are you bothered by sleepiness during the day?	YES	NO
Does snoring disturb		
A bed partner or a roommate?	YES	NO
Someone in the adjacent room?	YES	NO

SLMC-OSACS for Filipinos

BMI (kg/m^2)	None	Bothersome Daytime Sleepiness	Snoring Affecting Others Only	Both
19	1	4	5	7
21	1	4	5	8
23	2	4	5	8
25	2	4	6	8
27	2	4	6	8
29	2	5	6	8
31	2	5	6	9
33	3	5	6	9
35	3	5	6	9
37	3	5	7	9
39	3	6	7	9
41	3	6	7	9
43	3	6	7	10
45	4	6	7	10
47	4	6	8	10
49	4	6	8	10

Note:

Probability of sleep apnea is low for SLMC-OSACS <5.

Probability of sleep apnea is high for SLMC-OSACS ≥5.

Adapted from Chung F. Open Anesth J. 2011;5(Suppl 1-M2):7-11.

COHORT STUDY

Cohort Study on the Applicability of the Updated 2015 Lung Center of the Philippines Algorithm on Pre-operative Risk Assessment as a Predictor of Post-operative Pulmonary Complications

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ABSTRACT

Introduction: Pre-operative pulmonary evaluation is an essential prerequisite for lung resection because it estimates the impact of surgery on the already-compromised respiratory function. This study aims to assess the applicability of the updated Lung Center of the Philippines (LCP) 2015 algorithm on pre-operative risk assessment for predicting post-operative pulmonary complications (PPCs) among lung resection patients.

Methods: This cohort observational study included 78 patients for lung resection, evaluated by the updated 2015 LCP algorithm. The patients were followed up until discharge to observe for PPC development. PPC incidence was determined in relation to baseline demographic variables, value of predictive factors and the risk assessment.

Results: PPC incidence was 29% of patients. Prolonged air leak and nosocomial pneumonia were the most common PPCs. Mortality rate was 1.3%. Male gender, smoking history, smoking ≥20 years, FEV_1 % predicted and predicted post-operative (ppo) FEV_1 were shown to predict PPC development. The applicability of the updated algorithm in predicting PPC was found to be significant for the non-neoplastic group.

Conclusion: The updated 2015 LCP algorithm on pre-operative risk is applicable not only to neoplastic patients but also for non-neoplastic patients. The factors that predict PPC development include male gender, smoking history, smoking ≥20 years, FEV_1% predicted and ppo FEV_1 value. PPC incidence rate is the same as in other studies, with prolonged air leak and nosocomial pneumonia as the most common PPCs.

Keywords: pre-operative risk assessment, post-operative pulmonary complications

INTRODUCTION

Pre-operative pulmonary evaluation is a prerequisite to every lung resection procedure because it estimates the possible impact of surgery on the already-compromised respiratory function. It encompasses risk assessment, to identify patients at increased risk of pulmonary complications, and risk reduction, to institute corrective and preventive measures that will minimize the risk of respiratory morbidity and mortality. It also facilitates the adequate counselling of patients on treatment options and identifies possible steps to reduce long-term pulmonary disability (eg, pre-operative cardio-pulmonary rehabilitation).

Lung resection provides a great likelihood of cure for patients with localized lung disease, but the procedure is associated with a risk of mortality, decreased post-operative lung function and other complications.[1] It is generally accepted that post-operative lung function will decrease such that forced expiratory volume in 1 second (FEV_1) is reduced by 9%–17% post lobectomy and 34%–36% post pneumonectomy, while forced vital capacity (FVC) is reduced by 7%–11% post lobectomy and 36%–40% post pneumonectomy.[2] Serial studies have shown decline on lung function for several months following resection, but this may be recovered to a smaller extent within six months.[3]

The quest for the ideal pre-operative test for predicting patients at higher pre-operative risk began with spirometry in 1955.[4] Since then, varied scientific evidence has been presented for setting the most appropriate diagnostic tests for adequate evaluation and stratification. These tests include simple arterial blood gas determination, pre-operative pulmonary function tests/spirometry measuring FEV_1, diffusing capacity of the lung for carbon monoxide (DLCO), lung perfusion scan and cardiopulmonary exercise testing (CPET). The predictive factors for pulmonary morbidity and mortality used in these guidelines include FEV_1, DLCO, predicted post-operative (ppo) FEV_1, ppo DLCO, and the maximum amount of oxygen an individual can use (VO_{2max}). These predictive factors were then integrated and recommended as part of pre-operative evaluation algorithm.

The pre-operative algorithms for risk assessment available at present are from the American College of Chest Physicians,[5] the British Thoracic Society[6] and the European Respiratory Society/European Society of Thoracic Surgery.[7] The differentiating factor among these algorithms is the specific recommended stepwise order of the diagnostic tests to arrive at a specific risk stratification. These algorithms are also primarily used to risk assess patients with early-stage lung cancer. In our setting, the algorithms are used not only for lung cancer patients but also for patients with non-neoplastic conditions requiring lung resection, such as bronchiectasis, bulla and aspergilloma.

This study aims to assess the applicability of the updated Lung Center of the Philippines (LCP) 2015 algorithm on pre-operative risk assessment[8] in predicting PPCs among patients undergoing lung resection at the LCP. In this updated algorithm, CPET was escalated as the next diagnostic test if FEV_1 or DLCO is <80% predicted values. In comparison, the 2010 LCP algorithm, which was patterned from the American College of Chest Physicians Guidelines,[5] sets lung perfusion scan as the next diagnostic test if FEV_1 and DLCO are <80%. This study also aims to correlate the baseline demographic, clinical variables and predictive factors with the occurrence of PPCs.

The revision of the LCP algorithm on pre-operative risk assessment could be more cost-effective with the availability of CPET in our center (compared to lung perfusion scan) and as supported and validated by other evidence-based studies.[2,9,10]

METHODS

This is a cohort observational study conducted on adult patients ≥18 years old who were scheduled for lung resection from January 2016 to October 2016. Included were those who underwent the prescribed diagnostic tests for adequate risk stratification based on the latest 2015 LCP algorithm on pre-operative risk assessment (Appendix). Excluded were patients with incomplete diagnostic tests for adequate pre-operative evaluation using the LCP algorithm and those assessed to have high risk for cardiac complications by Goldman's score.

Baseline data were recorded, including age, sex, ward of admission, presence of co-morbidities, smoking history, underlying disease (neoplastic or non-neoplastic), surgical approach (thoracotomy or video-assisted thoracoscopic

surgery), type of resection (pneumonectomy, lobectomy or lesser resection), cardiac risk assessment by Goldman's score, smoking cessation (≥8 weeks before surgery) and post-operative use of incentive spirometry until discharge. The values of the predictive factors obtained from the diagnostic tests indicated in the algorithm (partial pressure of carbon dioxide [pCO_2], partial pressure of oxygen [pO_2], FEV_1, FEV_1 % predicted, ppo FEV_1, DLCO % predicted, ppo DLCO and VO_{2max}) were recorded. Lengths of post-operative hospital stay were determined.

The patients were followed up until discharge to observe for post-operative pulmonary complications (PPCs). PPC incidence rate was determined in relation to the baseline data, value of predictive factors, pulmonary risk assessment and length of post-operative stay.

Sample size for this study was computed to ≥76 using Fleiss with continuity correction and assuming 5% level of significance and a default statistical power of 80%.

Categorical variables were presented using frequency counts and percentages, while continuous variables were summarized using measures of central tendency. The statistical differences in the proportions of patients grouped per specified risk variable and the associations of risk factors to post-operative complications and clinical outputs to neoplastic disease were calculated using Pearson's chi-squared test or Fisher's exact test. Independent-samples t-test was used to determine difference and correlation between length of post-operative stay of patients and predictive values to incidence of complications. IBM SPSS version 20.0 was used to output the statistical tables. Significance level was set at 5%, indicating statistical difference and association. Binary logistic regression was employed to determine the joint association of variables that were deemed significant in the univariate assessment. Significance level was set at 10% for multivariate regression analysis.

We conducted this study in compliance with the ethical principles set in the Declaration of Helsinki. The Institutional Ethics Review Board of LCP reviewed and approved the study protocol and subsequent amendments prior to initiation. The investigator obtained a written and signed informed consent from each study participant prior to data collection.

RESULTS

A total of 119 patients were admitted for lung resection during the study period. Forty-one were excluded: 4 did not undergo spirometry due to hemoptysis, 36 had inadequate diagnostics precluding pre-operative evaluation using the 2015 LCP algorithm (11 with no baseline spirometry, 6 without DLCO component in spirometry, 15 did not undergo CPET, and 4 did not undergo lung perfusion scan) and 1 was assessed as high risk for cardiac complications. Seventy-eight satisfied the inclusion criteria and were assessed using the 2015 LCP algorithm on pre-operative risk assessment. Among them, 49 had FEV_1 % predicted and DLCO % predicted ≥80%, so they were labeled outright as low risk. The 29 with FEV_1 % predicted and DLCO % predicted <80% underwent CPET: 10 had VO_{2max} >20 ml/kg/min and were categorized as low risk, while 19 underwent lung perfusion scan, were found to have ppo FEV_1 and ppo DLCO ≥40%, and were categorized as moderate risk.

The mean age of participants was 55 years. Most were <65 years old. Out of the 23 patients who developed PPCs, 74% were male. Gender was a significant factor associated with the development of complications ($\chi 2=4.064$, $p=0.04$). Male patients were found to have approximately two times higher chance of getting complications (RR: 2.1). Forty-nine percent had non-neoplastic diseases, mostly post-tuberculous bronchiectasis, aspergilloma and bulla. Sixty-one percent of complication incidences came from the non-neoplastic group, but the diagnosis was not a significant factor in predicting complications ($p=0.216$). Seventy-four percent of those with PPC had a prior history of smoking. Previous

Table 1. Baseline Characteristics of Patients

Baseline Characteristics		With PPCs (n=23)		Without PPCs (n=55)		Total (n=78)		P-value
		n	%	n	%	n	%	
Age group	<65 years old ≥65 years old Mean ± SD	17 6 53.22±13.9	73.9 26.1	40 15 55.8±13.7	72.7 27.3	57 21 55.04±13.73	73.1 26.9	NS
Sex	Male Female	17 6	73.9 26.1	27 28	49.1 50.9	44 34	56.4 43.6	0.04
Ward	Service Pay	11 12	47.8 52.2	16 39	29.1 70.9	27 51	34.6 65.4	0.126
Diagnosis	Neoplastic Non-neoplastic	9 14	39.1 60.9	31 24	56.4 43.6	40 38	51.3 48.7	0.216
Smoking status	Smoker Non-smoker	17 6	73.9 26.1	19 36	34.5 65.5	36 42	46.2 53.8	0.002
Smoking pack years	<20 pack years ≥20 pack years Mean±SD	12 11 16.13±14.35	52.2 47.8	43 12 7.75±13.58	78.2 21.8	55 23 10.22±14.25	70.5 29.5	0.03
Co-morbidities	Breast cancer Bronchial asthma COPD Hypertension Goiter Diabetes mellitus None	0 2 3 6 0 5 11	0 8.7 13 26.1 0 21.7 47.8	1 1 5 15 1 12 27	1.8 1.8 9.1 27.3 1.8 21.8 49.1	1 3 8 21 1 17 38	1.3 3.8 10.3 26.9 1.3 21.8 48.7	NS 0.206 0.687 NS NS NS NS
Surgical approach	VATS Uniportal VATS Thoracotomy	15 4 4	65.2 17.4 17.4	31 16 8	56.4 29.1 14.5	46 20 12	59 25.6 15.4	0.558
Type of resection	Lobectomy	22	95.	50	90.9	72	92.3	0.347
	Pneumonectomy	1	4.3	1	1.8	2	2.6	
	Lesser resections	0	0	4	7.3	4	5.1	
Cardiac risk assessment	Low	20	87	50	90.9	70	89.7	0.687
	Moderate	3	13	5	9.1	8	10.3	
Smoking Cessation	Yes	21	91	52	95	73	94	0.594
	No	2	9	3	5	5	6	
Post-op incentive spirometry use	Yes	19	83	48	87	67	86	0.589
	No	4	17	7	13	11	14	

COPD = chronic obstructive pulmonary disease; PPC = post-operative pulmonary complications; SD = standard deviation; VATS = video-assisted thoracoscopic surgery.

smokers were three times more likely to get complications (RR: 3.35). Mean duration of smoking was 16 years in those with complication, 8 years in those without. Patients with ≥20 pack-year smoking history had two times higher likelyhood of getting complications (RR: 2.18). With a certainty level of 95%, smoking history and having ≥20 pack years significantly contributed to complications (p=0.002 and p=0.03, respectively) (Table 1).

Most participants had no known co-morbidities, were admitted at the pay ward, underwent VATS/lobectomy, had low-risk cardiac assessment, stopped smoking ≥8 weeks prior to surgery and used post-operative incentive spirometry until discharge. However, none of the abovementioned baseline data were statistically significant with respect to occurrence of PPCs.

Most of the patients who developed PPCs had significantly lower mean FEV_1 % predicted (68.53% vs 86.16%). Mean pO_2 was higher among those who developed complications (91.04 mm Hg vs 90.74 mm Hg), but more than half (57%) of those who developed complications had pO_2 <90 mm Hg. FEV_1 % predicted was the only predictive value statistically associated with occurrence of complication (p<0.001) (Table 2).

A comparison of means showed that the observed mean FEV1 % and ppo FEV1 were statistically significant to the development of PPCs (p=0.001 and p<0.001, respectively) (Table 3).

Binary logistic regression showed that significant variables in the univariate analysis, when combined, resulted in having smoking history and FEV_1 as significant predictors of PPC at 90% confidence level (Table 4).

Summarizing the PPC incidence per risk assessment using the 2015 LCP algorithm, a total of 59 patients were categorized as low risk (29, neoplastic; 30, non-neoplastic) while 19 were categorized as moderate risk (11, neoplastic; 8, non-neoplastic).

Chi-squared test showed significant association between the combination of type of disease and risk assessment and incidence of complications (p=0.036). The applicability of the algorithm in predicting PPC was statistically significant to the non-neoplastic group (p=0.09) (Table 5).

Using the 2015 LCP algorithm, PPC incidence was found to be at 29% (23/78 patients), the most common PPC being prolonged air leak (10%), followed by nosocomial pneumonia (8%) with noted Gram-negative isolated strains: three with *Klebsiella pneumoniae*, one with *Pseudomonas aeruginosa*, one with *Enterobacter cloacae* and one with *Acinetobacter baumannii*. There was no statistically significant difference between neoplastic and non-neoplastic disease when grouped according to the incidence of each PPC (Table 6).

Patients with complications had greater median post-operative stay (9 vs 6 days). The difference was statistically proven at 95% confidence level (H=3.66, p=0.003) (Table 7).

DISCUSSION

There are many pre-operative risk assessment algorithms and guidelines available for reference. All aim to systematically facilitate and adequately evaluate perioperative and long-term risks of pulmonary disability. These algorithms mostly differ on the order of diagnostic tests to request prior to risk stratification. The 2015 LCP algorithm for pre-operative risk assessment was patterned from the 2009 ERS/ESTS guideline,[7] but the cut-off values for the predictive factors such as ppo FEV_1, ppo DLCO and VO_{2max} were adapted from Bolliger et al.[9] Based on this study, the applicability of the updated 2015 LCP algorithm in predicting PPCs is not only for patients with lung cancer but also for patients with a diagnosis of bronchiectasis, aspergilloma or bulla (p=0.09). In contrast, in the latest guidelines available globally, the target clinical group for pre-operative evaluation is specifically designed for lung cancer patients.

Table 2. Predictive Diagnostic Test Factors of the Patients

Predictive Diagnostic Test Factors		With Complications		Without Complications		Total		P-value
		n	%	n	%	n	%	
pCO_2	>45 mm Hg	4	17	3	5	7	9	0.093
	≤45 mm Hg	19	83	52	95	71	91	
	Mean±SD	37.71±5.74		37.29±4.68		37.41±4.82		
pO_2	≥90 mm Hg	10	43.5	26	47.3	36	46.2	0.807
	<90 mm Hg	13	56.5	29	52.7	42	53.8	
	Mean±SD	91.04 ±13.04		90.74±10.81		90.83±11.43		
FEV_1 % predicted	≥80%	9	39.1	46	83.6	55	70.5	<0.001
	<80%	14	60.9	9	16.4	23	29.5	
	Mean±SD	68.53±21.35		86.16 ±12.89		80.97 ±17.67		
FEV_1	≥1.5 L	18	78.3	49	89.1	67	85.9	0.285
	<1.5 L	5	21.7	6	10.9	11	14.1	
	Mean±SD	1.89±0.45		2.09±0.49		2.03±0.48		
ppo FEV_1	≥40%	21	91.3	54	98.2	75	96.2	0.206
	<40%	2	8.7	1	1.8	3	3.8	
	Mean±SD	67.30±17.73		81.10±13.44		77.03±16.02		
DLCO % predicted	≥80%	11	47.8	37	67.3	48	61.5	0.13
	<80%	12	52.2	18	32.7	30	38.5	
	Mean±SD	80.78±13.32		82.70±10.42		82.13±11.31		
ppo DLCO	≥40%	23	100.0	54	98.2	77	98.7	0.99
	<40%	0	0.0	1	1.8	1	1.3	
	Mean±SD	73.02±12.57		76.32±13.21		75.35±13.03		
VO_{2max}	>20 ml/kg/min	6	20.6	5	17.3	11	37.9	0.99
	≤20 ml/kg/min	8	27.6	10	34.5	18	62.1	
	Mean±SD	19.6±3.57		20.43±6.28		20.15±5.18		

FEV_1=forced expiratory volume in 1 second; DLCO=diffusing capacity of the lung for carbon monoxide; pCO_2=partial pressure of carbon dioxide; ppo=predicted post-operative; pO_2=partial pressure of oxygen; SD=standard deviation; VO_{2max}=the maximum amount of oxygen an individual can use.

Table 3. Means of Analyzed Predictive Diagnostic Factors

Predictive Values	With Complications	Without Complications	P-value
pCO_2	37.71±5.74	37.29±4.68	0.727
pO_2	91.04 ±13.04	90.74±10.81	0.916
FEV_1	1.89±0.45	2.09±0.49	0.091
FEV_1 % predicted	68.53±21.35	86.16 ±12.89	0.001
ppo FEV_1	67.30±17.73	81.10±13.44	<0.001
DLCO % predicted	80.78±13.32	82.70±10.42	0.499
ppo DLCO values	73.02±12.57	76.32±13.21	0.311
VO_{2Max}	19.6±3.57	20.43±6.28	0.547

FEV_1=forced expiratory volume in 1 second; DLCO=diffusing capacity of the lung for carbon monoxide; pCO_2=partial pressure of carbon dioxide; ppo=predicted post-operative; pO_2=partial pressure of oxygen; SD=standard deviation; VO_{2max}=maximal oxygen consumption.

Table 4. Binary Logistic Regression of Significant Variables

Predictors	B	SE	Wald	df	P-value	Odds Ratio
Gender	–1.031	0.759	1.848	1	0.174	0.356
Smoking	–1.514	0.837	3.27	1	0.071	0.22
Smoking pack years	–0.018	0.81	0.001	1	0.982	0.982
FEV_1	0.071	0.021	11.074	1	0.001	1.074
Constant	–3.226	1.909	2.854	1	0.091	0.04

df=degrees of freedom; FEV_1=forced expiratory volume in 1 second.

Table 5. Post-operative pulmonary complication Incidence per Risk Assessment Among Neoplastic and Non-Neoplastic Patients

		With Complications		Without Complications		Total		P-value*	P-value†
Disease	**Risk Assessment**	n	%	n	%	n	%		
Neoplastic	**Low**	8	88.89	21	67.74	29	72.50	0.211	0.036 (<0.05)
	Moderate	1	11.11	10	32.26	11	27.50		
Non-Neoplastic	**Low**	9	64.29	21	87.50	30	78.95	0.090 (<0.10)	
	Moderate	5	35.71	3	12.50	8	21.05		

*P-values for main effect of risk assessment on incidence of complications per disease group (neoplastic or non-neoplastic)
†P-value for combined effect of disease group and risk assessment on incidence of complications.

Table 6. Incidence of Specific PPCs

PPC	Neoplastic		Non-Neoplastic		Total		P-value
	n	%	n	%	n	%	
Prolonged air leak	5	6.4	3	3.8	8	10.2	0.179
Nosocomial pneumonia	1	1.3	5	6.4	6	7.7	0.34
Hemothorax	1	1.3	3	3.8	4	5.1	1
Prolonged mechanical ventilator	0	0	2	2.6	2	2.6	0.234
Acute respiratory failure	1	1.3	1	1.3	2	2.6	1
Atelectasis	1	1.3	1	1.3	2	2.6	1
Bronchospasm	2	2.6	0	0	2	2.6	0.142
Death	0	0	1	1.3	1	1.3	1

PPC=post-operative pulmonary complication.

Table 7. Length of Post-operative Stay

	Minimum Stay (days)	Maximum Stay (days)	Median	Mean	Std. Deviation	Stat Value*	P-value
With Complications	5	15	9	8.65	2.95	3.66	0.003
Without Complications	2	13	6	6.4	2.02		
Total	2	15	7	7.06	2.53		

*Mann-Whitney Test

In both neoplastic and non-neoplastic groups, 70%–72% of those classified as low risk came out without complication (21/29 and 21/30 cases, respectively). In this study, sensitivity is the ability to identify patients (assessed as low risk) who will not experience complication; it was 88% for the non-neoplastic group and 68% for neoplastic. However, when it comes to classifying cases as moderate risk, the algorithm had better accuracy in predicting PPCs in the non-neoplastic group (63%) than in the neoplastic group (9%). Specificity was shown to be low for both groups (36% for non-neoplastic, 11% for neoplastic).

Overall PPC incidence in our study was 29%, with the most common being prolonged air leak (10%), followed by nosocomial pneumonia (8%). Mortality rate was 1.3%. These findings are similar to that of other studies. In a three-year local retrospective study by Catacutan et al, PPC rate in 53 patients was 32%, with the most common PPCs being nosocomial pneumonia (11%) and prolonged air leak (9%), while mortality rate was 4%.[11] In another four-year local retrospective study by Mapanao et al,[12] PPC

incidence was 43%, with nosocomial pneumonia (13%) and prolonged air leak (12%) as the most common and a mortality rate of 2%. A local prospective study by Aloc-Samaniego et al[13] found PPCs in 12% of 55 patients, with the most common PPC being prolonged air leak (17%), followed by hemothorax and pneumonia (both 3%), but with zero mortality. Globally, the overall incidence of PPC is approximately 30%; however, estimations may vary from 7% to 49%. Prolonged air leak (4%–26%), nosocomial pneumonia (15%–22%) and acute respiratory failure (2.4%–17%) have been found to be the most common causes of PPC.[3] In general, prolonged air leak carries a low mortality rate but great morbidity because it is associated with prolonged hospitalization, and pleural air leaks may further deteriorate pulmonary gas exchange by increasing the amount of wasted ventilation and work of breathing.[14] As for nosocomial pneumonia, many factors may influence this, including patient population, isolation procedures and antibiotic use; but the most common bacterial isolates are gram-negative organisms,[3] as in our case.

In our study, we have one mortality recorded: a 39-year-old with no known co-morbidities. He underwent right lung pneumonectomy due to recurrent non-massive hemoptysis secondary to post-tuberculous bronchiectasis. The patient's predictive factors were FEV_1 % predicted of 45%, ppo FEV_1 of 45%, DLCO % predicted of 73%, ppo DLCO of 76% and VO_{2max} of 15.8 ml/kg/min, so he was risk stratified as moderate risk. The patient also suffered from other PPCs, including hemothorax and prolonged mechanical ventilation use prior to demise. We found that the morbidity of post-operative complications in pneumonectomy was significantly higher than in lobectomy (p=0.01).[14] Lobectomy and pneumonectomy are consistently described with mortality rates of 2%–4% and 6%–8%, respectively.[14] FEV_1 % and DLCO <60% are also predictors of increased morbidity and mortality.[3]

Among the baseline demographic/clinical factors in this study, the major predictors of PPC were male gender and smoking history. Most of the patients that developed PPCs were male (74%), and male patients had approximately 2 times higher chance of getting complications (RR: 2.1). This is consistent with the study of Kearny et al,[15] in which 2/3 of those with complications were male, and the local study of Mapanao et al,[12] in which 77% of those with PPCs were males (p=0.04). It could be noted that 84% of the smokers in our study were males. Male gender developing PPCs with smoking history could be interrelated, because smoking is a proven risk factor for the development of post-operative complications. In this study, 74% of those with PPCs had a prior history of smoking. Previous smokers had 3 times higher likelihood of getting complications (RR: 3.35). Similarly, Smetana et al[16] found a relative risk of 1.4- to 4.3-fold in smokers for occurrence of complications. Mean smoking duration among those with complication was 16 years; among those who did not develop complication, it was 8 years. With a certainty level of 95%, smoking history and having ≥20 pack years significantly contribute to complications (p=0.002 and p=0.03, respectively). Age is not considered contributory to PPCs, and age alone is not a contraindication to surgery.[5] The mean age in this study was 53 years, and most patients were <65 years old. Factors such as tumor stage, patient life expectancy, performance status and co-morbidities should be taken into account in the surgical decision-making process.[3] Our study found that advanced age (>65 years) was not related with occurrence of PPCs, as stated by Lim et al,[6] who reported that elderly patients, while being aware of their lower health status pre-operatively (had poorer ECOG performance status and ASA scores compared with the younger subjects), had no significant differences in their quality of life at three months after surgery.[6] As to the factors that could be employ-

ed to decrease the occurrence of PPC, our study included smoking cessation and the use of incentive spirometry. The beneficial effects of smoking cessation include improvement in ciliary and small-airway function and a decrease in sputum production, which occur gradually over several weeks. The risk of PPC is said to be highest in patients who were smoking within the last two months and patients who had quit smoking for more than six months.[17] The correlation of timing of smoking cessation prior to surgery, in general, has only a minimal impact on PPC. In one study,[7] the patients enrolling in a smoking cessation program 6–8 weeks prior to elective surgery had decreased morbidity and a reduced need for post-operative ventilatory support. However, in another study,[15] patients still smoking at the time of surgery did not have significantly more complications than those who stopped smoking. Post-operative incentive spirometry use is said to decrease the risk of PPCs, because the lung expansion maneuver controls the adverse effects of surgery on lung and chest wall mechanics that cause atelectasis and retained secretions. However, a systematic review by Overend et al and a randomized controlled trial by Gosselink et al, both found no benefit of incentive spirometry.[18] Literature supports the use of CPAP therapy to decrease PPC.[7] In our study, both smoking cessation and post-operative use of incentive spirometry were not proven to be determinants for minimizing development of PPC. This might be attributed to the general consensus based on the abovementioned studies, but another loophole for this non-significance was the small sample representation (only 6% of our patients did not stop smoking prior to surgery, and only 14% did not use spirometry).

Among the predictive diagnostic factors in our study, only FEV_1 % and ppo FEV_1 were found to statistically significant and related to the development of PPC. Pulmonary function tests—in particular, FEV_1 and ppo FEV_1—have traditionally represented the key test in functional workup of surgical candidates.[19] Berry et al in 2007 reported that FEV_1 was an independent predictor of respiratory complications: patients with pre-operative FEV_1 <30% had an incidence of respiratory morbidity as high as 43%, while those with FEV_1 >60% had a morbidity rate of 12%.[7] In our study, the mean FEV % predicted of the patients with PPCs was significantly lower (68.53±21.35%) than those without (86.16%±12.89) ($p<0.001$). Mean ppo FEV_1 was lower among patients with PPC than those without (67.30±17.73% vs 81.10±13.44%). Kearney et al[15] found that ppo FEV_1 was the best predictor of complications after controlling for the effect of other risk factors in a multivariate analysis. Although ppo FEV_1 is fairly accurate in predicting the definitive residual value of FEV_1 three to six months after surgery, it substantially overestimates the actual FEV_1 observed in the initial post-operative days, when most complications occur.[6] Therefore, ppo FEV_1 should not to be used alone to assess candidates for lung resection, as it tends to underestimate the functional loss in the early post-operative phase and does not appear to be a reliable predictor of complications.[7]

Other predictive factors that were found to be statistically non-significant in our study but generally showed a correlation in development of PPCs include pCO_2 (37.71 mm Hg vs 37.29 mm Hg), DLCO % predicted (80.78% vs 82.70%), ppo DLCO (73.02 vs 76.32) and VO_{2max} (19.5 ml/kg/min vs 20.56 ml/kg/min). With regard to pCO_2 and pO_2, most studies have showed that hypercapnea and hypoxemia are not directly related to the development of PPCs. Kearney et al reported that in 30 patients with pCO_2 >45 mm Hg and desaturation to pO_2 <90 mm Hg, they did not find an increased occurrence of PPCs.[15] As for DLCO, it is recommended to systematically measure it in all lung resection candidates regardless of their pre-operative FEV_1 level, because ≥40% of them can have abnormal DLCO despite a normal FEV_1, and ppo DLCO has been shown to be a valid predictor of major morbidity

even in patients without airflow limitation.[19] The strong correlation between diffusing capacity and PPCs is probably due to the contribution of a reduced pulmonary capillary bed and alveolar capillary membrane to pulmonary complications.[20] The last predictive diagnostic factor is VO_{2max}, which is a value derived from CPET. The patients who developed PPCs in our study had a lower VO_{2max} than non-complicated patients (19.5±3.56 ml/kg/min vs 20.56±6.34 ml/kg/min). Most of the studies published so far agree 10–15 ml/kg/min indicates an increased risk for PPC and perioperative death compared with higher values of VO_{2max}.[5] On the other hand, VO_{2max} >20ml/kg/min has been reported to be safe for any kind of resection, including pneumonectomy. In one study by Brunelli et al, which included 200 participants with major anatomic lung resections and complete CPET, patients with VO_{2max} >20 ml/kg/min had no mortality and only 7% morbidity rate compared to those with VO_{2max} <12, whose mortality rate was 13%.[5]

This study involved only 78 patients, because most patients were excluded due to the diagnostic tests in the algorithm not being followed by most attending physicians. With the conclusion that the updated algorithm is predictive of PPCs specifically to non-neoplastic patients, we recommend that this algorithm be applied for all patients undergoing lung resection. This, in effect, will help increase the sample size for future studies, to strengthen the association of other clinical variables found to be non-significant in this study.

Other recommendations include a longer follow-up period not limited to the day of discharge, studying the correlation of pulmonary rehabilitation with the development of post-operative complications, and the possible effect of anesthesia and post-operative analgesia in PPC occurrence.

CONCLUSION

The updated 2015 LCP algorithm on pre-operative risk assessment in predicting PPCs is not only applicable to patients with lung cancer but also for those with non-neoplastic diseases. Moreover, this algorithm is more predictive in determining among the non-neoplastic group who with low risk will not develop complication and who in the moderate-risk group will develop complication. The factors that predict development of PPCs include male gender, smoking history, smoking ≥20 years, FEV_1 % predicted and ppo FEV_1 value. PPC incidence is 29%, almost the same as with other studies, with prolonged air leak and nosocomial pneumonia as the most common PPCs. There is also a longer hospital stay for patients developing PPCs.

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APPENDIX

Formulae for Calculating Predicted Post-operative Values for FEV_1 and DLCO

A. Anatomic Method

$$\text{ppo } FEV_1 \text{ (post lobectomy)} = \frac{\text{pre-operative FEV1 x (1–a/b)}}{\text{reference } FEV_1}$$

$$\text{ppo DLCO (post lobectomy)} = \frac{\text{pre-operative DLCO x (1–a/b)}}{\text{reference DLCO}}$$

a=number of functional or unobstructed segments to be resected
b=total number of functional or unobstructed segments.

B. Perfusion Method

$$\text{ppo } FEV_1 \text{ (post pneumonectomy)} = \text{pre-operative } FEV_1 \text{ x (1 – fraction of total perfusion of lung to be resected)}$$

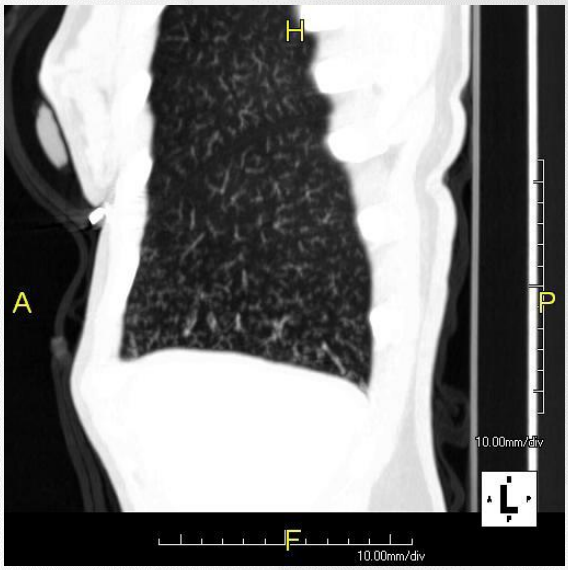
$$\text{ppo DLCO (post pneumonectomy)} = \text{pre-operative DLCO x (1 – fraction of total perfusion of lung to be resected)}$$

The total number of segments is 19 (10 right, 9 left). Distribution of segments:
- Right upper lobe=3
- Middle lobe=2
- Right lower lobe=5
- Left upper lobe=5 (3 upper division, 2 lingula)
- Left lower lobe=4

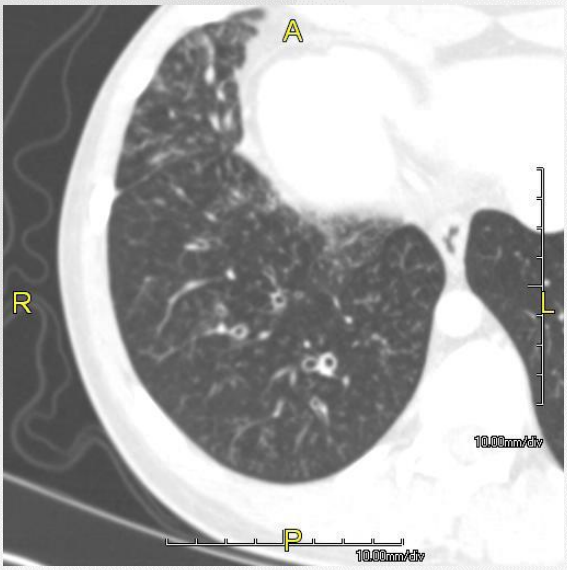
The ppo FEV_1 is expressed as percentage of predicted to calculate % ppo FEV_1.
The ppo DLCO and % ppo DLCO can be calculated using the same formula.
The percentage of ppo (% ppo) values of FEV_1 and DLCO are routinely used instead of absolute values.

IMAGE GALLERY

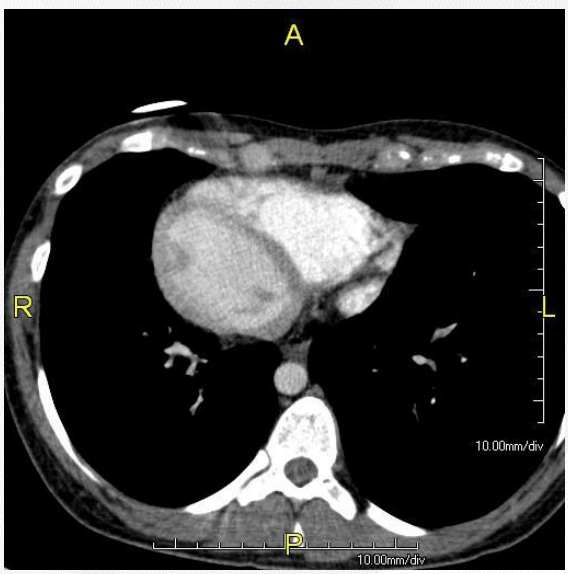
Primary Ciliary Dyskinesia



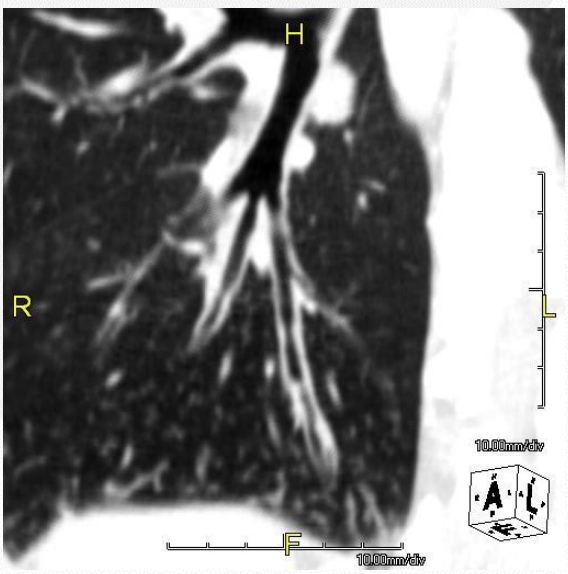
Sagittal reformatted CT image showing "tree in bud" appearance of impacted distal small airways in Kartagener Syndrome.



CT scan of the lower chest in primary ciliary dyskinesia showing mild bronchial wall thickening and bronchiectasis.



Axial CT image showing dextrocardia and situs inversus in a patient with Kartagener syndrome.



Sagittal reformatted CT image showing cylindrical bronchiectasis in Kartagener syndrome.

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NOTES

NOTES

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