PHILIPPINE JOURNAL OF CHEST DISEASES

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IN THIS ISSUE:

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PHILIPPINE JOURNAL OF CHEST DISEASES
AN OFFICIAL PUBLICATION OF THE PHILIPPINE COLLEGE OF CHEST PHYSICIANS

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TABLE OF CONTENTS

APRIL-JUNE 2016 VOLUME 17 NUMBER 2

From stepping stones to milestones

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

As they say, "time heals all wounds". And yet for the lungs, oftentimes, this saying sadly does not ring true.

Every pulmonary specialist hopes and prays that all patients with chronic lung disease are diagnosed quickly and efficiently, and respond immediately and safely to treatment. However, despite our best efforts, our clinical know-how and current diagnostic tools, there are instances when we reach that point when there is little more that we can do.

Or so we think.

The Philippine College of Chest Physicians has always emphasized the importance of relevant research in the field of pulmonary medicine. As an academic body, the PCCP advocates and invests in research to boost knowledge in the field, to answer clinical questions, validate existing information, and to provide hope that we can do more for our patients. The research that we do as a College ultimately benefits our patients; and should our patients be among those with chronic lung disease, then our research provides them with a bit more hope, and provides us with the opportunity to dream that, indeed, we can do more for them.

This issue celebrates the contributions of the PCCP to the existing body of knowledge on chronic lung diseases such as COPD, bronchial asthma and pulmonary tuberculosis. Each article provides us with something new to help us approach our patients, and brings

us closer and closer to fully understanding their conditions. After all, the diagnostic tests and therapeutic maneuvers we do for our patients started from the same humble beginnings: a tidbit – a morsel – of an idea that eventually matured into a full scientific paper.

Moreover, these papers are meant to be stepping stones for our fellows-in-training, their chance to flex their research muscles, and to develop their research acumen; all this aligned with PCCP's concept of the compleat pulmonologist: a strong clinician, a passionate advocate and a visionary researcher.

The PJCD offers itself to the College as the showcase of all scientific research created by members of the PCCP. It is the voice of PCCP's visionary researcher, and PCCP's platform in sharing knowledge and ideas. It is a journal that should not be bereft of articles since the College is never lacking in curiosity, ideas and research skills. And that is why, with this issue, after much effort, the PJCD comes closer to fulfilling a long-standing commitment to the PCCP community to release four issues in a year, bringing us to the cusp of our dream of being internationally indexed. Indeed, every issue of the PJCD has become a milestone for the PCCP.

And just like chronic lung disease, which remain perpetual challenges to diagnose and treat, the PJCD is the perpetual challenge of the PCCP: not easy, but now made possible with all of us working together.

INTERHOSPITAL CASE PRESENTATION

A rare case of chest wall abscess secondary to blunt trauma

Benjamin G. Hernandez Jr, MD, FPCP; Rizalyn D. Piñera, MD, FPCP; Marlon A. Tiu, MD, DPCP; Chona A. De Vera, MD, FPCP, FPCCP; Eloisa S. de Guia, MD, FPCP, FPCCP

Veterans Memorial Medical Center, Quezon City

LEARNING OBJECTIVES, RELEVANCE AND SIGNIFICANCE

Chest wall abscess is a rare clinical entity. Closed blunt chest trauma rarely causes chest wall abscess; to our knowledge, only 8 previous cases have been reported.

In this case, we aim to present a rare type of a disease and discuss the diagnosis, risk factors, differential diagnosis and management of chest wall abscess secondary to blunt trauma.

THE CASE

PE was a 58-year-old male diabetic who came in with the chief complaint of difficulty in urinating.

Four days prior to admission, the patient had gotten involved in a motor vehicular accident. He had been thrown forward towards the steering wheel and hit his chest. He was immediately brought to the emergency room, where he complained of tenderness on his right anterior chest second intercostal space (ICS) mid-clavicular line. He had stable vital signs, no penetrating injury, no hematoma or bruising, no bleeding, and no swelling on his chest. A chest radiograph T-cage revealed no fracture (Fig. 1).

He was diagnosed with costochondritis secondary to blunt trauma and was given an oral analgesic, which afforded relief. He was then discharged improved.

At home, due to the recurrence of the chest pain, the patient sought the service of a traditional healer, or *albularyo*, who gave him a hard massage, which provided temporary relief.

A few hours prior to admission, the patient complained of difficulty in urinating associated with hypogastric pain and accompanied with fever and chills. He also noticed that his urine had changed in color from yellowish to brownish. This led him to consult at the emergency room.

Urinalysis revealed pus cells of more than 100 per high power field (HPF), red blood cells of 90–100 per HPF, and glycosuria (+4). Complete blood count (CBC) revealed leukocytosis (21 x 10^9 cells/L) with predominance of segmenters. The patient was subsequently admitted.

A known diabetic, the patient was maintained on gliclazide and metformin. As a known hypertensive, he was maintained on losartan and amlodipine. The patient had been diagnosed with benign prostatic hypertrophy in 2002 and had since been attending regular check-ups at the outpatient department of the Veterans Memorial Medical Center. He was not asthmatic, had no history of allergy to any food or drug, and had no history of pulmonary tuberculosis treatment.

He had a family history of diabetes on his paternal side and hypertension on his maternal side; the rest of his family history was unremarkable.

He was a smoker with a 82-pack-year history; an occasional alcoholic drinker; and he denied any history of illegal drug use.

On physical examination, the patient was conscious, coherent, and not in cardiorespiratory distress.

On admission to the emergency room, he has the following vital signs: blood pressure of 120/70 mmHg; cardiac rate of 89 beats per minute; and respiratory rate of 20 cycles per minute. He had pinkish palpebral conjunctiva, anicteric sclera, no cervical lymphadenopathies, and no neck vein engorgement.

Chest and lung findings revealed symmetrical chest expansion with no retractions. There was point tenderness at the right second ICS mid-clavicular line. There were no wheezes, but he had vesicular breath sounds. The rest of the physical exam findings were unremarkable. He was admitted with these working diagnoses: (1) lower urinary tract symptoms secondary to benign prostatic hypertrophy; (2) complicated urinary tract infection (UTI); (3) type 2 diabetes mellitus; (4) stage 2 hypertension; and (5) costochondritis secondary to blunt trauma.

Upon admission, an antibiotic regimen was started for the UTI. Tranexamic acid was given for the gross hematuria, and tramadol was given as needed for pain. Chest radiograph, posterior-anterior (PA) view revealed mild hilar congestive changes (Fig. 2), to consider pneumonitis (right side). Blood and urine culture were collected. Maintenance medications were continued. Capillary blood glucose was monitored, revealing elevated results ranging from 200 to 400 mg/dl. Hence, patient was referred to endocrinology service, where fasting blood sugar, lipid profile, and Hba1c tests were requested. These came out with elevated results. A repeat urinalysis showed decreasing pus cells, 20–40 per HPF, and negative for glycosuria. Metformin dose was maximized. Insulin (Humulin N) 24 units in the morning and 12 units in the afternoon/evening were started. Supplemental doses of insulin were also given. The rest of the medications were continued.

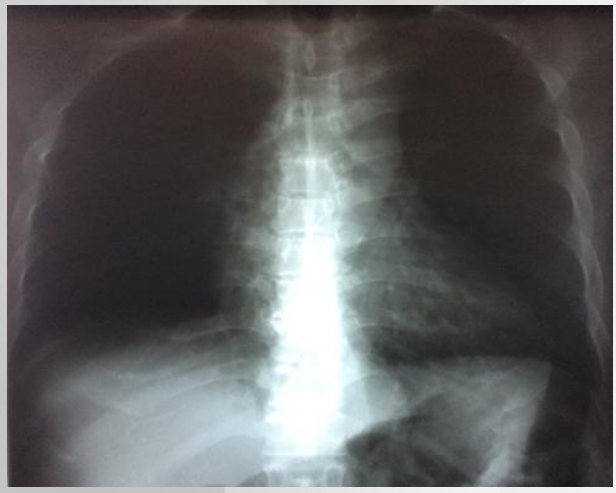

Figure 1. Chest radiograph thoracic cage view showing normal findings, no fracture noted

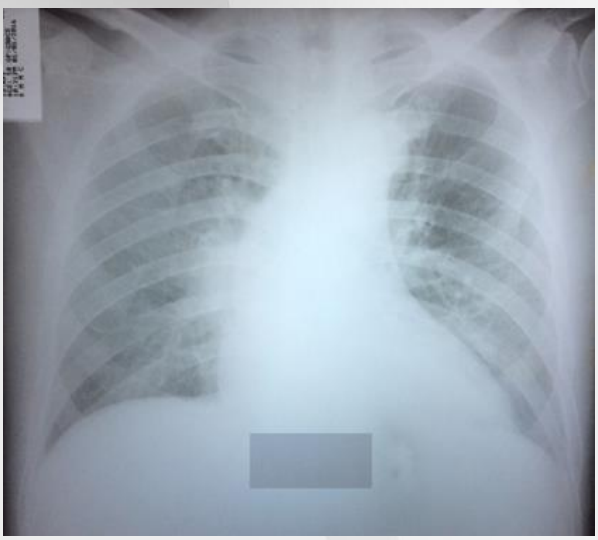

Figure 2. Chest radiograph PA view revealing mild hilar congestive changes

During his stay at the ward, the patient developed occasional non-productive cough with febrile episodes, chills, and intermittent tolerable chest pain on his right chest, aggravated by cough-

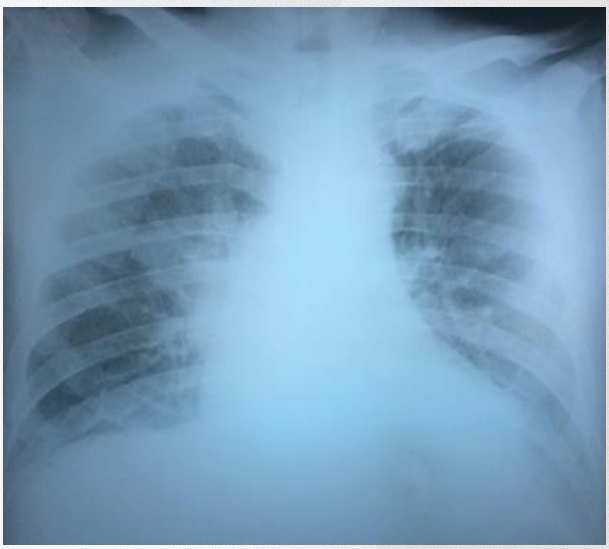

Figure 3. Chest radiograph PA view revealing bilateral pneumonia bilateral with probable minimal bilateral pleural effusion

-ing. Auscultation revealed crackles on bilateral lung fields. A repeat chest radiograph PA view was done (Fig. 3). It revealed bilateral pneumonia with probable bilateral minimal pleural effusion. He was now diagnosed with hospital-acquired pneumonia (HAP), and antibiotics were shifted to intravenous (IV) cefepime 2 g every 8 hours.

The next 6 days of his stay were unremarkable, with no more episodes of fever or chills but still with tolerable right-sided chest pain. Medications were continued, and the patient improved clinically. Blood culture results were released, showing positive for growth of coagulase-negative *Staphylococcus*.

On day 12 of hospital stay, patient had stable vital signs, decreasing episodes of cough, and no febrile episodes. Patient was noticed to have a soft, tender anterior chest wall mass measuring 2x2 cm in diameter on the right second ICS (Fig. 4). Chest radiograph PA–lateral upright view revealed a homogenous density on the anterior mediastinum (Fig. 5), to consider perihilar mass right. He was scheduled for a chest computed tomography (CT) scan with IV contrast. This revealed a pleural-based lobulated and septated hypodense mass with a thick capsule, measuring 4.6x8.3x8.4 cm in the right upper anterior medial hemithorax (Fig. 6). There was an extension of the mass into the anterior

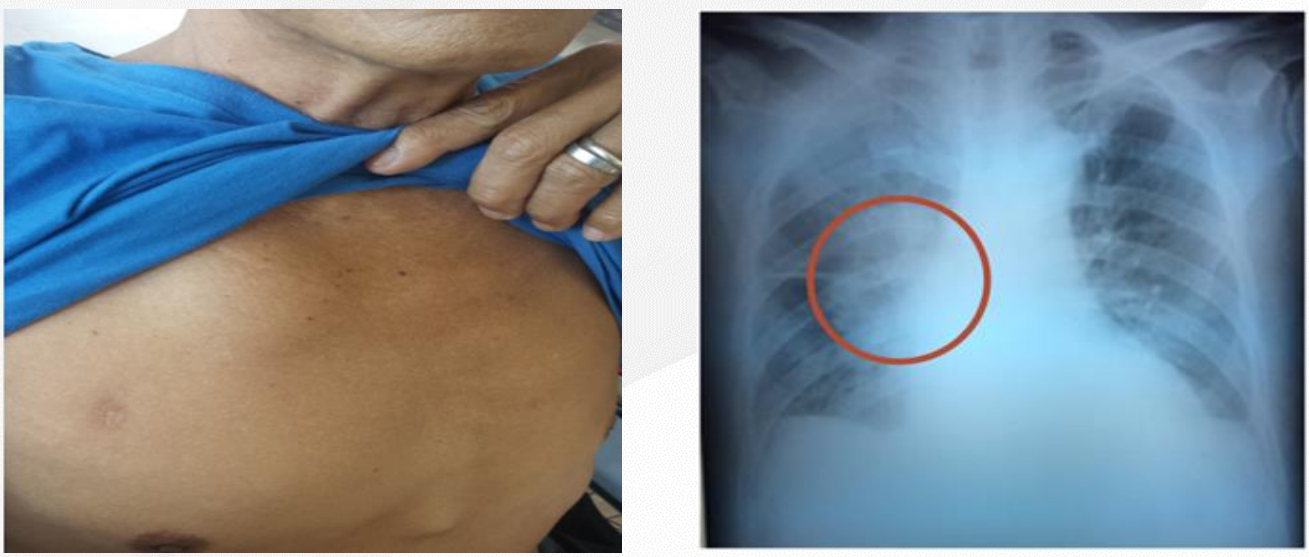

Figure 4. A. Anterior chest wall with a poorly visible, soft, tender mass. B. Chest x-ray showing a 2x2 cm mass on the right mid-lung fields .

chest wall; the extension measured 3.4x2.4x3.7 cm and abutted the pectoral muscles and also indented the pericardium. The scan impression was a hypodense pleural-based mass with extension to the anterior chest wall in the right upper hemithorax, to consider abscess formation but neoplasm was not totally ruled out.

The patient was referred to thoracic and cardiovascular surgery, where ampicillin-sulbactam and clindamycin were started. Patient underwent incision and drainage (Fig. 7). A rapid-frozen section of the specimen revealed the mass to be benign. Noted was 200 cc of purulent, not foul-smelling discharge, which was eventually drained from the anterior chest wall at the level of the fourth ICS. A sternochondral fracture was found intraoperatively on the right second rib.

Histopathology revealed fragments of granulation tissues with neovascularization and areas of fibroblastic proliferation with dense infiltration by lymphocytes and plasma cells (Fig. 8). Gram stain of the anterior chest wall abscess revealed plus 4 pus cells with no growth noted after 7 days of incubation and also negative for acid-fast bacilli. A repeat chest radiograph revealed marked regression of the previously noted inhomogeneous opacity at the level of the second ICS (Fig. 9).

The next hospital days of the patient were unremarkable. Patient was discharged with the following final diagnoses: chest wall abscess secondary to blunt trauma secondary to motor vehicular accident; diabetes mellitus type 2; complicated UTI; benign prostatic hypertrophy (BPH); stage 2 hypertension; and HAP, early onset.

Upon follow-up of our patient 12 weeks postoperatively, he reported no chest pain and no fever episodes. On physical exam, there was a noticeable resolution of the anterior chest wall mass that was previously noted on his anterior chest (Fig. 10). There was also clearing of the abscess on repeat chest CT scan (Fig. 11).

DISCUSSION AND COMMENTARY

Chest wall infections are uncommon but potentially life threatening due to their negative impact on respiratory mechanics and their likelihood to spread to the pleural space and med-

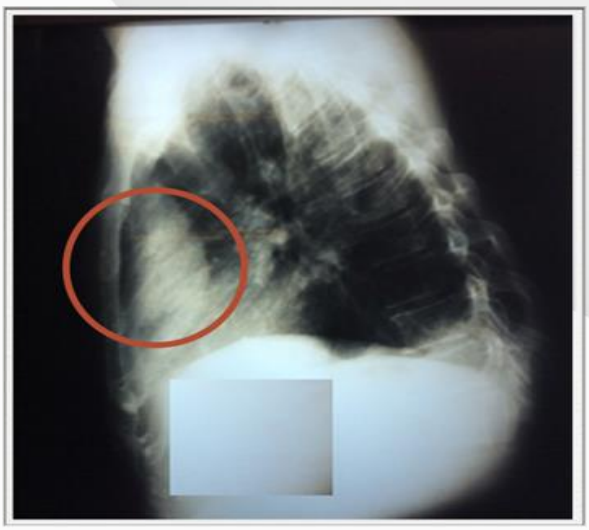

Figure 5. Chest radiograph, PA view (left) showing perihilar densities, lateral upright view (right) showing perihilar densities

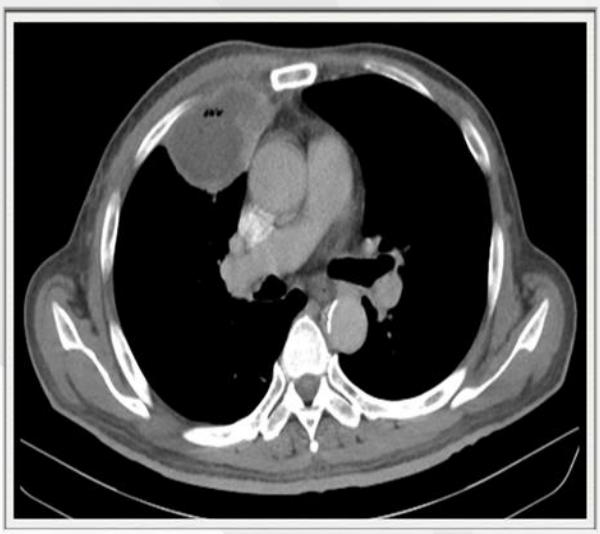

Figure 6. Chest CT scan with IV contrast revealing a pleural-based lobulated and septated hypodense mass with thick capsule

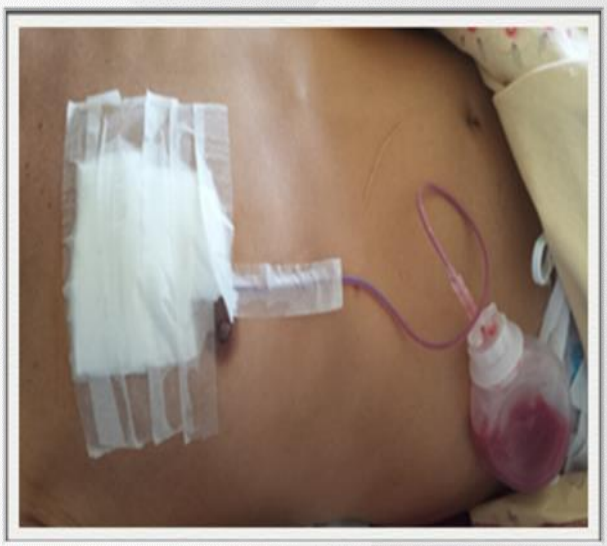

Figure 7. Patient inserted with Jackson-Pratt drain for chest wall abscess

-iastinum. An abscess is a circumscribed collection of purulent exudate frequently associated with swelling and other signs of inflammation such as fever and pain on site of infection; a cavity formed by liquefactive necrosis within solid tissue.[1]

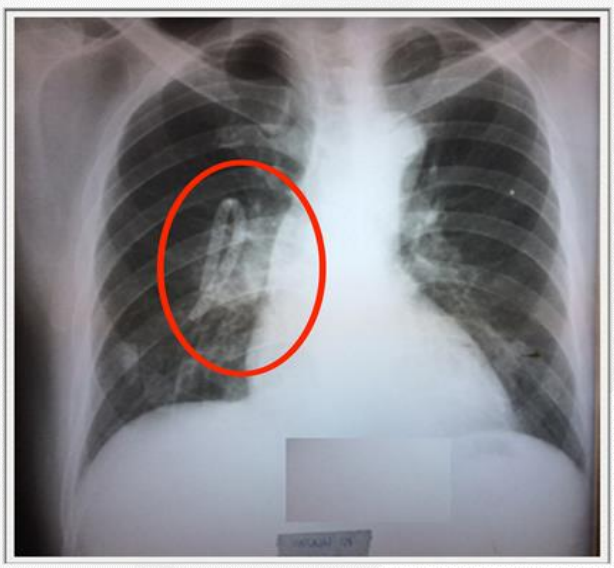

Figure 9. Repeat chest radiograph PA view revealing marked regression of inhomogeneous opacity at the level of the second ICS

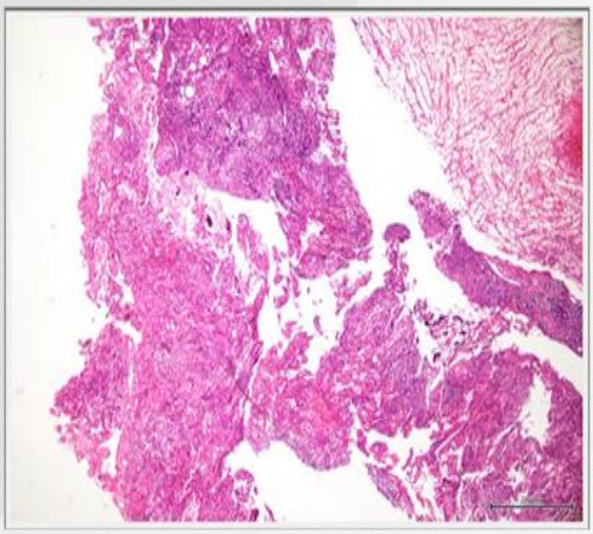

Figure 8. Fragments of granulation tissues with neovascularization and areas of fibroblastic proliferation with dense infiltration by lymphocytes and plasma cells

Chest wall abscess can evolve from soft tissue infection, osteomyelitis of the ribs, infection of the costochondral junction, and infection of the sternoclavicular joint.[2] Primary chest wall abscess is a rare clinical entity occurring as a result of a hematogenous spread of bacterial, fungal, or mycobacterial organisms. On the other hand, secondary chest wall abscess can result from the spread of infection from the lungs or pleura, open trauma, or after a thoracic wall surgery. Chest wall abscess can result from direct contamination or penetrating chest trauma; inoculation by hematogenous spread; and extension from adjacent infections of the chest wall, head and neck, or retroperitoneum. Direct contamination is the most common cause of chest wall abscess.

Chest trauma is classified as either blunt or penetrating, with blunt trauma being the cause of most thoracic injuries.[3] Chest wall trauma is the second most common cause of death in the young age group, and motor vehicular crashes cause most of the thoracic injuries.[4] Blunt chest trauma puts multiple structures at risk of injuries such as

rib fracture, blunt aortic injury, pulmonary contusions, and lacerations. Major vehicle collisions represent the most common cause of thoracic injury among emergency department patients. Several factors are associated with a higher risk of thoracic injury; these include high-speed collision, not wearing a seatbelt, extensive vehicular damage, and steering wheel deformity.[5]

Three collisions can cause blunt trauma: the collision of a vehicle into another object, the patient striking against the inside of the vehicular passenger compartment, and the structures within the body striking the wall of that region or getting torn from their attachment. Injuries from a direct impact are usually less dangerous and affect mainly the soft tissues of the chest wall; occasionally, a localized injury to the osseous part of the chest wall can occur. If the impact of the collision is centered on the anterior chest, the sternum will receive the initial energy exchange. The sternum stops moving, but the thoracic cavity continues to move forward. If the tensile strength of the ribs is exceeded, fractured ribs may result.[4]

Closed blunt chest trauma rarely causes chest wall abscess. To our knowledge, only 8 previous cases have been reported. The chest trauma was caused by a motor vehicle accident in 1 case, fall or blunt assaults in 3 cases, a bicycle accident in 1 case, cardiopulmonary resuscitation in 2 cases, elbowing during a basketball game in 1 case, and sumo wrestling exercises in 1 case.[6] In most cases, hematoma formation around a fracture was identified as a cause of secondary infection contracted by the hematogenous spread of a pathogen. Fractures were found in 4 of the 8 cases. In 5 cases, the abscess appeared more than 2 months after the blunt trauma. In 5 of the 8 cases, the pathogenic organisms were indigenous skin bacteria.[7]

The most common presenting symptoms are fever and anterior chest pain.[6] Outcome depends on early diagnosis, the degree of immunosuppression, the causative organism and the extent of infection. Risk factors include an

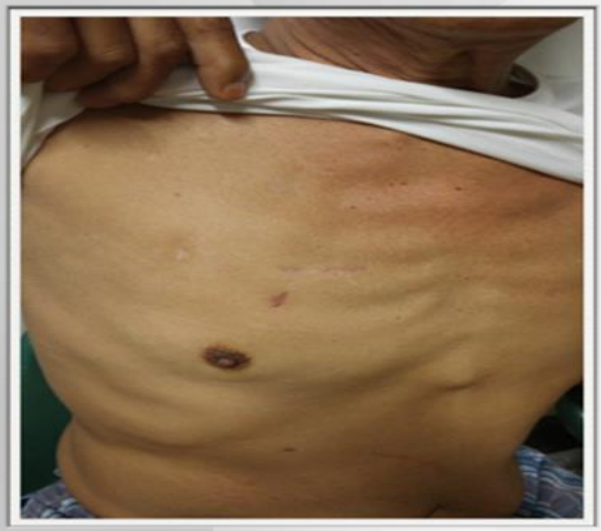

Figure 10. Patient's anterior chest showing resolution of chest wall mass

immunocompromised state, diabetes, previous trauma or surgery.

Patients with diabetes have infections more often than those without, and the course of infection is also more complicated in this group. One of the possible causes of this increased prevalence of infections is defects in immunity. Different disturbances in humoral innate immunity have been described in diabetic patients. Most studies show decreased chemotaxis and phagocytosis of diabetic polymorphonuclear cells, monocytes and macrophages. The defects in immunity in patients with diabetes were clearly stated in a study done by Geerlings and Hoepelman[8]: the decrease in complement factor 4, decrease in cytokine response after stimulation, decrease in chemotaxis, phagocytosis of polymorphonuclear cells, monocytes and macrophages, and increased adherence of microorganisms in diabetic cells .

Our patient had an enlarged prostate, which could have caused the development of lower urinary tract symptoms. Moreover, adherence of a microorganism to mucoepithelial cells in diabetic patients is an important step in the development of UTI. The patient's poorly cont-

rolled diabetes played a role in the pathogenesis because disturbances in cellular innate immunity could have led to septicemia. Lastly, the motor vehicular accident that caused the blunt chest trauma led to the development of a hematoma. All these factors (ie, the uncontrolled diabetes, UTI with bacteremia, and the hematoma) led to the development of our patient's chest wall abscess.

Hematoma formation and potential sources of bacteremia create opportunities for chest wall abscess. In our patient's case, the hematoma was identified as a site of secondary infection inoculated by coagulase-negative *Staphylococcus*. The case we reported demonstrates that an anterior chest hematoma caused by blunt chest trauma poses a risk of chest wall abscess in a patient with poorly controlled diabetes.

Literature review of primary chest wall abscess showed that 4 pathogens are responsible for the majority of cases: *Actinomyces* spp., *Staphylococcus aureus*, *Candida albicans* and *Salmonella* spp. *S. aureus* was the major causative organism in the previously reported cases of chest wall abscess caused by blunt chest trauma. In our case, blood cultures were positive for coagulase-negative *Staphylococcus*. However, culture of the abscess showed no growth of organism, probably because the patient was already on IV antibiotics for the treatment of HAP and UTI prior to the drainage.

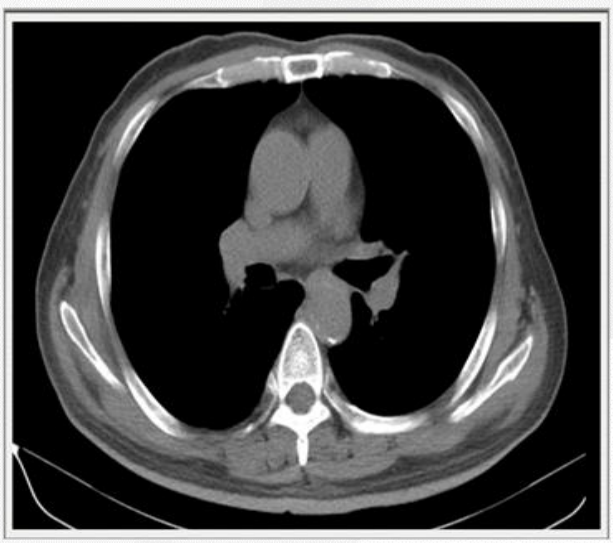

Figure 11. Repeat chest scan showing clearing of the abscess

Staphylococcus epidermidis is the most prevalent coagulase-negative species, accounting for approximately 60%–70%. They are commonly implicated as the causative agents in UTI, catheter-related infections, surgical wound infections, osteomyelitis, and native valve endocarditis.[9] Patients who are most at risk include surgical patients, those with foreign body placement and immunocompromised hosts.

Among the previously reported cases, the ancillary procedures commonly requested were CBC, which shows leukocytosis with predominance of stabs; erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) to document acute inflammation; and blood culture with susceptibility studies to find out if there is evidence of bacteremia. Blood chemistry tests such as blood urea nitrogen (BUN), creatinine, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) are used to check for liver and kidney involvement. Chest radiography looks for involved structures in the chest wall, mediastinum, and lung parenchyma. Chest CT scan is used to differentiate abscess from hematoma by comparing attenuation and the presence of discernible walls and air bubbles. Transthoracic echocardiography is requested in patients with bacteremia suspected of having endocarditis. Management includes IV antibiotics and early surgical drainage.

LEARNING POINTS

- Chest wall abscess is a rare clinical entity.
- Closed blunt chest trauma rarely causes chest wall abscess, but it can.
- Risk factors include an immunocompromised state, diabetes mellitus, previous trauma, and surgery.
- Treatment with IV antibiotics and surgical drainage is the mainstay of treatment.

RECOMMENDATIONS FOR PRACTICE AND RESEARCH

Chest wall abscess secondary to blunt trauma is rare. In our pulmonology practice, the chance of encountering such cases is very low. Nevertheless, we must still include chest wall abscess in our differential diagnosis whenever a similar case is encountered. Due to the rarity of chest wall abscess, the literature available is scarce. Thus we recommend filing case reports whenever such case is encountered.

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PROSPECTIVE STUDY

Prevalence of depression among COPD patients in Veterans Memorial Medical Center

Rei Paolo L. Diaz, MD, DPCP; Tito C. Atienza, MD, FPCP, FPCCP
Veterans Memorial Medical Center, Quezon City

ABSTRACT

Background: Depressive symptoms are common among patients with chronic obstructive pulmonary disease (COPD), but these conditions have not been fully investigated in Veterans Memorial Medical Center. The present study assessed depression in patients with COPD at Veterans Memorial Medical Center.

Objectives: The objective of this study is to determine the prevalence of depression, the association of the severity of depression with the severity of COPD, and the risk of depressive symptoms in patients with COPD at Veterans Memorial Medical Center.

Methods: This prospective cohort study enrolled 252 patients with COPD. Depression was evaluated using the Hospital Anxiety and Depression Scale (HADS). Body mass index, degree of airflow obstruction, and the numbers of exacerbations and hospitalizations were used to assess COPD severity. Multivariate logistic regression models were used to test the association between depression and the clinical profile of COPD.

Results: The prevalence of depression in patients with COPD was 54%. The patients who had more advanced ages, female sex, lower educational levels, lower household incomes, more family members, more advanced stages of COPD, and a history of smoking were more likely to suffer from depressive symptoms. Multivariate analyses showed that depression was significantly associated with more advanced stages of COPD.

Conclusion: This study confirmed that the prevalence of depression in patients with COPD at Veterans Memorial Medical Center is high and comparable to other reported cases. Patients with COPD who had depression had more advanced stages of COPD.

Keywords: depression, COPD, chronic obstructive pulmonary disease

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a largely preventable and treatable disease that is responsible for substantial human and economic burdens throughout the world.[1,2] It is currently the fourth leading cause of death in the United States and is expected to surpass stroke within the next decade to become the third leading cause of death.[2,3]

COPD consists of a number of conditions characterized by airflow inflammation and destruction of the pulmonary parenchyma. These processes lead to the clinical hallmarks of COPD, which are airflow limitation and dyspnea, or shortness of breath. Some patients will have sufficient destruction of alveoli to produce hypoxemia, which further contributes to dyspnea and to decreased exercise capacity.[4] The diagnosis

of COPD is based on the documentation of a post-bronchodilator forced expiratory volume in 1 second (FEV_1)/forced vital capacity (FVC) of 70%.[2,5,6]

Patients with COPD may have a spectrum of symptom severities ranging from short-term depressive symptoms to dysthymia (long-term chronic symptoms that are not disabling) to clinical depression.[2] A few studies have reported that approximately two-thirds of COPD patients with depression have moderate-to-severe depression. However, the prevalence of minor or subclinical depression may be even higher in this population, assuming that it is similar to other chronic illnesses.[2,7,8] In one study, it was reported that approximately one-fourth of COPD patients had unrecognized subclinical depression.[9] Such patients commonly have a high burden of physical disability and are at risk for major depression.[2]

Depression often appears in patients with COPD. Prevalence estimates vary widely, due in part to the use of varied measurement tools and to the different degrees of illness severity across studies.[2,10] In stable COPD, the prevalence of clinical depression ranges between 10% and 42%.[2,7,10-28,] The risk of depression is higher in patients with severe COPD, compared to control subjects,[2,11] with the highest rates (up to 62%) being found in oxygen-dependent patients.[2,16] In patients who have recently recovered from an acute exacerbation of COPD, the prevalence of depression is high and ranges between 19.4% and 50%.[2,29-34] In a systematic review of 64 studies that focused on patients with severe disease, the prevalence of depression ranged from 37% to 71%; these figures are comparable to, or higher than, prevalence rates in other advanced diseases such as cancer, AIDS, heart disease and renal disease.[2,35]

One of the most common but often unrecognized and thus least treated comorbidity of COPD is depression.[36,37] Increasing evidence suggests that depression may have direct effects on health status, hospitalization and exacerbation of COPD, rather than being consequences or markers of disease severity.[36-39]

Depression is often untreated or undertreated in patients with COPD.[2,40] In two studies, fewer than one-third of the patients were receiving appropriate treatment.[2,10,35] Untreated or incompletely treated depression has major implications in terms of reduced compliance with medical treatment, increased frequency of hospital admissions, prolonged length of stay, and more frequent consultations with primary care physicians.[2,10,25,29] Lack of treatment is also associated with poor quality of life and premature death.[2,9,29,40,41] Thus, detecting depression in patients with COPD is of great importance.

This study aims to determine the prevalence of depression among admitted patients and outpatients with COPD at Veterans Memorial Medical Center from September 2013 to September 2014; determine the association of the severity of depression in patients with COPD in terms of patient demographics, stage of COPD, number of exacerbations of COPD, and number of hospitalizations related to COPD; and determine the risk of depressive symptoms in patients with COPD.

METHODS

This is a prospective cohort study with a 6-month follow-up period, conducted from September 2013 to September 2014 in Veterans Memorial Medical Center. The study protocol was approved by the research ethics boards responsible for Veterans Memorial Medical Center, and written informed consent was obtained from all participants.

This number of participants appropriate for this study (ie, 252) was determined using a computation based on a 95% level of confidence with a relative error of 10%. The computation was based on "Anxiety and Depression in COPD" by Kunik et al,[2] which showed a 20% estimated prevalence of depression in patients with COPD.

All participants were seen in the wards and in the outpatient departments of Veterans Memorial Medical Center. Included in the study were patients aged 50–90 years; diagnosed with COPD using the standards of the Global Initiative for Chronic Obstructive Lung Disease (GOLD); and with no known psychiatric conditions, no primary diagnosis of asthma, and no previous lung volume reduction surgery, lung transplantation, or pneumonectomy. The subjects must also have voluntarily agreed to join the study by signing the informed consent form. Excluded from the study were patients with coexisting active pulmonary tuberculosis, pneumothorax, or lung cancer; inability to perform spirometry; physical or mental illness that made the patient incapacitated to participate in the study; or the presence of any condition that might have compromised the ability of the patient to sign the written informed consent.

General characteristics such as age, sex, education level, socioeconomic data, smoking status (ie, current, former, or never), duration of COPD, comorbidities, number of exacerbations that did not require hospitalization, previous hospitalizations for COPD exacerbation, participation in pulmonary rehabilitation, and home oxygen therapy were recorded based on patient reports. Subject weight and height were measured before carrying out pulmonary function tests, and body mass index (BMI) was calculated. Cigarette smoking was measured in pack years.

Tobacco smoking is established as a major risk factor for COPD, but emerging evidence suggests that other risk factors are important, especially in developing countries. An estimated 25%–45% of patients with COPD have never smoked. The burden of non-smoking COPD is therefore much higher than previously believed. Risk factors associated with COPD, aside from tobacco smoking, are biomass fuel, occupational exposure to dusts and gases, history of pulmonary tuberculosis, respiratory tract infections during childhood, outdoor air pollution, and poor socioeconomic status.[42-50] In this study, non-smokers were included because other risk factors for COPD mentioned above were present in the patients enrolled.

Depression was measured using the Hospital Anxiety and Depression Scale (HADS).[37,51] The HADS was specifically developed for the detection of anxiety and depression in patients with somatic conditions. It is a validated screening tool for symptom severity in cases of anxiety and depression in patients with chronic diseases, including COPD.[37-39] It is divided into an anxiety subscale (HADS-A) and a depression subscale (HADS-D), both containing 7 items rated 0–3, thus giving a possible maximum score of 21 for anxiety and depression. Scores <8 indicate no clinical distress; scores 8–10 indicate possible psychiatric morbidity; and scores ≥11 indicate probable pathologic levels of distress.[37,51]

Spirometry and bronchodilator response tests were carried out by respiratory therapists at Veterans Memorial Medical Center. The tests were performed and interpreted according to the standardized guidelines of the American Thoracic Society (ATS).[37,52] Patients carried out the pulmonary function test at least 12 hours after the withdrawal of long-acting inhaled bronchodilators and without the use of any short-acting bronchodilators within the last 4 hours. Patients then performed post-bronchodilator spirometry 15 minutes after inhaling salbutamol (200 µg). GOLD classification was for the diagnosis of COPD in which the documentation of a post-bronchodilator is $FEV_1/FVC \leq 70\%$. The same classification was used for COPD stages and was defined as described in the updated GOLD, the 2014 edition. For patients who already had their spirometry 12 months prior to recruitment, the results of the said test were assessed and repeat spirometry was no longer done.

Patients were monitored through 6 monthly consultations to document the occurrence and characteristics of COPD exacerbations or hospitalizations. At each consultation, patients were asked questions about their history, including medical interventions and changes in respiratory

symptoms in the past month. Patients were also encouraged to report to the investigator whenever they experienced worsening symptoms. A symptom-based exacerbation was confirmed if the patient experienced the worsening of at least 1 of 3 key symptoms (ie, increased frequency of cough, increased sputum production or change in sputum character, and increased dyspnea) for at least 48 hours. An event-based exacerbation was confirmed if the patient experienced the worsening of at least 1 key symptom, plus a change in at least 1 of 2 medications (eg, use of antibiotics and/or use of systemic corticosteroids for at least 5 days). The numbers of event-based exacerbations and hospital admissions were recorded.[38,53]

The computer-based analysis program Statistical Package for Social Science (SPSS) version 13.0 was used for all calculations. The minimal statistical significance level for all analyses was $P<0.05$. Group comparisons for categorical variables were performed using Pearson's chi-square test or Fisher's exact test. To evaluate the risk factors for depression, multivariate logistic regression analysis was performed, incorporating all factors that obtained values of $P<0.05$ in the bivariate analysis.

RESULTS

Out of the 252 enrolled patients with COPD, 135 (54%) had HADS–D scores >8, suggesting that these patients had probable depressive symptoms or clinical depression. Thirty-six from this subgroup had HADS-D scores >10; this suggests that about 14% of our total enrolled patients suffered from clinical depression. These COPD patients with depressive symptoms had more frequent exacerbations and hospitalizations than the COPD patients with no depressive symptoms or who had HADS-D scores <8 (Table 1). We also found that increased disease severity (according to the GOLD stages) was correlated with increased frequency of depressive symptoms (Table 2).

Gender, educational attainment, smoking status, family size, and level of income all were significantly associated with the patients' severity of depression (Table 1). A larger percentage of females than males had a HADS-D score ≥11. A higher HADS-D score (ie, ≥11) correlated most with patients whose highest educational attainment was only elementary education. Patients whose highest level of education was high school had HADS-D scores between 8 and 10, and college graduates tended to have HADS-D scores ≤8. Past smokers tended to obtain HADS-D scores ≥8, while those who had never smoked were more likely to obtain a HADS-D score ≤7. Those with ≤5 family members tended to obtain a HADS-D score of 8–10, while those with >5 members in the family tended to obtain a HADS-D score ≥11. Those with lower income level tended to obtain a HADS-D score ≥11, while those with higher income levels were more likely to obtain a HADS-D score ≤7.

Those with FEV1 ≤49 were more likely obtain a HADS-D score >8, while those with FEV_1 ≥50 were more likely to have a HADS-D score <8 ($p<0.001$). Those with <2 reported exacerbations per year were more likely to obtain a HADS-D score ≤7, while those who reported ≥2 exacerbations per year were more likely to have a HADS-D score ≥11 ($p<0.001$). Those with <1 hospitalization per year were more likely to have a HADS-D score ≤7, while those who ≥1 hospitalization per year were more likely to have a HADS-D score ≥11 ($P<0.001$). On the other hand, the *P*-value of 0.811 suggests that BMI does not affect depression level.

The *P*-value of 0.014 suggests that COPD stage B significantly affects the level of depression. The odds ratio (OR) of 0.014 indicates that the occurrence of COPD stage B decreases the likelihood of having a HADS-D score >7 by 71.4 times.

On the other hand, the *P*-value of 0.059 is only significant at 10% level, which suggests that the presence of COPD stage C significantly increases the chance of having a HADS-D score >7 by 1.624 times, compared to other stages of COPD. The presence of COPD stage D was found to be non-significant since all who had COPD stage D had >7 HADS-D scores. In summary, results showed that as COPD stages go from B to D, the chance of HADS-D scores >7 increases as well.

The *P*-value of <0.001suggest that age is significantly related to the occurrence of HADS-D score >7. Specifically, results showed that those aged 50–79 years were more likely to have decreased occurrence of higher depression scores (HADS-D ≥8): by 13 times, for 50–59 years; 18 times, 60–69 years; and 16 times, 70–79 years. On the other hand, results showed that those who are ≥80 years old had

Table 1. Association of Demographic Characteristics of Patients with COPD with Level of Depression

	HADS-D Score			P-value
	≤7 (n=117)	8–10 (n=99)	≥11 (n=36)	
Gender (n, %)				
Female	37 (31.6)	38 (38.4)	20 (55.6)	0.034
Male	80 (68.4)	61 (61.6)	16 (44.4)	
Educational attainment (n, %)				
Elementary	19 (16.2)	28 (28.3)	25 (69.4)	<0.001
High school	37 (31.6)	62 (62.6)	10 (27.8)	
College	61 (52.1)	9 (9.1)	1 (2.8)	
Smoking status (n, %)				
Smoker	75 (64.1)	82 (82.8)	28 (77.8)	0.007
Non-smoker	42 (35.9)	17 (17.2)	8 (22.2)	
Current smoker	0	0	0	
No. of family members (n, %)				
<2	3 (2.6)	9 (9.1)	2 (5.6)	0.012
3–5	52 (44.4)	52 (52.5)	10 (27.8)	
6–8	45 (38.5)	20 (20.2)	16 (44.4)	
≥9	17 (14.5)	18 (18.2)	8 (22.2)	
Monthly family income, ₱				
<5,000	10 (8.5)	0	1 (2.8)	<0.001
5,000–10,000	18 (15.4)	50 (50.5)	19 (52.8)	
11,000–15,000	20 (17.1)	20 (20.2)	2 (5.6)	
16,000–20,000	27 (23.1)	18 (18.2)	2 (5.6)	
>20,000	42 (35.9)	11 (11.1)	2 (5.6)	
BMI, kg/m^2				
<18.5	17 (14.5)	12 (12.1)	4 (11.1)	0.811
Normal	91 (77.8)	85 (85.9)	32 (88.9)	
>25	9 (7.7)	2 (2.0)	0	
FEV1, %				
<30	0	10 (10.1)	19 (52.8)	<0.001
30–49	45 (38.5)	52 (52.5)	9 (25.0)	
50–79	72 (61.5)	37 (37.4)	8 (22.2)	
>80	0	0	0	
Exacerbations per year				
<2	97 (82.9)	44 (44.4)	9 (25.0)	<0.001
≥2	20 (17.1)	55 (55.6)	27 (75.0)	
Hospitalization per year				
<1	101 (86.3)	52 (52.5)	8 (22.2)	<0.001
≥1	16 (13.7)	47 (47.5)	28 (77.8)	

BMI, body mass index; COPD, chronic obstructive pulmonary disorder; FEV1, forced expiratory volume in 1 second; HADS-D, Hospital Anxiety and Depression Scale - Depression.

Table 2A. Association of COPD Stages with Level of Depression

	HADS-D Score		
	≤7 (n=117)	8–10 (n=99)	≥11 (n=36)
COPD A	0	0	0
COPD B	74 (63.2)	3 (3.0)	0
COPD C	43 (36.8)	52 (52.5)	16 (44.4)
COPD D	0	44 (44.4)	20 (55.6)

COPD, chronic obstructive pulmonary disorder; HADS-D, Hospital Anxiety and Depression Scale - Depression.

Table 2B. Odds Ratio of Depression with COPD Stages

Factors	**Depression**		
	Odds Ratio	95% CI	P-value
COPD A	-	-	-
COPD B	0.014	0.004, 0.047	0.014
COPD C	1.624	0.982, 2.684	0.059
COPD D	-	-	0.997

CI, confidence interval; COPD, chronic obstructive pulmonary disorder.

8.556 times more chance of having HADS-D ≥8. Educational attainment also turned out to be a significant factor, where being an elementary graduate increased one's chance of obtaining HADS-D of ≥8 by 17 times, while being a high school graduate increased the probability by 11.87 times. Those who reached college level were more likely to have decreased occurrence of depression by 6.10 times. Moreover, results showed that past smokers had 2.464 times increased chances of having HADS-D ≥8.

Those with FEV1 ≤49 were more likely obtain a HADS-D score >8, while those with FEV_1 ≥50 were more likely to have a HADS-D score <8 ($p<0.001$). Those with <2 reported exacerbations per year were more likely to obtain a HADS-D score ≤7, while those who reported ≥2 exacerbations per year were more likely to have a HADS-D score ≥11 ($p<0.001$). Those with <1 hospitalization per year were more likely to have a HADS-D score ≤7, while those who ≥1 hospitalization per year were more likely to have a HADS-D score ≥11 ($P<0.001$). On the other hand, the *P*-value of 0.811 suggests that BMI does not affect depression level.

The *P*-value of 0.014 suggests that COPD stage B significantly affects the level of depression. The odds ratio (OR) of 0.014 indicates that the occurrence of COPD stage B decreases the likelihood of having a HADS-D score >7 by 71.4 times.

On the other hand, the *P*-value of 0.059 is only significant at 10% level, which suggests that the presence of COPD stage C significantly increases the chance of having a HADS-D score >7 by 1.624 times, compared to other stages of COPD. The presence of COPD stage D was found to be non-significant since all who had COPD stage D had >7 HADS-D scores. In summary, results showed that as COPD stages go from B to D, the chance of HADS-D scores >7 increases as well.

The *P*-value of <0.001suggest that age is significantly related to the occurrence of HADS-

Table 3. Risk of Depressive Symptoms in Patients with COPD, Multivariate Logistic Modeling

Factors	Depression		P-value
	OR	95% CI	
Age, y			<0.001
50–59	0.076	0.03, 0.192	<0.001
60–69	0.055	0.023, 0.129	<0.001
70–79	0.063	0.026, 0.154	<0.001
≥80	8.556	-	<0.001
Female gender	1.629	0.971, 2.733	0.065
Educational attainment			<0.001
Elementary	17.016	7.276, 39.794	<0.001
High school	11.87	25.827	<0.001
College	0.164	-	<0.001
Smoking	2.464	1.386, 4.381	0.002
No. of family members			0.086
<2	2.397	0.582, 9.873	0.226
3–5	0.78	0.382, 1.592	0.494
6–8	0.523	0.247, 1.11	0.091
≥9	1.529	-	0.173
Monthly family income, ₱			<0.001
<10,000	4.565	2.333, 8.933	<0.001
10,000–15,000	2.009	0.911, 4.429	0.084
15,001–20,000	1.353	0.626, 2.921	0.442
≥20,000	0.548	-	0.020
BMI, kg/m^2			0.069
<18.5	4.235	0.791, 22.665	0.092
Normal	5.786	1.22, 27.436	0.027
>25	0.222	-	0.054
FEV, %	3.2	1.909, 5.364	<0.001
Exacerbation >2 per yr	0.133	0.074, 0.241	<0.001
Hospitalization >1/y	0.127	0.068, 0.237	<0.001

BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disorder; FEV, forced expiratory volume.

D score >7. Specifically, results showed that those aged 50–79 years were more likely to have decreased occurrence of higher depression scores (HADS-D ≥8): by 13 times, for 50–59 years; 18 times, 60–69 years; and 16 times, 70–79 years. On the other hand, results showed that those who are ≥80 years old had 8.556 times more chance of having HADS-D ≥8. Educational attainment also turned out to be a significant factor, where being an elementary graduate increased one's chance of obtaining HADS-D ≥8 by 17 times, while being a high school graduate increased the probability by 11.87 times. Those who reached college level were more likely to have decreased occurrence of depression by 6.10 times. Moreover, results showed that past smokers had 2.464 times increased chances of having HADS-D ≥8.

Results also showed that income was one of the significant factors, where those with an income less than ₱10,000 were 4.565 times more likely to have higher depression scores (HADS-D ≥8), while those whose income was above ₱20,000 were more likely to have lower probability of obtaining a higher depression score (HADS-D ≥8) by 1.82 times. Lastly, FEV1, exacerbations and hospitalizations also turned out to be significant factors affecting the level of depression score, where FEV1 ≤50 increased the chance of having HADS-D ≥8 by 3.20. Moreover, those with <2 exacerbations per year

were 7.52 times more likely to have decreased chances of having HADS-D ≥8, while <1 hospitalization per year also decreased the probability of higher HADS-D score by 7.87. Gender, size of family and BMI turned out to be non-significant in affecting the chances of higher HADS-D scores.

DISCUSSION

The present study found the prevalence of depressive symptoms among patients with COPD in Veterans Memorial Medical Center (54%) was comparable to previous reported cases. Previous studies have reported depressive symptoms ranging from 22.8% to 57%, using the HADS as their screening tool.[10,37] The average age of patients in the previous studies were ≥60 years, which is comparable to the ages of patients in this study. We observed that the prevalence of depressive symptoms increased with the GOLD stage, as established in previous studies.[37,54-56] These corresponding increases suggest that when the physician detects greater severity of COPD, they should consider giving psychiatric intervention along with medical treatment.

The present study showed correlation between depressive symptoms and age, sex, education level, household income, number of family members and history of smoking. This is partially consistent with the results of previous studies.[10,37,56-58] Every physician therefore needs to be aware that depression is a common condition among COPD patients. The present results showed that patients who were older, female, with lower education levels, lower household incomes, more family members, and a history of smoking suffered from depressive symptoms more frequently. A previous study has reported susceptibility to depression among female patients with COPD.[37,57] Consistent with this result, our data confirmed that the frequency of depression in female patients with COPD differed significantly from that in male patients. The increase in depression with lower educational levels could be due to the patients' lower degree of understanding of COPD. The COPD patients with low family income tended to suffer from depression; this is likely due to the burden of additional costs for their medications and consultations. Patients with a higher degree of airflow limitation reported more symptoms of depression, and pulmonary function was found to be a predictor of depression.[11,37] In our study, lower FEV_1, more frequent exacerbations, and hospitalizations related to COPD showed higher frequencies of depressive symptoms.

CONCLUSION

Patients with COPD are at an increased risk for depressive symptoms. Patients who are older, female, with lower education levels, lower household incomes, more family members, more advanced stages of COPD, and a history of smoking are more likely to suffer from depressive symptoms. The present study adds evidence with regard to the usefulness of the HADS in assessing how depressive symptoms affect the health outcomes of patients with COPD. The HADS should be included when assessing COPD severity, given that anxiety and depression are significant but treatable comorbidities of COPD. Our findings show the importance of screening for depressive symptoms in patients with COPD – particularly those with older ages, female sex, lower education levels, lower household income, advancing stages of COPD, and a history of smoking – so as to provide adequate patient care. Further studies are needed to shed greater light on the effectiveness of treating depressive symptoms among these patients and the efficacy of screening for identifying those who might benefit from specific therapy.

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A

CROSS-SECTIONAL ANALYTIC STUDY

The association between the level of COPD severity and hyperinflation

Bernadette E. Magnaye, MD, DPCP; Aileen Guzman-Banzon, MD, FPCP, FPCCP; Ma. Encarnita Limpin, MD, FPCP, FPCCP; Fernando G. Ayuayo, MD, FPCP, FPCCP
Philippine Heart Center, Quezon City

ABSTRACT

Background: Recent studies have shown that most of the decline in lung function of chronic obstructive pulmonary disease occurs in milder disease. Early intervention could prevent progressive functional deterioration, interrupt the symptoms' vicious cycle, and lower the threshold for initiating treatments appropriate to the stage of the disease.

Methodology: This is a cross-sectional analytic study among COPD patients diagnosed by pulmonary function test with post-bronchodilator study FEV1/forced vital capacity (FVC) ratio <0.70 consistent with airflow obstruction. Lung volume study was done among those who had not had lung volume study.

Results: Fifty-nine patients were included in the study. They had a mean age of 63 years, a mean height of 160 cm, and a mean weight of 66 kg. Eighty percent were male, and 95% had a smoking history with 31 mean pack years. Mean TLC was correlated with all Global Initiative for Chronic Obstructive Lung Disease (GOLD) stages: GOLD 1 (93), GOLD 2 (120.7±104.4), GOLD 3 (94.2±23.4) and GOLD 4 (54); P=0.5506. The mean RV was correlated with all GOLD stages: GOLD 1 (99), GOLD 2 (174.61±228.8), GOLD 3 (139.28±42.7) and GOLD 4 (134); P=0.8695. The mean RV/TLC ratio was correlated with all GOLD stages: GOLD 1 (28), GOLD 2 (50.42±11.4), GOLD 3 (54.36±8.8) and GOLD 4 (66); P=0.0348.

Conclusion: This study has shown good association of lung volume study, specifically, RV/TLC ratio, among the different levels of COPD severity and has established the presence of hyperinflation.

Keywords: COPD, hyperinflation, TLC, RV, RV/TLC

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is an inflammatory airway disease comprised of airway inflammation, mucociliary dysfunction and consequent airway structural changes. It is characterized by chronic inflammation of the airways, the lung tissues and pulmonary blood vessels. This is a result of exposure to inhaled irritants such as tobacco smoke.[1] These irritants cause inflammatory cells such as neutrophils, $CD8^+$ T-lymphocytes, B-cells and macrophages to accumulate.[2] These inflammatory mediators sustain the inflammatory process and lead to tissue damage, as well as a range of systemic effects. Chronic inflammation is present from the outset of the disease and leads to various structural changes in the lungs; this further perpetuates airflow limitation and results in persist-

ent expiratory airflow limitation and, often, hyperinflation, which, along with gas exchange abnormalities, interacts to cause dyspnea and functional limitation.

During exercise, respiratory rate increases to accommodate increased respiratory demands. This hyperpnea induces phasic activity of expiratory muscles in both healthy individuals and in those with COPD.[3] The combined effects of decreased lung elastic recoil pressure and increased airways resistance in patients with COPD result in an increased mechanical time constant for lung emptying in many alveolar units. Thus, as the respiratory rate and expiratory flow increases, the expiratory time available for exhalation can become insufficient, complete exhalation of the inhaled air to the relaxation volume becomes increasingly compromised, and end expiratory lung volume usually increases with hyperpnea. In addition, similar to healthy subjects, patients with COPD recruit expiratory muscles to increase their pleural and alveolar pressures in an effort to increase expiratory flow.[2] However, in COPD patients, the airways typically collapse when the pleural pressure becomes positive, thereby preventing increased expiratory flow. As a result, exhalation may not be completed prior to the onset of the next breath, causing an increase in operational lung volumes and progressive air retention called air trapping.

Spirometry is a widely available tool that quantifies the abnormalities in COPD and can be fundamental in diagnosing, monitoring and establishing the prognoses of individuals with this condition. The presence of a post-bronchodilator forced expiratory volume in 1 second (FEV_1)/forced vital capacity (FVC) ratio of <0.70 confirms the clinical diagnosis of COPD. Severity is measured on the basis of FEV_1 as mentioned in the Global Initiative for Chronic Obstructive Lung Diseases (GOLD) criteria of COPD.[4] Lung volumes are very useful in detecting and physiologically characterizing the nature of lung diseases. An absolute increase in lung volume measurements such as total lung capacity (TLC), functional residual capacity (FRC) and residual volume (RV) provides an insight into the extent of airway and parenchymal abnormalities in COPD. Hyperinflation implies an abnormal increase in the volume of gas in the lungs at the end of tidal (functional residual capacity [FRC]) or maximal (residual volume [RV]) expiration; moreover, it is sometimes inferred from an increase in the RV/TLC (Motley index), commonly used as a surrogate of air trapping.[5] This study hopes to correlate the association between the level of COPD severity and lung volume changes as a measure of hyperinflation.

METHODOLOGY

This was a cross-sectional, analytic study conducted at the pulmonary laboratory of the Philippine Heart Center (PHC) from October 2014 to October 2015. Enrolled in the study were all diagnosed COPD patients who were referred for pulmonary function test (PFT) at PHC's pulmonary laboratory, as well as all those in an outpatient basis, who met the following criteria: (1) had a post-bronchodilator study FEV1/FVC ratio of <0.70 and FEV_1 consistent with airflow obstruction, and (2) had PFT done at the pulmonary laboratory of PHC. Patients with any of the following diseases that might interfere with the test performance were excluded from the study: unstable cardiovascular status or recent myocardial infarction; recent pulmonary embolism; thoracic, abdominal or cerebral aneurysm; recent surgery of the thorax or abdomen; hemoptysis of unknown origin; or presence of an acute disease process and malignancy.

Lung volume study was done among those who had not had lung volume study. Patients from the outpatient department were recruited and a basic spirometric examination was performed. The subjects signed an informed consent document. Demographic characteristics such as age, sex, occupation, height, recognized

risk factor (eg, exposure to biomass fuel) and smoking history were obtained.

Spirometric tests with lung volume study were performed by a single respiratory specialist using the Vmax System™ (SensorMedics a subsidiary of VIASYS healthcare), with airglow measured by calibrated Pneumotach™; Version IVS-0101-12-2A. The subjects completed at least 3 acceptable maximal forced and expiratory slow maneuvers, with "acceptable" being defined as when the flow volume loop (FVL) ECode is 0000 and the variability from one breath to the other is ≤10%. To assess improved ventilatory conditions, the patients were tested 20 minutes after inhalation of 2.5 mg salbutamol. The subjects performed two acceptable and reproducible tests. TLC, RV and RV/TLC were obtained by constant-volume different-pressure body plethysmography and expressed as a percentage of the predicted value according to Morris/Polgar standard PF reference. TLC, RV and RV/TLC value in liters were obtained, and the ratio was computed, expressed in percentage. TLC, RV and RV/TLC with hyperinflation were associated with the different levels of COPD severity, based on GOLD criteria in reference to FEV_1.

Sample size was computed using Epi Info version 7. The minimum sample size required was 66, based on the following parameters: 95% level of confidence, maximum tolerable error of 10%, and percent hyperinflation among COPD patients of 22%.

Data analysis was done using Stata SE version 12. Descriptive statistics include mean and standard deviation (SD) for quantitative variables, and frequency and percent distribution for qualitative variables. Comparison of lung volume studies across different severities of COPD was done using analysis of variance (ANOVA). Multiple comparison procedures were done when the result of ANOVA was significant. The level of significance was set at P=0.05.

This study complies with the ethical principles set forth in the Declaration of Helsinki. The study protocol and informed consent document were reviewed and approved by PHC's Institutional Ethics Review Board (IERB). Prior to any subject's participation, an investigator adequately explained the aims, methods, anticipated benefits and potential risks of the study and obtained a written informed consent afterward. The informed consent was signed and personally dated by both the subject and the investigator who conducted the informed consent discussion. One copy of the informed consent document was given to the subject. The investigators preserved the confidentiality of all subjects taking part in the study and ensured that the subjects' anonymity was maintained.

RESULTS

Fifty-nine patients were included in the study. Eighty percent of them were male. The group had a mean age of 63 years, a mean height of 160 cm, and a mean weight of 66 kg. Ninety-five percent of the patients had smoking history, with a total of 31 mean pack years.

Table 1. Baseline Characteristics of Patients Included in the Study

Characteristic	Mean±SD	n (%)
Gender		
Male		47 (80)
Female		12 (20)
Smoking history, PY	30.51±22.1	56 (95)
No smoking history	NA	3 (5)
Age (years)	62.57±9.4	59 (100)
Height (cm)	159.67±9.1	59 (100)
Weight (kg)	66.0±16.7	59 (100)

Table 2 shows that mean TLC is correlated with all GOLD stages: GOLD 1 (93), GOLD 2 (120.7 ± 104.4), GOLD 3 (94.2 ± 23.4) and GOLD 4 (54); P=0.5506. The mean RV was correlated with all GOLD stages: GOLD 1 (99), GOLD 2 (174.61 ± 228.8), GOLD 3 (139.28 ± 42.7) and GOLD 4 (134); P=0.8695.

The mean RV/TLC ratio was correlated with all GOLD stages: GOLD 1 (28), GOLD 2 (50.42±11.4), GOLD 3 (54.36 ±8.8) and GOLD 4 (66); *P*=0.0348, which is statistically significant.

DISCUSSION

The degree of airflow limitation can be assessed by more complex spirometric indexes such as TLC, RV or RV/TLC ratio. TLC seems to remain unaltered during exercise in patients with moderate to severe COPD; however, in early COPD, simultaneous increases in TLC allow ventilation to increase to meet higher demands by ventilation perfusion inequalities.

The mean TLC and RV as shown in Table 2 were not statistically significant in correlation with hyperinflation to the different levels of COPD severity. There is, however, a statistically significant association of hyperinflation at all COPD levels using RV/TLC ratio, or the Motley index, with a *P*-value of 0.0348. Moreover, due to increased elastic and resistive loads, left ventricular dysfunction may develop, increasing left ventricular afterload. Right ventricular afterload is also increased because of the pulmonary vascular resistance associated with breathing at lung volumes close to TLC. In one study, RV/TLC was also a prognostic factor for survival at 5 years but not independent of age and FEV_1.

The therapeutic intervention that effectively reduces lung hyperinflation should reduce dyspnea and improve exercise endurance, and this has been shown to correlate well with reduction in the simultaneous operating lung volumes.

LIMITATION OF THE STUDY

The number of subjects in the GOLD 1 (mild) and GOLD 4 (very severe) COPD groups were limited because patients in GOLD 1 might not seek consultation at once even when symptoms of the disease are observed, while those in GOLD 4 were symptom limited and refused to perform a repeat pulmonary function test.

CONCLUSION

This study has shown a good association of lung volume study, specifically, RV/TLC ratio, among the different levels of COPD severity and established the presence of hyperinflation.

DISCLOSURE

The authors have no conflict of interest in this study.

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Table 2. Correlation of Lung Volumes and COPD Severity Using GOLD Criteria

	GOLD 1[a]	GOLD 2[b]	GOLD 3[c]	GOLD 4[d]	P-value
Mean TLC	93	120.7±104.4	94.2±23.4	54	0.5506
Mean RV	99	174.61±228.8	139.28±42.7	134	0.8695
Mean RV/TLC ratio	28	50.42±11.4	54.36±8.8	66	0.0348

COPD, chronic obstructive pulmonary disorder; GOLD, Global Initiative for Chronic Obstructive Lung Disease; RV, residual volume; TLC, total lung capacity.

[a]Mild: FEV_1 ≥80% predicted. [b]Moderate: FEV_1 50%–79% predicted. [c]Severe: FEV_1 30%–49% predicted. [d]Very severe: FEV_1 <30% predicted.

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CROSS-SECTIONAL STUDY

Comparative study on the clinical profile, treatment response and level of asthma control between elderly and adult asthmatic patients seen at the asthma clinic–OPD of the Lung Center of the Philippines

Jessica P. Catalan, MD; Dina V. Diaz, MD, FPCCP
Lung Center of the Philippines, Quezon City

ABSTRACT

Objective: To compare the clinical profile, treatment response and level of asthma control between elderly asthmatic patients and adult asthmatic patients seen at the asthma clinic–outpatient department of the Lung Center of the Philippines (LCP).

Methods: This is an observational cross-sectional study performed among 102 elderly and adult asthmatics at the asthma clinic of the LCP. The authors determined baseline characteristics, spirometric results, and treatment response through comprehensive chart reviews and interviews. The levels of asthma control between the two groups were evaluated using the Asthma Control Test (Filipino version) questionnaire.

Results: This study found significant differences between the adult asthmatic group and the elderly asthmatic group in terms of age of asthma onset (mean: 29.3 vs 39.3, p=0.03) and family history of atopy (19.6%, p<0.01, adult group). The authors found no significant differences in spirometric measurements, treatment response and level of asthma control between the adult and the elderly groups. A high proportion of uncontrolled asthma was noted among both the adult and the elderly asthmatics, at 31.3% and 39.3%, respectively.

Conclusions: Adult asthmatics had earlier asthma onset compared with elderly asthmatics. Around one third of patients, whether adult or elderly, had uncontrolled asthma.

Keywords: asthma, asthmatics, asthma control test, elderly, spirometry, treatment response

Asthma is a heterogeneous disease characterized by chronic airway inflammation. It is defined by a history of respiratory symptoms (eg, wheezing, shortness of breath, chest tightness and cough that vary over time and intensity) that are associated with variable expiratory airflow.[1]

It is often said that bronchial asthma is a disease of younger people, but as the population ages, asthma's prevalence among older people also increases. The mortality and morbidity rates suggest that older people suffer disproportionately from the burden of asthma and airways diseases. The reasons often relate to the pulmonary changes associated with aging, perceptions of dyspnea, difficulties in asthma diagnosis, the burden of medications, and the

presence of comorbidities.[2]

The prevalence of asthma among the elderly is similar to the non-elderly adult population, but in most situations, the disease is underdiagnosed and undertreated in this cohort. Underdiagnosis may occur because of an age-related reduction in perception of shortness of breath,[3] while the undertreatment may be due to side effects of medications, effects of concomitant medications, and the cost of medicines.

Based on 2001–2010 data from the National Health Interview Survey (NHIS), the estimated average annual prevalence of asthma among the US elderly is approximately 7%.[4] In the 2014 global burden of asthma report of the Global Initiative for Asthma (GINA), the prevalence of asthma in different countries ranged from 1% to 18% of the population.[1,5,6]

The asthma of most adults is reasonably controlled with a simple regimen of inhaled drugs. Mild-to-moderate asthma can be controlled with beta-agonists with or without usual or low doses of anti-inflammatory agents. Emergency department visits and hospitalization for asthma seem to be related to several psychosocial factors such as lower socioeconomic status, inaccessibility of medical care and coexisting diseases.[3] The coexistence of comorbidities is now recognized as an integral part of the core management of asthma**.** The clinical disease of elderly asthmatics is more severe and more frequently associated with comorbidities than that of their non-elderly adult counterparts. In addition, medication strategies for asthma have been dominantly derived from studies focused on younger cohorts, so effective medication strategies have not been well explored among the elderly.[7]

Overall, asthma in the elderly is associated with significant morbidity and mortality, hence requires careful monitoring. Usually, people with asthma who are over 65 years old have fewer asthmatic symptoms and are less likely to report these symptoms and present themselves to medical care. The current controversies in the management of asthma in the elderly relate to the utility of asthma management education and the effectiveness of current treatment algorithms, which were dominantly derived from younger age groups.

This study identifies unmet needs for the management of asthma in the elderly. Its objective is to compare the clinical profile, treatment response and level of asthma control of elderly asthmatic patients with that of non-elderly adult asthmatic patients who were seen at the asthma clinic–outpatient department (OPD) of the Lung Center of the Philippines (LCP).

METHODOLOGY

This observational cross-sectional study includes asthmatic patients who sought consult at the asthma clinic–OPD of LCP, aged 18–59 years old (classified as "adult") or 60 years old and above (classified as "elderly"), who were diagnosed with bronchial asthma with corresponding spirometric results. The following were excluded from the study: asthmatic patients with concomitant lung diseases such as chronic obstructive pulmonary disorder (COPD), cystic fibrosis, restrictive lung diseases, pulmonary tuberculosis and bronchiectasis; asthmatic patients with unstable cardiac diseases such as congestive heart failure and arrhythmia; andanyone with a history of smoking.

We used the outpatient logbook to identify adult patients and elderly patients who were scheduled for follow-up at the asthma clinic. One week before each scheduled follow-up, we collected each patient's chart from the medical records section and screened the patient based on the inclusion and exclusion criteria. A comprehensive review of each patient's chart provided baseline characteristics and clinical profile. On the day of the patient's follow-up visit at the asthma clinic, we evaluated those who met the inclus-

-ion criteria and who signed the informed consent form. After each follow-up, we interviewed the patients to collect information that was not present in the outpatient chart. We also administered the Asthma Control Test (ACT) questionnaire. Each session lasted between 30 minutes and 1 hour.

Parameters such as demographic profile; family and personal history, including atopy; course of respiratory symptoms and age of onset were determined during the chart reviews and interviews. We identified medications, comorbidities, and histories of exacerbation and admissions, to identify treatment response. The levels of asthma control were measured by administering the ACT–Filipino version.

Sample size determination and analysis of data

Basing from a US study that reported the estimated prevalence of asthma in the elderly as 7.0% and using the z-value of 1.96 from the standard normal distribution corresponding to the desired confidence interval (CI) of 95% and 0.075 desired precision, we computed the required sample size to be 51. The chi-square test of independence was used to compare the 2 groups at 5% level of significance.

RESULTS

One hundred two patients were included in the study. The mean age of elderly asthmatic patients was 66 years, while for adult asthmatic patients, the mean age was 52 years. There were significant differences in the weight, body mass index (BMI) and mean age of onset between the two groups. Adult asthmatic patients had significantly higher weights and BMIs than elderly patients. Elderly patients have a significantly later onset of asthma, at 39.3 years of age (vs 29.3, $p<0.05$) (Table 1).

Gender distribution, history of smoking or alcohol consumption, duration of asthma, personal history of atopy, history of pneumonia, personal history of atopy, history of pneumonia, use of steroids, medication for asthma and history of environmental exposure were statistically the same between the two groups. A significantly higher proportion among the elderly (49% vs 26%, $p=0.025$) had hypertension. All in all, 53% of elderly patients had at least one comorbid condition; among adult patients, comorbid conditions were present only in 29% of the cohort ($p=0.027$). Family history of atopy was significantly higher in the adult group than in the elderly group (18% vs 6%, $p=0.075$) (Table 2).

Spirometry results between the two groups revealed no significant difference. However, elderly asthmatic patients had lower forced expired volume in 1 second (FEV1) and forced vital capacity (FVC) as compared with their adult counterparts. The degrees of change in pre- and post-bronchodilator were similar between the groups (Table 3).

We found no significant difference in the histories of exacerbation, admissions and intubation between the two groups (Table 4).

The ACT 2010 Filipino-version questionnaire showed no significant difference in the ACT scores and levels of asthma control (ie, uncontrolled, partially controlled, or controlled) between the two groups. More adult and elderly asthmatics had partially controlled asthma (47%, 49%) or uncontrolled asthma (31.3%, 39.2%) than controlled asthma, based on ACT scores (Table 5).

DISCUSSION

The results showed that the demographic characteristics, duration of asthma, personal history of atopy, history of pneumonia, use of steroids, medication for asthma and history of environmental exposure were statistically the same for adult

Table 1. Mean age, corresponding anthropometric measurements and age of onset among asthmatic patients

Profile	Adult (n=51)		Elderly (n=51)		p-value
	Mean	SD	Mean	SD	
Age (yr)	52.02	6.28	66.12	5.63	<0.001
Weight (kg)	57.71	10.00	53.35	9.89	0.029
Height (cm)	155.41	5.27	155.33	6.22	0.945
Body mass index (kg/m^2)	23.96	4.46	22.06	3.99	0.025
Age of onset (years)	29.3	5.53	39.3	6.33	0.03

and elderly asthmatic patients. Among the 102 patients in this study, the mean age for adult patients was 52 years old, while for the elderly asthmatic patients, it was 66 years old. This means we can predict an increasing number of elderly asthmatics in 10 years time.

The elderly group had a significantly higher mean age of asthma onset (39±6 vs 29±6, p=0.03), while the adult group had a significantly higher family history of atopy (20% vs 6%, p <0.01). Atopy plays a critical role in the inception of asthma among children and young adults. It has been established that total serum immunoglobulin E (IgE) decreases with advancing age.[8] According to the Tucson Epidemiological Study and the National Health and Nutrition Examination Survey (NHANES 2005–2006), IgE peaks by 20 years of age and is lowest after 70 years.[3] Therefore, asthma in the elderly is often characterized as non-atopic and intrinsic.

The durations of asthma did not differ significantly between the two groups. However, the results showed that majority of patients in either group had asthma duration of 1-30 years (72.5% for adults and 70.6% for elderly). The age of onset and the duration of asthma are important parameters in the identification of phenotypes such as late-onset asthma and long-standing asthma.[9] From the results, most of the elderly patients presented with late-onset asthma (ie, 70.6% occurring 1–30 years before the study date).

Recognition and identification of comorbid diseases is an integral partof the core management of asthma. We found significantly more hypertension among the elderly (49%) than among the adult patients (25.5%). In several studies, asthma in the elderly is associated with cardiovascular and hypertensive diseases.[10] Asthma has a weak association with depression, diabetes mellitus, dyslipidemia, osteoporosis and rhino-sinusitis; but it has a strong association with gastroesophageal reflux and allergic rhinitis.[3,11,12]

We found no significant differences between the spirometric results of the two groups. This may be due to the small mean age difference between the adult and the elderly group (52 vs 66 years old, respectively). However, elderly asthmatic patients had non-significantly lower FEV1 and FVC results than their adult counterparts. This could be explained by the normal physiologic change of aging, which predicts a linear decline of FEV1 with advancing years. The estimated rate of decline is initially 25–30 ml/yr, starting at 35–40 years of age and doubling to 60 ml/yr after the age of 70.[3] The normal lung function declines with age due to increased stiffness of the chest wall, increased residual volume from loss of elastic recoil, and reduced respiratory muscle function.[13] The result is a decrease in the FEV1/FVC ratio, a reflection that most elderly have spirometric features suggestive of obstructive lung disease. This often leads to asthma being misdiagnosed as COPD, resulting in underdiagnosis and undertreat-

Table 2. Demographic characteristics, asthma history and history of environmental exposure

Profile	Adult (n=51)		Elderly (n=51)		p–value
	n	%	n	%	
Sex					0.815
Female	40	78.4	38	74.5	
Male	11	21.6	13	25.5	
Medical history					
GERD	1	2.0	0	0	0.984
Diabetes mellitus	7	13.7	9	17.6	0.788
Hypertension	13	25.5	25	49.0	0.025*
Obesity (BMI >25 kg/m^2)	25	49.0	13	25.5	0.024
None	36	70.6	24	47.1	0.027*
Alcohol drinking (none)	51	100	51	100	0.843
Smoking (none)	51	100	51	100	0.843
Duration of asthma					
1–10 yr	9	17.6	14	27.5	0.239
11–20 yr	17	33.3	10	19.6	
21–30 yr	11	21.6	12	23.5	
31–40 yr	10	19.6	6	11.8	
41–50 yr	4	7.8	7	13.7	
51–60 yr	0	0.0	2	3.9	
Personal history of atopy					
With history	9	17.6	3	5.9	0.124
Without history	42	82.4	48	94.1	
Family history of atopy					
With history	10	19.6	3	5.9	0.075†
Without history	41	80.4	48	94.1	
History of pneumonia					
With history	8	15.7	6	11.8	0.774
Without history	43	84.3	45	88.2	
Use of steroids	51	100	51	100	0.921
Asthma medications					
SABA	37	72.5	34	66.7	0.533
LAMA	0	0	1	2.0	
LABA	0	0	1	2.0	
LABA + ICS	51	100	49	96.1	
Environmental exposure					
Inhaled allergens	32	62.7	28	54.9	0.549
Domestic combustion	20	39.2	23	45.1	0.687
Environmental tobacco smoke	9	17.6	11	21.6	0.795
None	14	27.5	16	31.4	0.830

*Significant at 5%; †Significant at 10%
GERD = gastroesophageal reflux disease; BMI = body mass index; SABA = short-acting beta-agonis; LAMA = long-acting muscarinic antagonist; LABA = long-acting beta-agonist; ICS = inhaled corticosteroids.

Table 3. Spirometry results among adult and elderly asthmatic patients

Spirometry Test (L)	Adult (n=51)		Elderly (n=51)		p–value
	Mean	SD	Mean	SD	
FEV1	1.34	0.65	1.25	0.60	0.46
FEV1 pre-BD	59.80	18.5	59.69	19.8	0.64
FEV1 post-BD	1.46	0.67	1.39	0.61	0.49
FEV1 post-BD	69.25	19.5	69.55	19.8	0.94
FVC	2.18	0.76	2.06	0.65	0.43
FVC pre-BD	75.59	20.5	74.48	19.4	0.78
FVC post–BD	2.27	0.71	2.15	0.65	0.41
FVC post-BD	81.27	17.5	79.49	17.64	0.61

FEV1 = forced expiratory volume in 1 second; BD = bronchodilator; FVC = forced vital capacity.

Table 4. Treatment response among adult and elderly asthmatic patients

	Adult (n=51)		Elderly (n=51)		p-value
	n	%	N	%	
History of exacerbation					0.834
Yes	17	33.3	17	33.3	
1–2 per year	12	70.6	11	64.7	
>2 per year	5	29.4	6	35.3	
No	34	66.7	34	66.7	
History of admission					0.785
Yes (1–2 per year)	8	15.7	8	15.7	
No	43	84.3	43	84.3	
History of intubation					1.000
Yes	1	2.0	0	0	
No	50	98.0	51	100	

Table 5. Level of asthma control among adult and elderly asthmatic patients

Asthma Control Test score	Adult (n=51)		Elderly (n=51)		p value
	n	%	n	%	
Uncontrolled (≤19)	16	31.3	20	39.2	0.380
Partially controlled (20-24)	24	47	25	49	
Controlled (25)	11	21.5	6	11.7	

ment of the disease.

Weiner et al measured the lung function and recorded the asthma symptom scores of 30 elderly asthmatics, 15 of whom had long-standing asthma, while the rest had late-onset asthma. The study concluded that elderly patients with long-standing asthma had the most severe airway obstruction and complained of fewer asthma symptoms. This is referred to as a process of adaptation, with the possibility of impaired awareness of bronchoconstriction in the elderly, which may lead to undertreatment of the disease.[14] This may lead to an increased rate of asthma-related mortality due to delayed self-referral during acute asthmatic attacks.

The use of drug therapy for both the adult and the elderly asthmatic groups for this study utilizes a combination of inhaled corticosteroids and long-acting beta-2 agonists. Pharmacological treatment of asthma in the elderly needs to be

carefully administered, because this group is more likely to experience medication side effects. Polypharmacy also frequently results in an increased risk of drug interactions. Inhaled corticosteroids are the mainstay of therapy for asthma.[1,3,15] However, there have been issues regarding the underuse of these drug in the elderly group due to undesirable local effects such as oral candidiasis and dysphonia.[3]

This study reveals the equal use of short-acting beta-2 agonist inhalers as a reliever therapy and the combination of inhaled corticosteroids with long-acting beta-2 agonists as maintenance therapy for both adult and elderly groups. It is more important among elderly patients to minimize the use of sympathomimetics because these can induce undesirable side effects such as tremors, tachycardia and arrhythmia. Unfortunately, most asthma clinical trials have excluded elderly asthmatics, so data on the efficacy and safety of drugs were not available for this age group.

Treatment response for asthmatic patients is measured on the basis of frequency of exacerbations, the number of hospital admissions, and the history of intubation. The results showed no significant difference in terms of treatment response between the two groups. The rates of exacerbation and hospital admission were statistically the same. However, factors related to exacerbations may be more multi-factorial among the elderly due to the presence of comorbidity and decreased socioeconomic, physical and cognitive capabilities.

The ACT was used in this study to evaluate the levels of asthma control for both groups. We found no significant difference in the ACT scores for the adult and the elderly groups. However, both groups were found to have high rates of uncontrolled asthma (31.4%, 39.4%) and partially controlled asthma (47.1%, 49%). This suggests that in a high proportion of older adults and elderly, asthma is only partially controlled or not controlled at all.

A study done by Marincu et al evaluated 126 elderly patients based on the rates and predictors of uncontrolled bronchial asthma. They found out that 30% of patients had uncontrolled asthma, based on ACT score <19. Six predictive factors were identified for uncontrolled asthma; these include infectious exacerbation, occupational exposure, mixed ventilator dysfunction, persistent airway obstruction, duration of disease and current smoking status.[16,17]

This study found that the levels of asthma control between the adult and the elderly groups were almost the same. However, the proportions of partially controlled and uncontrolled asthma were high in both groups. The assumption that elderly patients have more difficult asthma control was not proven. This could be because most of the patients in the adult group were older adults, with a mean age of 52. The older adult patients may have the same profile as the elderly patients in terms of comorbidities, medications, treatment response, and level of adherence. Had there been a more evenly distributed age range within the group of adult patients, there could have been a more clear-cut comparison between the two groups to establish their clinical differences.

This study identified that more than 30% of asthmatics in both groups had uncontrolled asthma (31.3%, adult; 39.2%, elderly). Based on the most recent data from the Centers for Disease Control and Prevention (CDC),[18] 50% of asthmatic adults had uncontrolled asthma during the years 2006–2010. Locally, we lacked data on the prevalence of uncontrolled asthma in the Philippines. From the results, with more than 30% of both the adult and the elderly asthmatic patients demonstrating uncontrolled asthma, we find a significant health concern: patients with uncontrolled asthma are at high risk for severely impaired quality of life, exacerbations, hospitalization and death.

LIMITATIONS AND RECOMMENDATIONS

To date, current asthma guidelines do not include specific topics in the management of asthma in the elderly. There is no supporting evidence that the drugs used for adult groups are as efficacious for managing asthma in the elderly population, because most cohort studies exclude the elderly. In addition, guidelines do not present complicated situations such as multiple comorbidities and polypharmacy, which are common cases in the elderly group. In effect, physicians are prone to undertreating the disease in this cohort. Thus, many elderly asthmatics suffer from poor disease control due to poor symptom perception, poor self-management and poor adherence to medications.

The patients from the asthma clinic of LCP are a reflection of the growing population of elderly asthmatics. In 10 years, the number of elderly patients will approximately double. These patients are at an increased risk for morbidity and mortality from uncontrolled asthma. To achieve good asthma control, the associated comorbidities should also be controlled and treated. More importantly, we should identify specific needs and address health concerns to achieve better asthma control.

Failure to achieve adequate control of asthma reveals a gap between what is known to be efficacious in asthma care and what might be achieved if optimal medication combined with management strategies could be implemented.[12]

We recommend the identification and use of specific instruments to evaluate asthma control in the elderly, as well as to improve self-management and adherence. LCP conducts asthma seminars for newly enrolled patients at the asthma clinic. It also hosts a regular refresher course and assembly for all members of the asthma club, to ensure that all asthmatic patients are competent and confident with the self-management of their disease. Education is essential for achieving patient self-management and for improving adherence.

As the premier institution for managing chest and lung diseases in the Philippines, the LCP has a growing number of asthmatic members every year. Therefore, its asthma clinic is the best setting for clinical research and advancement. The asthma guidelines that we followed have been revised almost annually to keep it updated and to address the concerns of the physicians and asthmatic patients in achieving optimal asthma control.

Attention should be given to the elderly group, the most vulnerable group of asthmatics, to identify their needs and concerns and bring us closer towards a more specialized management of asthma.

The subject population in this study is representative of the asthmatic patients seeking consult at the asthma clinic. However, the adult group (n=51) was composed mostly of older adults whose clinical profiles and characteristics were almost the same as the elderly group's; this may have resulted in less comparative effects.

The levels of adherence in the two groups were not determined; therefore, the accuracy and reliability of the treatment response is questionable. In addition, this study only utilized the latest available spirometry test results of the patients; no serial spirometry tests were done to document treatment response.

A serial asthma control test administered during follow-up visits after identified exacerbations and the modification of treatment regimens will identify predictive factors for exacerbation, response to treatment, and levels of asthma control among the elderly group.

Quality of life and level of knowledge about asthma were not assessed in either group. Among the elderly group, it may be an area of interest to establish the relationship between quality of life, level of knowledge about asthma, and levels of asthma control.

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CROSS-SECTIONAL ANALYTIC STUDY

The accuracy of BronkoTest in detecting bacterial infection in patients with chronic lung diseases

Ritaville E. Elorde, MD; Ma. Encarnita B. Limpin, MD, FPCP, FPCCP; Fernando G. Ayuyao, MD, FPCP, FPCCP

Philippine Heart Center, Quezon City

ABSTRACT

Background: Bacteria that cause infection in the airways is associated with neutrophil recruitment. Its correlation with the degree of yellow-green coloration of the sputum is due to neutrophil myeloperoxidase accumulation. The purulence of sputum can therefore be used as a gauge for bacterial infection. The BronkoTest, a standardized sputum color chart, was developed as a tool for assessing sputum color. In this study, the diagnostic accuracy of BronkoTest in detecting bacterial infection in patients with chronic lung diseases such as chronic obstructive pulmonary disease (COPD) and bronchiectasis is determined.

Methodology: This was a prospective cross-sectional study involving patients who have been diagnosed with chronic lung diseases such as COPD and bronchiectasis, presenting with sputum production. A fresh sputum sample was obtained from each patient and simultaneously assessed by the doctor, patient, and nurse by comparing them with the colors of the BronkoTest color chart. Samples that were graded as 1 or 2 were categorized as mucoid sputum, while those with grades 3 to 5 were categorized as purulent. Gram staining and culture were subsequently done.

Results: A total of 89 patients participated in the study. Eighty-five percent of the population had COPD, and 15% had bronchiectasis. Eighty-four percent of the patients were treated with inhaled corticosteroids; this was significantly associated with sputum purulence (p=0.013). A higher rate (61%) of bacterial growth was found among purulent samples. The most common bacterium isolated was *Klebsiella pneumonia*. Test sensitivity and specificity were found to be 88.89% and 63.69%, respectively.

Conclusion: The assessment of sputum color using BronkoTest in patients with chronic respiratory diseases such as COPD and bronchiectasis provides both the patients and the physicians with a simple and noninvasive method for determining bacterial presence and the patients' need for and likely response to antibiotic therapy.

INTRODUCTION

Chronic lung diseases such as emphysema and chronic bronchitis (referred to as chronic obstructive pulmonary disease [COPD]) and bronchiectasis are characterized by persistent cough, sputum production and recurrent chest infections, which lead to the deterioration of quality of life. Patients with any of these diseases manifest airway inflammation with recruitment of neutrophils to the airway lumen, resulting in purulent secretions and a variety of potential adverse consequences.[1] Overall, the presence of bacteria that cause infection in the airways is mostly associated with neutrophil recruitment, thus correlating with the degree of yellow-green coloration of the sputum due to neutrophil myelo-

peroxidase accumulation. Therefore, the purulence of sputum can be used as a gauge for bacterial infection, reflecting the likelihood of bacterial presence, as well as bacterial load, inflammation, and damaging potential of the secretions due to their proteolytic enzyme content.[1]

The Anthonisen criteria say the presence of at least 2 of the following symptoms indicate that a condition will benefit from antibiotic treatment: increased dyspnea, sputum volume, and sputum purulence. However, purulence is a subjective term and not further defined.[1] According to the study of Daniels et al, sputum color assessed with a sputum color chart is a better marker for bacterial involvement than sputum color reported by patients.[2]

The BronkoTest (Appendix), a standardized sputum color chart, was developed as a tool that aids in associating the patient's normal chest-related symptoms with the changes that occur during an exacerbation. Sputum colors are graded 1 to 5, with the higher numbers corresponding with darker sputum color and associated with higher bacterial load. This facilitates the identification of a need for and likely response to antibiotic therapy.[3] This study aims to determine the diagnostic accuracy of BronkoTest in detecting bacterial infection among patients with chronic lung diseases.

METHODOLOGY

This was a cross-sectional study conducted in the Philippine Heart Center (PHC) from January 2015 to January 2016. This study was reviewed and approved by the Institutional Ethics Review Board of PHC, and all the enrolled patients provided written informed consent.

All admitted patients and outpatients aged 18 years old and above; diagnosed with chronic lung diseases based on clinical history, spirometry, and chest radiography or computed tomography (CT) scan findings; and presenting with increasing sputum production were enrolled. Those that had undergone or were undergoing antibiotic treatment in the 4 weeks prior to the sputum color examination using BronkoTest were excluded.

Upon consultation, demographic characteristics, ie, age, gender, body mass index (BMI), smoking history, and medication use, were collected. Fresh sputum samples were obtained and stored in transparent sterile containers. Samples containing more than minimal salivary contamination were discarded. The samples were simultaneously assessed by the doctor, patient, and nurse.

Sputum samples were compared with the colors of the BronkoTest color chart. Each color has an assigned value: 1 (white) and 2 (opaque) reflect the nature of mucoid sputum, while 3 to 5 reflect increasing degrees of yellow-green coloration and were interpreted as purulent.

After macroscopic assessment, the sputum samples were Gram stained, and sputum samples with >25 polymorphonuclear (PMN) leukocytes and <10 squamous epithelial cells (SEC) per low-power field (LPF) were labeled as adequate specimens and representative of the lower airways. Subsequently, cultures were performed. Sputum samples with bacterial isolates were considered colonized, or positive for bacterial infection.

Sample size was calculated using Epi Info version 7. The minimum sample size requirement was 91 based on the following parameters: level of significance of 0.05, maximum tolerable error of 10%, and a specificity of 39% based on the study of Daniels et al.[2]

Data analysis was done using Stata SE 13. Descriptive statistics include mean and standard deviation for quantitative variables, and frequency and percent distribution for qualitative variables. The prevalence of bacterial infection, the area under the receiver operating characteristic (ROC) curve, and the sensitivity,

specificity, positive predictive value, and negative predictive value of BronkoTest in detecting bacterial infection were estimated with 95% confidence level. Inter-rater reliability was measured using kappa test.

Table 1 shows the demographic characteristics of the population. A total of 89 patients were included. Eighty-five percent had COPD and 15% had bronchiectasis. According to the sputum color chart, 56 sputum samples (63%) were purulent: 44 from COPD patients and 12 from patients with bronchiectasis. Eighty-four percent of the patients were maintained on inhaled corticosteroids (ICS).

As demonstrated in Table 2, sputum samples were considered adequate in 73 out of 89 subjects (82%) with >25 PMN/LPF. The investigator graded the sputum samples from the patients as follows: grade 1 or 2 (mucoid) for 33 patients, grade 3 for 36 patients, grade 4 for 20 patients, and grade 5 for 0 patients. Among the mucoid sputum samples, 21 showed >25 PMN cells/lpf, while 93% of the 56 purulent samples contained >25 PMN/lpf cells. Most of the purulent sputum samples yielded organism that stained Gram positive, Gram negative, or both, but 42% revealed no microorganisms.

Five of 33 mucoid sputum cultures subsequently grew pathogens: 3 (60%) of the 5 cultures revealed *Klebsiella pneumoniae*, 1 (20%) had *Pseudomonas aeruginosa*, and 1 (20%) had *Acinetobacter baumannii*. Among the 56 purulent sputum samples, 34 (61%) had positive culture results, of which 13 (38%) revealed *K. pneumoniae*, 7 (21%) had *P. aeruginosa*, 5 (15%) had *Stenotrophomonas maltophilia*, 3 (9%) had *Streptococcus pneumonia*e, 3 (9%) had *Enterobacter cloacae*, 1 (3%) had *Streptococcus hemolyticus*, 1 (3%) had *Acinetobacter iwoffii* (3%), and 1 (3%) had *Staphylococcus aureus* (Table 3).

Purulent sputum was associated with 40 of the 45 samples that were positive for bacteria. This result gave an overall sensitivity of 89%. However; some of the purulent samples had cultures that were negative for bacteria, giving a specificity of 63.69% (Table 4).

An investigator, the patient, and a nurse graded each patient's sputum sample using the color chart. Agreement between the investigator

Table 1. Demographic Data

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

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

Table 2. Sputum Characteristics and Gram Stain

Variables (%)	Grade 1[a] (n=15)	Grade 2[b] (n=18)	Grade 3[c] (n=36)	Grade 4[d] (n=20)	Grade 5[e] (n=0)	Total (n=89)
PMN/lpf						
>25 cells	9 (60.0)	12 (66.67)	32 (88.89)	20 (100)	0	73 (82.02)
≤25 cells	6 (40.0)	6 (33.33)	4 (11.11)	0	0	16 (17.98)
Gram stain results						
None	13 (86.67)	13 (72.22)	9 (25.0)	2 (10.0)	0	37 (41.57)
Gram +	1 (6.67)	1 (5.56)	8 (22.22)	8 (40.0)	0	18 (20.22)
Gram –	1 (6.67)	1 (5.56)	6 (16.67)	5 (25.0)	0	13 (14.61)
Both	0	3 (16.67)	13 (36.11)	5 (25.0)	0	21 (23.60)

[a]White; [b]Gray; [c]Yellow; [d]Yellow green; [e]Green
PMN, polymorphonuclear.cells; lpf, low-power field.

Table 3. Sputum Color and Culture results

Variables (%)	Grade 1[a] (n=15)	Grade 2[b] (n=18)	Grade 3[c] (n=36)	Grade 4[d] (n=20)	Grade 5[e] (n=0)	Total
Culture						
No	13 (86.0)	15 (83.33)	11 (30.56)	5 (25)	0	44 (49.44)
Yes	2 (13.33)	3 (16.67)	25 (69.44)	1 (75.)	0	45 (50.56)
Bacterial isolate						
None	13 (86.67)	15 (83.33)	15 (41.67)	7 (35.0)	0	50 (56.18)
Klebsiella pneumonia	2 (13.33)	1 (5.56)	8 (22.22)	5 (25.0)	0	16 (17.98)
Pseudomonas aeruginosa	0	1 (5.56)	5 (13.89)	2 (10.0)	0	8 (8.99)
Stenotrophomonas maltophilia	0	0	2 (5.56)	3 (15.0)	0	5 (5.62)
Streptococcus pneumonia	0	0	1 (2.78)	2 (10.0)	0	3 (3.37)
Enterobacter cloacae	0	0	3 (8.33)	0	0	3 (3.37)
Streptococcus hemolyticus	0	0	1 (2.78)	0	0	1 (1.12)
Acinetobacter iwoffii	0	0	0	1 (5.0)	0	1 (1.12)
Staphylococcus aureus	0	0	1 (2.78)	0	0	1 (1.12)
Acinetobacter baumannii	0	1 (5.56)	0	0	0	1 (1.12)

[a]White; [b]Gray; [c]Yellow; [d]Yellow green; [e]Green

and the patient was 87.8% in the mucoid group and 93.3% in the purulent group. Agreement between the investigator and the nurse was 97% in purulent group and 98.2% in purulent group (Table 5).

DISCUSSION

In the current study, the nature of sputum was compared with a standard color chart, BronkoTest. This study demonstrates that a higher rate (61%) of bacterial growth is present in purulent samples, while 15% of mucoid samples also showed bacterial growth. Stockley et al reported that mucoid sputum yielded positive bacterial culture in 38% of 34 exacerbations but noted that the bacterial load was low and only 2

patients deteriorated without antibiotics.[1]

This study shows a sensitivity of 89% and specificity of 64%. The study of Daniels et al[2] also used the 5-point sputum chart and showed 90% and 52% sensitivity and specificity, respectively.

This study also shows that 74% of patients who were maintained on ICS developed sputum purulence (*P*=0.013). Recent studies indicate that ICS are known to increase the risk of pneumonia in patients with COPD.[4] There are evidences supporting the effect of ICS on the human pulmonary host defense, acting through several biological pathways such as an inhibitory action on macrophage functions, a decrease in cytokine production, and nitric oxide expression, which may result in failure to control infection.[5,6] An important problem for clinicians is whether the presence of bacteria in a sputum sample represents infection or colonization. A possible way to discern infection from colonization is through assessment of the presence of systemic inflammation using the C-reactive protein (CRP) test; this was not done in this study, but Daniels et al[2] has confirmed the relationship between sputum color and systemic inflammation.

CONCLUSION

Assessing sputum color using BronkoTest in patients with chronic respiratory diseases such as COPD and bronchiectasis predicts bacterial presence and provides both the patients and the physicians with a simple and noninvasive method to determine the need for and likely response to antibiotic therapy.

DISCLOSURE

The manufacturer or distributor of BronkoTest has no participation in the conception, conduct, and publication of this study.

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Table 4. Diagnostic accuracy

	Culture		
Type of Sputum	**(+) Growth**	**(–) Growth**	**Total**
Purulent	40	16	56
Mucoid	5	28	33
Total	45	44	89

Sensitivity=88.89%; Specificity=63.69%; Positive Predictive Value=71.43%; Negative Predictive Value=84.8%.

Table 5. Inter-observer Variability

Observer, %	Grade 1[a] (n=15)	Grade 2[b] (n=18)	Grade 3[c] (n=36)	Grade 4[d] (n=20)	Grade 5[e] (n=0)	Kappa
Investigator	15 (16.85)	18 (20.22)	36 (40.45)	20 (22.47)	0	_
Patient	14 (15.73)	15 (16.85)	35 (35.33)	25 (28.09)	0	0.749
Nurse	16 (17.98)	18 (20.22)	35 (39.33)	20 (22.47)	0	0.984

[a]White; [b]Gray; [c]Yellow; [d]Yellow green; [e]Green

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CROSS-SECTIONAL ANALYTIC STUDY

Comparative Analysis of GeneXpert MTB/RIF Assay Testing with MTB Culture Among PTB Category II–Treated Patients

Edel Joey L. Reyes, MD, FPCP; Eloisa S. De Guia, MD, FPCP, FPCCP
Veterans Memorial Medical Center

ABSTRACT

Objective: To evaluate the validity of the GeneXpert MTB/RIF assay for the detection of multidrug-resistant (MDR) tuberculosis (TB) among patients treated under pulmonary TB (PTB) category II. (VMMC) and Batasan Health.

Methods: This was a cross-sectional study of all patients who had been enrolled in the category II treatment regimen of two NTP accredited centers: Veterans Memorial Medical Center and the Batasan Health Center. We assessed the performance of GeneXpert MTB/RIF, an automated molecular test for TB and resistance to rifampin (RIF), in patients with suspected drug-sensitive or MDR PTB undergoing category II treatment from 2011 to 2013

Results: A total of 71 cases of category II PTB patients were included. Of these, 25.4% were smear positive and 74.6% were smear negative. The mean age of patients was 45.98±16.41 years. Thirty-nine patients (55%) were male. The sensitivity and specificity of GeneXpert MTB/RIF in detecting MTB were 100% and 91.8% respectively. Two patients showed resistance to RIF and isoniazid, confirmed by drug sensitivity testing, with a sensitivity and specificity of 100% and 98.5% respectively. The prevalence of MDR-TB among category II PTB patients was 4%.

Conclusions: The GeneXpert MTB/RIF assay provided sensitive detection of TB and RIF resistance directly from untreated sputum, comparable to validated studies. It is a reliable tool as a surrogate for MDR-TB detection.

INTRODUCTION

Tuberculosis (TB) is an ancient disease, but it is not a disease of the past. After disappearing from the world public health agenda in the 1960s and the 1970s, TB returned in the early 1990s due to several causes, including the emergence of the human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome pandemic and the increase in drug resistance.[1] The danger of TB is real. According to the World Health Organizations (WHO), the Philippines is number nine in the list of top high-burden TB countries in the world and also one of the world's highest burdens in multidrug-resistant TB (MDR-TB).[2] Furthermore, the 2011 report of the WHO Commission on Macroeconomics and Health emphasized that TB is the world's most common infectious disease, causing 1.4 million deaths each year.[3]

TB has non-specific clinical features; therefore, diagnosis usually requires laboratory testing. TB diagnosis in highly endemic countries relies heavily on century-old technologies, such as the smear microscopy. Though simple and inexpensive, its specificity and sensitivity is poor, particularly in HIV-positive patients and in child-

ren. In contrast, TB culture can become positive with as few as 10 organisms per ml of sputum. In general, the sensitivity of TB culture is reported to be between 80%–85%, with a specificity of 98%. Therefore TB culture can detect more cases of active TB disease than sputum microscopy alone. This is the basis for its inclusion in the routine diagnostic work-up of most countries and in the International Standards for Tuberculosis Care.

The spread of multidrug-resistant TB (MDR-TB) strains poses a significant challenge to overall TB disease control. With MDR-TB, there is resistance to the first-line drugs consisting of isoniazid (INH) and rifampicin (RIF). It is imperative that there be better MDR-TB case detection and treatment outcomes to help halt the spread of MDR-TB.

Recommendations for the prompt detection and appropriate treatment of MDR-TB cases have been defined by the National Tuberculosis Program (NTP) in 2013. As patterned from the WHO TB Disease Registration Group, TB cases are assigned categories based on history of previous pulmonary TB (PTB) treatment: Treatment Failure, Relapse, Treatment After Lost to Follow-up (TALF), Previous Treatment Outcome Unknown (PTOU), and Others for those who are still smear positive despite retreatment. Following NTP 2013 guidelines, these patients undergo a category II regimen.

In December 2010, the WHO endorsed the GeneXpert MTB/RIF (*Mycobacterium tuberculosis*/rifampicin) assay for the rapid diagnosis of TB and MDR-TB.[4] The GeneXpert MTB/RIF is a cartridge-based nucleic acid amplification test (automated) that can identify *M. tuberculosis* DNA and rifampicin resistance. Being an amplification test, MTB/RIF test offers a potential solution for improving TB diagnosis. Molecular testing enables speed, and the GeneXpert MTB/RIF assay is feasible for use in peripheral laboratories and clinics by unskilled personnel.

The objective of this study was to evaluate the validity of the GeneXpert MTB/RIF assay for the detection of MDR-TB among patients treated under PTB category II, in comparison with the current gold standard, the MTB culture, at two Quezon City TB–directly observed treatment, short course (DOTS) centers, the Veterans Memorial Medical Center (VMMC) and Batasan Health Center, from 2011 to 2013.

METHODS

This was a cross-sectional study of all PTB-diagnosed patients, registered at the VMMC TB-DOTS and the Batasan Health Center from 2011 until 2013, who received category II treatment and complete ancillary MDR-TB screening tests; namely, the acid-fast bacilli (AFB) smear, the GeneXpert MTB/RIF assay, TB culture and drug sensitivity testing (DST). All PTB category II patients with indeterminate results from the GeneXpert MTB/RIF assay, the MTB culture, and the DST, as well as all patients with extrapulmonary TB, were excluded. Review of the patients' charts focused on demographic information, the diagnosis that necessitated enrollment to category II treatment, and the results of the GeneXpert MTB/RIF assay testing and the TB culture.

Correlation on positive results from the AFB smears (i.e., AFB detected) and the GeneXpert MTB/RIF tests were done, confirmed on the MTB culture (i.e., growth of *M. tuberculosis*) and DST results. Patients were divided into four PTB categories for analysis: (1) smear positive, culture positive; (2) smear negative, culture positive; (3) smear positive, culture negative; and (4) smear negative, culture negative. All patients underwent GeneXpert MTB/RIF assay determination for RIF resistance, while all patients with MTB culture growth underwent DST to determine resistance to first-line drugs (INH, RIF).

Using the population proportion formula for estimating sample size, the number of samples

collected was ≥59 based on a 95% confidence level, 10% relative error, and a GeneXpert MTB/RIF assay assured accuracy of 96%.

Data was encoded and tallied using a spreadsheet program. Clinical and laboratory data were compiled in databases. Qualitative and quantitative values were presented as mean ± SD, frequency and percent distribution. The kappa statistic was applied to the data to determine the degree of agreement of GeneXpert MTB/RIF results with MTB culture results, as the gold standard was to be performed using the analysis of variance. Test validity of the GeneXpert MTB/RIF assay was evaluated using the sensitivity/specificity analysis, positive predictive value (PPV) and negative predictive value (NPV). A 2x2 table was used to test the validity.

RESULTS

A total of 71 patients who were enrolled at the TB-DOTS center of the VMMC or the Batasan Health Center fulfilled the inclusion criteria. Majority of the patients (n=53; 75%) were from the Batasan Health Center.

There was a wide variation in the patients' ages. The youngest was 18 years old, the oldest was 87, and the mean age was 45.98±16.41. The sample was composed of 55% males and 45% females, a ratio that approximates 1.2. There were more AFB smear-negative patients (74.6%) than AFB smear-positive ones (24.4%) (Table 1).

The group of patients with a PTB diagnosis of Others predominates at 84.5%, followed by the Relapse, Treatment Failure, Return After Default (RAD), and Transfer-in groups, in descending order (Table 2).

Correlation of direct sputum smear microscopy (DSSM) results with MTB culture to confirm detection showed a sensitivity of 81% and a specificity of 98% (Table 3).

The correlation of GeneXpert MTB/RIF assay results with the standard MTB culture showing confirmed detection showed an excellent sensitivity at 100% and a specificity of 92% (Table 4). The PPV was less than the NPV, at 83.3% and 90% respectively.

The use of the GeneXpert MTB/RIF assay as a surrogate for MDR-TB correlated with the detection of RIF + INH resistance via DST showed a sensitivity of 100% and a specificity of 96%. However, despite a high NPV, the PPV was only 67% (Table 5).

The estimated prevalence rate of MDR-TB burden in the study was 4.26 (95% CI 0.64%–14.5%).

DISCUSSION

Seventy-three Filipinos die of TB every day. Each person with active TB can spread the disease to 10 other Filipinos each year. However, significant developments have been made toward improved case detection and treatment,[5] and efforts are now being directed at improving diagnostic capabilities in DOTS facilities and hospitals.

Table 1. Baseline characteristics of enrolled patients

Characteristics (N=71)	Value
Mean age (years)	45.98±16.41
Sex Male Female	 39 (54.9%) 32 (45.1%)
Smear Positive Negative	 18 (25.4%) 53 (74.6%)

Table 2. Distribution of PTB diagnosis of enrolled patients

PTB Diagnosis (N=71)	n (%)
Relapse	7 (9.9%)
RAD	3 (4.2 %)
Treatment Failure	2 (2.8%)
Others	60 (84.5%)
Transfer-in	1 (1.4 %)

PTB, pulmonary tuberculosis; RAD, return after default.

Table 3. Diagnostic evaluation of a positive AFB smear compared with standard MTB culture

	MTB Culture			
	Sensitivity	**Specificity**	**PPV**	**NPV**
AFB smear	81.0% (17/21)	98.0% (49/50)	94.4% (17/18)	92.4% (49/53)

MTB, Mycobacterium tuberculosis*; PPV, positive predictive value; NPV, negative predictive value; AFB, acid-fast bacilli*

Table 4. Diagnostic evaluation of GeneXpert MTB/RIF assay compared with positive standard MTB culture

	MTB Culture and DST with Resistance for RIF/INH			
	Sensitivity	**Specificity**	**PPV**	**NPV**
GeneXpert MTB/RIF assay for MTB RIF resistance	100%	98.55%	66.7%	96.15%

MTB, Mycobacterium tuberculosis*; PPV, positive predictive value; NPV, negative predictive value; RIF, rifampicin*

Table 5. Diagnostic evaluation of GeneXpert MTB/RIF assay in diagnosing RIF resistance compared with positive standard MTB culture and DST resistance for RIF and INH

	MTB Culture			
	Sensitivity	**Specificity**	**PPV**	**NPV**
GenXpert MTB/RIF assay for MTB	100%	91.8%	83.3%	90.0%

MTB, Mycobacterium tuberculosis*; DST, drug sensitivity test; RIF, rifampicin; INH, isoniazid; PPV, positive predictive value; NPV, negative predictive value*

Diagnostic delay, defined as the time interval between the advent of symptoms and the confirmation of the disease, promotes disease progression and higher mortality, as demonstrated in several studies.[6] It is a contributing factor to the TB epidemic, facilitating disease transmission of MDR-TB.[7]

This study showed that among the PTB category II–treated patients under the NTP protocol, the group of patients with a diagnosis of Others was significantly larger than those groups with other diagnoses (i.e., Relapse, RAD, Treatment Failure or Transfer in). This finding is consistent with the recent 2012 WHO data.

All category II–treated patients under the NTP protocol are also suspected to have drug-resistant TB (DR-TB). These are retreatment cases, including non-converters of category I treatment, persons living with HIV, and persons exposed to contacts with confirmed DR-TB. It is therefore imperative that prompt detection and treatment be initiated.[8] Furthermore, these patients require an additional second-line treatment regimen.

The available tests utilized by the NTP for diagnosing TB are DSSM, MTB culture with DST, and rapid molecular diagnostic tests such as the GeneXpert MTB/RIF assay. DSSM is still considered fundamental to the detection of infectious cases and case finding. It is inexpensive and has a high specificity; however, it is nonsensitive, prone to false-negative smear-negative TB results, and it cannot test for drug resistance.[9,10] This study found high sensitivity and specificity in sputum AFB when correlated with MTB culture. At present, the closest that we have to a gold standard for active TB diagnosis is

the performance of both a liquid and a solid culture test for MTB. However, MTB cultures have median turnaround times measurable in weeks, which cause unnecessary delays in diagnosis and therapeutic intervention.

The GeneXpert MTB/RIF assay enables TB detection and RIF-resistance testing near the point of care, thus facilitating rapid screening for TB and drug resistance. It can simultaneously detect MTB complex DNA and mutations associated with RIF resistance directly from sputum specimens in less than 2 hours, and it minimizes staff manipulation and biosafety risks.[11,12] The GeneXpert MTB/RIF assay is more sensitive than sputum smear microscopy in detecting TB, and its accuracy is similar to that of culture.[13] The GeneXpert MTB/RIF assay has a pooled sensitivity of 90% and a pooled sensitivity of 98%, which has been consistently evaluated as approaching the sensitivity and specificity of culture in adult sputum samples (90.4% sensitivity and 98.4% specificity).[14] In this regard, the use of the GeneXpert MTB/RIF assay significantly improves the likelihood of timely treatment initiation for TB and MDR-TB.[15]

This study showed that the GeneXpert MTB/RIF assay has sensitivity and specificity values comparable to published validity reports by Boehme (97.6% and 98.1% respectively) and Cepheid (99.7% and 98.5% respectively).[14,16] Translated to PTB detection among smear-negative patients, the results validate earlier reports on its utility in improving TB detection. Earlier TB detection could prevent TB-related deaths by catching patients at an earlier time. According to Boehme et al, the GeneXpert MTB/RIF assay had a sensitivity of 92% for all culture-positive specimens with one sputum sample, which increased to 96% for two samples and 98% for three. Furthermore, for culture-positive, sputum-negative specimens, the sensitivity gained from using one sputum sample was 73%, rising to 90% when three samples were used. It has been shown repeatedly that no site consistently had a sensitivity lower than 83% even for culture-positive, sputum-negative specimens. In compliance with NTP standards, in partnership with the policies of the WHO and the International Standards on TB Care (ISTC), diagnostic yields using GeneXpert MTB/RIF may be perfected as NTP facilities gain more experience.

With a good sensitivity profile, the use of GeneXpert MTB RIF assay is equally comparable to the standard MTB culture and DST in identifying MDR-TB. This suggests that RIF resistance is a good predictor of MDR-TB in practice. Among notified cases of PTB in the Philippines in 2012, the WHO estimates that the incidence of MDR-TB in is 4.0% (95% CI 2.9–5.5) in new TB cases and 21% (95% CI 14–29) in retreatment TB cases. This study identified a 4.26% (95% CI 0.64–14.57) prevalence of MDR-TB. While this is below the national prevalence identified in the retreatment group, the high sensitivity profile and efficiency in turnaround time of results may still ensure better and earlier detection of MDR-TB. Accordingly, identifying MDR-TB among smear-negative patients facilitates improved case detection, in tune with the objectives of our national TB health policy and the WHO TB Xpert Project.

In a 2013 Cochrane review on the use of GeneXpert MTB/RIF in the rapid detection of TB and drug resistance, the following were noted: (1) GeneXpert MTB/RIF, when used as a replacement for smear microscopy to screen 1,000 people, picks up 150 (88%) and falsely diagnoses 17 (2%) with TB; and (2) if used as a replacement for culture-based DST, GeneXpert MTB/RIF is also able to detect an equivalent of 141 out of 150 cases (94%) of RIF resistance. According to the review, when GeneXpert MTB/RIF is used as a follow-on test on a negative smear microscopy result, it picks up 67% of cases.[17] These are the cases that would have been missed by microscopy as smear-negative TB. In practical application, it is precise-

ly in these smear-negative patients that improvements in diagnostic tests are needed and where the biggest impact can be seen. Therefore, GeneXpert MTB/RIF may also be valuable as an add-on test following negative smear microscopy.

CONCLUSIONS

Among the patients who were enrolled in the category II treatment regimen in the two TB-DOTS centers, more fell into the diagnosis category of Others than the retreatment categories of Relapse, RAD, Treatment Failure, and Transfer-in.

The results of the GeneXpert MTB/RIF assay are indeed promising. This test is much easier to use than sputum microscopy and has a higher sensitivity and specificity than culture in a subset of patients who are culture-negative but are positive for TB nonetheless.

The GeneXpert MTB/RIF test has a high sensitivity and specificity for detecting RIF resistance, thus hastening MDR-TB detection. Results of this study verified the globally consistent validity profile of GeneXpert MTB/RIF testing in our local setting.

An advantage in identifying RIF resistance to get drug resistance results is the matter of speed: it only takes hours rather than weeks, which is the case when MTB culture is used.

Once this device is made affordable and available nationwide, it can facilitate early disease detection across vulnerable regions in the country, like the urban poor communities and retreatment groups who are most likely to fail on first-line PTB treatment.

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RETROSPECTIVE STUDY

Assessment of risk for VTE and VTE prophylaxis based on the Thrombosis Risk Assessment Form for Medical and Surgical Patients among ICU patients

Julie Christie G. Visperas, MD, FPCP, FPCCP ; Rosario Pinkie V. Siapno, MD, FPCP
University of Sto. Tomas, Manila

ABSTRACT

Objectives: This study aimed to assess the risk for venous thromboembolism (VTE) and prophylaxis regimen used in admitted patients in the intensive care unit (ICU) using the Thrombosis Risk Assessment Form for Medical and Surgical Patients.

Methods: This was a retrospective study that included patients admitted at the ICU and cardiovascular unit of the University of Santo Tomas Hospital. All patients admitted from December 1, 2013 to March 31, 2014 were included in the study. The authors reviewed and reported data from a structured questionnaire called the Thrombosis Risk Assessment Form for Medical and Surgical Patients, which was launched in the hospital in 2013 and was used upon admission of each patient.

Results: Fifty-two patients were included. Majority belonged to the above 60 years old age group (62%, n=32). The most common cause for admission was respiratory (31%). The most common risk factor for VTE was the patient's age being more than 60 years old (55%). Eighty-three percent were in the highest risk category. Twenty-one patients were given anti-embolic stockings; 3 were given enoxaparin alone; while 8 were given enoxaparin in combination with graduated compression stockings. Nine patients had a contraindication for receiving pharmacologic VTE prophylaxis.

Conclusion: Majority of patients admitted at the ICU were in the highest-risk category. The most commonly utilized prophylaxis in these patients was graduated compression stockings.

Keywords: venous thromboembolism prophylaxis, VTE, embolism

INTRODUCTION

Venous thromboembolism (VTE) is a clinical disease entity encompassing pulmonary embolism (PE) and deep venous thrombosis (DVT). It represents a potentially fatal disease process with a clinical presentation that is often silent or nonspecific and for which a wide range of diagnostic techniques are available, many with technical and interpretive limitations. Although estimates vary widely, the best available information suggests that at least five million episodes of venous thrombosis occur annually in the United States. The overall average age- and sex-adjusted annual incidence of acute PE is approximately 70/100,000.[1]

Since VTE may present in a variety of settings, it requires the involvement of various

medical specialties for its prevention, diagnosis, and management. A close coordination between the different services involved is necessary in the care of patients at risk for developing VTE, with special emphasis on preventing its occurrence, as prevention is of prime importance, especially in the hospital setting.

VTE prophylaxis is underutilized in Asia possibly because of the misconception that its incidence is lower in Asians than in Caucasians. The available data on VTE in Asia are limited due to the lack of well-designed multicenter randomized controlled trials as well as non-standardized research designs, making data comparison difficult. Emerging data indicate that VTE incidence is not low in Asia and is comparable to that reported in Western literature.[2]

In-hospital patients in general are at increased risk for VTE. Any disruption of the Virchow's triad, namely, endothelial injury, hypercoagulable state, and circulatory stasis, will predispose a patient to VTE. Critically ill patients are at increased risk of VTE due to predisposing conditions, sepsis, trauma, and post-admission events. Individual identification of suspected VTE, encompassing both DVT and PE cases, could be a difficult task. However, prophylaxis of all admitted patients may not be cost effective, especially in a developing country such as the Philippines. Thus, risk assessment and stratification for DVT and subsequent anti-thrombotic prophylaxis in moderate to severe risk category patients is the most rational alternative

At the University of Santo Tomas (UST) Hospital, a thrombosis risk assessment form was launched in May 2013. This form is now being utilized for all admitted patients, to determine the risk stratification and give recommendations for prophylaxis of VTE.[3]

This study aimed to determine the assessment of risk for VTE and the prophylaxis regimen used in ICU-admitted patients using the Thrombosis Risk Assessment Form for Medical and Surgical Patients.

METHODOLOGY

This was a retrospective observational study at the ICU and cardiovascular unit of the UST Hospital. All patients admitted at the ICU and cardiovascular unit from December 1, 2013 to March 31, 2014 were included in the study. Review of the structured questionnaire, the Thrombosis Risk Assessment Form for Medical and Surgical Patients, was used for the risk assessment and stratification of DVT in critically ill patients. Demographic data, including patient's age and sex, were collected. Other baseline information such as admitting diagnosis, comorbid conditions, and any procedures done were also included.

The thrombosis risk assessment form (Appendix) comprises five steps, with the first step being the identification of the patient's baseline risk factors (BRF) depending on the clinical setting of admission: whether the surgery was minor or major, and whether there was sepsis, myocardial infarction, congestive heart failure, a central venous pressure (CVP) line, paralysis, or bed confinement. The second step checks associated risk factors (ARF), which are divided into clinical risk factors and hypercoagulable states. The third step computes for the total risk factor (TRF) score, which is the sum of the BRF score and the ARF score. Step 4 is the identification of the patient's risk classification (i.e., whether the patient falls under low, moderate, high, or highest risk classification) through the number of risk factors observed in the patient. Step 5 identifies which VTE prophylaxis recommendations should be used in the patient, referring to the recommendations listed under the classifications in step 4 and noting any contraindications for prophylaxis.

The data were described using mean and frequency count and percentages. Prevalence rates were computed for all risk factors identified.

This study was submitted to and was approved for implementation by the Institutional

Review Board (IRB) of the UST Hospital. Permission to review the charts of patients included in the study was secured from the medical director. All pieces of information obtained during this study, including hospital records, personal data, and research data, were kept confidential.

RESULTS

Fifty-two patients were included in this study. Thirty-two (62%) were >60 years old, and 27 (52%) were female. Other patient characteristics, including reasons for admission, are listed in Table 1. Sixteen (31%) were admitted due to respiratory causes such as pneumonia or chronic obstructive pulmonary disease (COPD), while 13 (25%) were admitted due to neurologic causes such as cerebral infarcts, subarachnoid hemorrhage, or subdural hematoma. Cardiac causes were less frequent, with 8 (15%) being admitted for atherosclerotic heart disease/coronary artery disease/ hypertension/ischemic heart disease, and 6 (11%) for ST-elevation myocardial infarction/unstable angina/sick sinus syndrome.

Among risk factors associated with clinical setting, the most common was the patient's medical condition (67%, n=35). Other risk factors were stroke (21%, n=11), major surgery (8%, n=4), multiple trauma (2%, n=1), and confinement to bed for 72 hours (2%, n=1).

Most patients were admitted as emergency cases (87%, n=45). Only 13% (n=7) were admitted as elective cases.

Figure 1 shows that the most common risk factor associated with patient is having an age >60, observed in 34 out of the 52 patients included in this study.

Forty-three (83%) were in the highest risk category for developing VTE (Table 2).

Table 1. Patient characteristics

Variable	N (n=52)	Percentage (%)
Age group (years)		
<20	0	0
21-30	3	6
31-40	4	8
41-50	4	8
51-60	9	17
>60	32	62
Gender		
Male	25	48
Female	27	52
Admitting diagnosis		
Multiple trauma	1	2
STEMI/unstable angina/sick sinus syndrome	6	11
ASHD/CAD/hypertension/ischemic heart disease	8	15
Respiratory (CAP, HAP, aspiration, COPD)	16	31
Neurologic (hypertensive bleed, ICH, chronic subdural hematoma, SAH, infarct)	13	25
Gynecologic (abnormal uterine bleeding, surgery)	2	4
Urologic	2	4
Cancer (non-small-cell lung cancer)	1	2
Septic shock	1	2
Acute kidney injury, dengue	2	4

STEMI, ST-elevation myocardial infarction; CAD, coronary artery disease; CAP, community-acquired pneumonia; HAP, hospital-acquired pneumonia; COPD, chronic obstructive pulmonary disease; ICH, intracerebral hemorrhage; SAH, subarachnoid hemorrhage.

Figure 1. Frequency of VTE risk factors associated with ICU patients

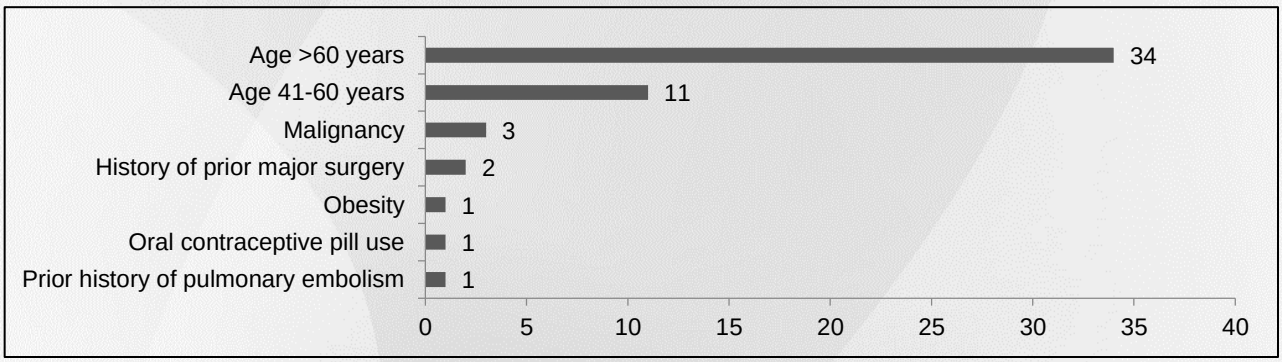


Table 2. Distribution of ICU patients by level of VTE risk

Risk Factor Assessment	N	Percentage
Highest risk	43	83%
High risk	8	15%
Moderate risk	0	0%
Low risk	1	2%

ICU, intensive care unit; VTE, venous thromboembolism.

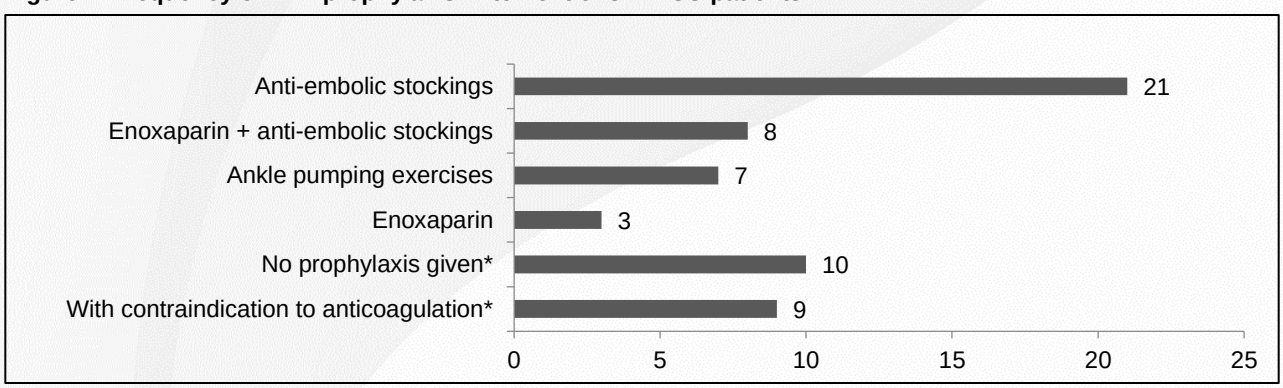
Figure 2 shows the prophylactic recommendations applied. Twenty-one patients were given anti-embolic stockings. Eight were given an anticoagulant, namely enoxaparin, with anti-embolic stockings. Nine patients were contraindicated to receive pharmacologic intervention.

DISCUSSION

Looking into the Thrombosis Risk Assessment Form for Medical and Surgical Patients, there are BRFs and ARFs to consider summing up to the total risk factor and the corresponding VTE prophylaxis recommendation in patients. In this study, the most significant BRF is found in medical patients. ICU admission commonly involves patients with acute medical illness. Spyropoulos et al. found that most patients admitted with acute medical illness are at increased risk for VTE during and following hospital admission.[4] We observed the same thing in our study: medical illness is the most common BRF for VTE in the ICU.

Analyzing the ARF score in this study, we found that the most significant ARF is being

Figure 2. Frequency of VTE prophylaxis interventions in ICU patients



*A total of 10 patients did not receive VTE prophylaxis. Nine had contraindication to prophylaxis, and one had low risk for VTE.

being>60 years of age. The next most significant ARF was being 41-60 years old. Majority of the patients admitted at the ICU in this study were elderly. As mentioned in the research by Ho and Litton, clinical diagnosis of VTE in the elderly is particularly difficult, making adequate VTE prophylaxis useful in reducing the mortality and morbidity of the disease.[5]

Calculating the total risk factor score, we found that more than 80% of patients included in this study were at the highest-risk category for VTE. This category included total risk factors ≥5. Recommendations for those with highest risk include anticoagulants with our without mechanical prophylaxis.[3] Having the majority of patients at highest risk for VTE further supports the need to give VTE prophylaxis to those admitted at the ICU. However, the VTE prophylaxis recommendations only prescribed anti-embolic stockings for 40% of the patients. Enoxaparin with or without anti-embolic stockings was prescribed to only 21% of patients. This left 20% who either had prophylaxis limited to ankle pumping exercises or had contraindications to anticoagulation. This suggests that not all patients to whom mechanical and pharmacologic prophylaxis were recommended received the appropriate prophylaxis regimen. This may have been because the presence of other comorbidities and risk factors prevented the use of anticoagulants for which the use of non-pharmacologic mechanical VTE prophylaxis may be appropriate but is underutilized. Another explanation is the clinicians' perceived risk of bleeding due to pharmacologic antithrombotic agents.[4]

CONCLUSION

Majority of the patients admitted at the ICU were assessed to have the highest risk for developing VTE based on the baseline and additional risk score on the Thrombosis Risk Assessment Form for Surgical and Medical Patients. The recommendations for prophylaxis that were used were mostly non-invasive, in the form of anti-embolic stockings. Few were given pharmacologic prophylaxis in the form of enoxaparin. There is underutilization of pharmacologic means for prophylaxis and possibly over-reliance on anti-embolic stockings as a modality for VTE prophylaxis.

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APPENDIX

Thrombosis Risk Assessment Form for Medical and Surgical Patients among ICU patients

UNIVERSITY OF SANTO TOMAS HOSPITAL
España Blvd., Manila 1015
Tel No. (632)731-3001 to 29; http://www.usthospital.com.ph
DEPARTMENT OF MEDICINE

THROMBOSIS RISK ASSESSMENT FOR MEDICAL AND SURGICAL PATIENTS

STEP 1: Check Risk Factors associated with Clinical Setting (Baseline Risk Factor Score)- Choose only ONE

Score 1 factor	Score 2 factors	Score 3 factors	Score 5 factors
☐ Minor surgery	☐ Major surgery (>45min.) ☐ Laparoscopic surgery (>45min.) ☐ Patients confined to bed >72 hours ☐ Immobilizing plaster cast ☐ Central venous access	☐ Major surgery with - Myocardial infarction or - Congestive heart failure or - Severe sepsis/infection ☐ Medical patient with additional risk factors	☐ Elective major lower extremity arthroplasty ☐ Hip, pelvis or leg fracture ☐ Stroke ☐ Multiple trauma ☐ Acute spinal cord injury (paralysis)

Baseline Risk Factor Score (BRF Score)
(If BRF Score = 5 go to STEP 4) → ☐

STEP 2: Check Risk Factors associated with Patient

Clinical (Score 1 factor each unless otherwise noted)	**Hypercoagulable States (Thrombophilia)** (Score 3 factors each)	
	INHERITED	ACQUIRED
☐ Age 41 to 60 years ☐ Age over 60 years (2 factors) ☐ History of DVT/PE (3 factors) ☐ History of prior major surgery ☐ Pregnancy, or postpartum (<1 month) ☐ Malignancy (2 factors) ☐ Varicose veins ☐ Inflammatory bowel disease ☐ Obesity (>20% of ideal body weight) ☐ Oral contraceptives or hormone replacement therapy	☐ Factor V Leiden / Activated protein C resistance ☐ Antithrombin III deficiency ☐ Protein C or S deficiency ☐ Dysfibrinogenemia ☐ Prothrombin 20210A ☐ Homocysteinemia	☐ Lupus anticoagulant ☐ Antiphospholipid antibodies ☐ Myeloproliferative disorders ☐ Disorders of plasminogen & plasmin activation ☐ Heparin-induced thrombocytopenia ☐ Hyperviscosity syndrome ☐ Homocysteinemia

Additional Risk Factor Score (ARF Score) → ☐

STEP 3: Total Risk Factor Score (TRF Score) = BRF + ARF Score → ☐

STEP 4: Identify Recommended Prophylactic Regimen for each Risk Group depending on TRF Score

Low Risk (1 factor)	**Moderate Risk (2 factors)**	**High Risk (3-4 factors)**	**Highest Risk (5 or more factors)**
No Specific Measures Early Ambulation	IPC or LDUH (q12h) or LMWH or GCS	GCS* and IPC or LDUH (q8h) or LMWH	GCS* and IPC + (LDUH or LMWH) or ADH or LMWH Oral Anticoagulants

**Combining GCS with other prophylactic methods (LDUH, LMWH or IPC) may give better protection than any modality alone*

STEP 5: Choose from Modalities listed below guided by Step 4

Contraindication to anticoagulants? ☐ Yes ☐ No If yes, elaborate: _____

☐ Graduated compression stockings (GCS) ☐ Intermittent pneumatic compression (IPC) ☐ Plantar Pneumatic Compression ☐ Adjusted dose Heparin (ADH) (Regimen:_____)	☐ Enoxaparin 40mg/SC q 24 h ☐ Fondaparinux 2.5 mg/SC q 24 h ☐ Nadroparin 3,800 IU/ SC q 24 h ☐ Tinzaparin 3,500 IU/SC q 24 h ☐ Tinzaparin 4,500 IU/SC q 24 h ☐ Low dose unfractionated heparin (LDUH) 5,000 U/SC q 8h	☐ Dabigatran 220 mg/tab po q 24h ☐ Rivaroxaban 10mg/tab po q 24 h ☐ Others: _____ ☐ No prophylaxis

Modified from: GP Claggett, MD et al: Prevention of Venous Thromboembolism. *Chest* 1998; 114:531S-560S.; 1997 International Consensus Statement: Prevention of Venous Thromboembolism, Guidelines According to Scientific Evidence; and Caprini JA, Arcelus JI et al: Clinical assessment of venous thromboembolism risk in surgical patients. *SeminThrombHemos*t 1991;17(suppl 3):304-312.

Examining Physician's Signature over printed name:_____ Date:_____

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Email: secretariat@philchest.org
Phone: (+632) 924 9204