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Simple Approaches Yielding High Impact Changes

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

"There is always one more thing to learn."
- Steve Jobs. Apple

As the Philippine Journal of Chest Diseases continues its quest to help inform its members of the latest research endeavors of the College, it is clear that the PJCD contributes to member learning and development as well. Moreover, it is hoped that the PJCD's featured articles motivate others to ask more significant questions, and drive them to pursue more relevant research. After all, to quote from Steve Jobs, a master of forward thinking and innovation, "There is always one more thing to learn".

And indeed, there is always one more thing to learn … and another. And a next.

Such is the beauty of learning – there seems to be no end to it. And when somebody, somewhere, develops an easier way of doing things (and for things that matter, more importantly) then its value escalates. In this issue of the PJCD, we highlight articles which help demonstrate how perhaps new, or different, approaches to assessing and managing patients, are able to enhance patient care.

Our first article by King Kay and Moral shows us that oxygen saturation can be a useful alternative to the PF ratio in evaluating patients with respiratory failure. This is important since not all healthcare facilities have immediate access to arterial blood gas determination, and not all patients are able to afford it, even if the test is available. This opportunity to provide appropriate yet more affordable care greatly impacts the way the less fortunate are able to receive medical care; instead of resorting to the usual "clinical eye" as the only means of validating diagnoses and monitoring progress, the simpler way of using oxygen saturation is now shown to be a viable alternative.

The second article by Sillano et al emphasizes the value of the simple question that responds to the current government's appeal to eliminate or decrease waiting time for services. "How long do patients wait prior to the start of TB treatment?". Indeed, such is not the stuff of which award-winning papers or clinical trials are made of, but such is research which positively impacts patient care in public health facilities. Clearly, the issue of appropriate and efficient health care cannot be considered separately. Imagine a TB patient who needs to wait for almost a month prior to initiating treatment, and all the time continuing to be a public health threat.

The papers of Gulay, et al., and Dadulla and Aquino provide a glimpse of outcomes among

critically ill patients. According to Gulay, et al, the early detection of delirium among ICU patients may allow for early interventions in order to prevent neurocognitive impairment such as memory and processing speed. This clearly emphasizes the holistic approach to patient care to include mental health. In the same way, the paper of Dadulla and Aquino sheds light on two very common conditions facing pulmonary specialists: tuberculosis (TB) and cancer. Based on their retrospective data, TB and malignancy do not only mimic each other, but they also occur together in many instances, making their diagnosis more challenging.

Moreover, the study of Veracruz and Germar, is a timely reminder of the value of the chest radiograph as a diagnostic tool for pneumonia. The paper validates the importance of clinical findings such as fever and sputum production as the cornerstones of diagnosis, with the x-ray providing support. This is not new information for us, but the study sends a clear message to clinicians: the chest x-ray should not be considered routine for all patients with cough; rather, it is best requested for patients demonstrating signs and symptoms highly suggestive of pneumonia.

To complete this issue of the PJCD, Pasanting-Lim describes the characteristics of patients with primary bronchogenic carcinoma among the young and the old. Although oftentimes we declare that "age is but a number", it can be considered, in one way or another, among those factors which can contribute to illness. However, despite how often we clinicians attribute age as a potential confounder, this retrospective review tells us otherwise: that comparing young and old patients with lung cancer, there appears to be no significant difference in treatment and, more importantly, survival. This is one aspect of lung cancer with may benefit from analysis of prospective data.

Yes, Steve Jobs' message is clear: that "There is always one more thing to learn". And as every passionate researcher knows, this translates into "there is always one more study to do". And knowing that research is not for the faint-hearted, nor is it for anyone and everyone, a pat on the back to all those who continue to contribute to the growth of the PJCD.

Mabuhay ang PCCP researcher!

RETROSPECTIVE COHORT STUDY

Oxygen Saturation Index as a Surrogate of PaO2/FiO2 Ratio in Acute Respiratory Distress Syndrome

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ABSTRACT

Background: Acute respiratory distress syndrome (ARDS) is characterized by noncardiogenic pulmonary edema, lung inflammation, hypoxemia and decreased lung compliance. It is diagnosed by using the Berlin criteria, which considers PaO_2/FiO_2 Ratio. Recently, oxygenation index (OI), another measure of oxygenation dysfunction, has been suggested as a more accurate means of determining severity of respiratory failure. Other studies showed that oxygen saturation index (OSI), which is the result of (MAP x FiO2)/SPO2, has a strong linear association with OI and PaO2/FiO2 ratio in patients with type 1 respiratory failure. This study aimed to determine the performance of oxygen saturation index (OSI), as a surrogate of PaO_2/FiO_2 ratio in the diagnosis of ARDS.

Methods: Review of records was done on patients diagnosed with ARDS from January 2012 to December 2015 at the University of Santo Tomas Hospital, Philippines. Simultaneous arterial blood gas, pulse oximetry and ventilator settings were recorded during the first 1, 24, 48 and 72 hour of mechanical ventilation. PaO_2/FiO_2 Ratio, OI and OSI were then calculated. Descriptive statistics and two-way scatterplots were used to describe the correlation of PaO_2/FiO_2 Ratio, OI and OSI. A linear modeling was used to derive predictive equation for PaO_2/FiO_2 Ratio using OSI, oxygen saturation (SpO_2), respiratory rate (f) and MAP.

Results: Eighty-five arterial blood gas, SpO_2 and MAP values from 27 patients (mean age of 57 years; 55% males) were included. Analysis showed that PaO_2/FiO_2 ratio was inversely related to OI and OSI, with stronger linear correlation with OI than OSI. OI and OSI were directly related. The following predictive equation of PaO_2/FiO_2 ratio was derived: PaO_2/FiO_2 ratio=exp (3.33 + 0.03*[SpO_2] – 9.92*[OSI] – 0.02*[f] + 0.06*[MAP]) (R^2=61.41%).

Conclusion: OSI may be a noninvasive surrogate measure of oxygen dysfunction in patients with ARDS.

INTRODUCTION

Acute respiratory distress syndrome (ARDS) is a constellation of clinical and physiologic observations characterized by noncardiogenic pulmonary edema, lung inflammation, hypoxemia and decreased lung compliance.[1] It is often fatal if not recognized and managed in a timely manner. It evolves through a number of different phases, from alveolar capillary damage to lung resolution to a fibroproliferative phase.[2] However, the exact pathogenesis is still unclear; hence no gold standard diagnostic test is currently available.

According to the most recent consensus initiated by the European Society of Intensive Care Medicine and endorsed by the American Thoracic Society and the Society of Critical Care Medicine, the Berlin Definition of ARDS includes the following: 1) within one week of known clinical insult or new or worsening respiratory symptoms; 2) chest radiograph or computed tomography scan

finding of bilateral opacities not fully explained by effusions, lobar/lung collapse, or nodules; 3) respiratory failure not fully explained by cardiac failure or fluid overload, excluded by objective assessment (e.g., echocardiography); 4) oxygenation dysfunction classified as mild, moderate or severe based on PaO_2 (partial pressure of oxygen)/fio_2 (fraction of inspired oxygen) ratio with Positive End Expiratory Pressure (PEEP) or continuous positive airway pressure (CPAP) $\geq 5cmH_2O$.[3]

PaO_2/FiO_2 ratio is an arterial blood gas-derived oxygenation criteria. It is a simplified and reliable method for estimating the degree of intrapulmonary shunting.[4,5] Evidence shows that a PaO_2/FiO_2 ratio of ≥150mmHg suggests acceptable physiologic shunt and compatible to successful weaning trial.[4]

Oxygenation index (OI) is another measure of oxygenation and is determined as follows: (Mean Airway Pressure [MAP] x FiO_2)/PaO_2. It was originally used as a criterion in identifying neonates who would benefit from extracorporeal membrane oxygenation (ECMO). However, in adults, it has recently been suggested as a more accurate means of determining severity of respiratory failure compared to PaO_2/FiO_2 ratio, and is a statistically significant predictor of death, failure of conventional ventilation, and need for rescue therapies such as inhaled epoprostenol, paralytics, airway pressure release ventilation and ECMO.[6-8] As the parameter involves MAP, any change in PEEP, peak inspiratory pressure (PIP), inspiratory time, and respiratory rate, which can all affect MAP, is reflected in the OI.

However, both the PaO_2/FiO_2 Ratio and OI require arterial blood gas determination, which can be technically difficult to perform, and is costly and not readily available in some centers. The pulse oximeter is an alternative, reliable, and inexpensive means of monitoring hypoxemia by measuring the approximate oxyhemoglobin saturation (SpO_2). It has a good correlation with arterial oxygen saturation (SaO2) when the SaO2 is 95% or greater.[9] In an attempt to find other non-invasive invasive means of determining oxygenation in type 1 respiratory failure patients, Otekeiwebia et al studied the performance of oxygen saturation index (OSI), which is the result of (MAP x FiO_2)/SPO_2, and found it to have a strong linear association with OI and PaO_2/FiO_2 ratio in patients with type 1 respiratory failure.[10]

Currently, there is no published data in adults regarding the use of OSI as a surrogate to PaO_2/FiO_2 Ratio in patients with ARDS. This study aimed determine the performance of OSI as compared with PaO_2/FiO_2 ratio in the diagnosis of ARDS in patients at the University of Santo Tomas Hospital (USTH) Intensive Care Unit from January 2012 to December 2015.

METHODOLOGY

All patients, of any age and gender, diagnosed with ARDS based on the Berlin criteria, admitted at the USTH Intensive Care Unit from January 2012 to December 2015 were included in the study. Patients with incomplete data and those with ARDS admitted at the regular ward were excluded. Request for permission to review the medical charts were done. The name, age, gender, co-morbidities and outcome of each patient were recorded.

Simultaneous arterial blood gas, pulse oximetry and mechanical ventilator setting were extracted from the ventilator flowsheet during the first 1, 24, 48 and 72 hour of mechanical ventilation. The PaO2/FiO2 Ratio, OI and OSI were calculated from the given data.

Measures of central tendency were used to describe continuous numerical variables and percentage frequency distribution for categorical data. Descriptive statistics and two-way scatterplots were used to characterize the relationship between PaO_2/FiO_2 Ratio, OI and OSI. A linear modeling was used to derive the predictive equation for OSI between PaO_2/FiO_2 ratio and OSI.

RESULTS

Out of the 43 records reviewed, 27 patients fulfilled the inclusion and exclusion criteria, 56% (n=15) of which were males, with a mean age of 57 years old (20 to 90 years). Forty-eight percent of the patients were eventually discharged, with an average of 27 days of confinement. Most common co-morbidities included pneumonia, chronic kidney disease, urinary tract infection and pulmonary congestion. There was an almost equal distribution between ARDS severity classes (Table 1).

Table 1. Clinical profile of included parients

Age (mean, range)	57 years old (20-90)
Gender (n,%)	
Male	15 (56%)
Female	12 (44%)
Outcome (n,%)	
Discharged	13 (48%)
Expired	11 (41%)
Transferred	3 (11%)
Length of stay (days, range)	27 (1-74)
Comorbidities (n)	
HAP	7
CAP	7
CKD	6
UTI	6
Pulmonary congestion	5
VAP	5
PCP	5
Hypertension	4
HCAP	4
PTB	4
Bronchial asthma	3
Myocardial infarction	3
AKI	3
COPD	3
CAD	2
Diabetes mellitus	2
SLE	2
CHF	2
Pulmonary contusion	2
AML	2
Febrile neutropenia	2
Septic shock	2
Candidiasis	2
Others	23
ARDS severity (n,%)	
Mild	29 (34%)
Moderate	32 (38%)
Severe	24 (28%)

HAP, hospital-acquired pneumonia; CAP, community-acquired pneumonia; CKD, chronic kidney disease; UTI, urinary tract infection; VAP, ventilator-associated pneumonia; PCP, *Pneumocystis carinii* pneumonia; HCAP, health care-associated pneumonia; PTB, pulmonary tuberculosis; AKI, acute kidney injury; COPD, chronic obstructive pulmonary disease; CAD, coronary artery disease; SLE, systemic lupus erythematosus; CHF, congestive heart failure; AML, acute myelogenous leukemia; ARDS, acute respiratory distress syndrome.

Eighty-five arterial blood gas, SpO2 and MAP values from these patients were recorded. The averages for the three tests for the four time interval have no significant differences (Table 2).

Correlation matrix showed that the PaO_2/FiO_2 ratio was inversely related to OI and OSI (Tables 3 and 4), but the correlation was stronger with OI than with OSI.

OI was also found to be a significant indicator of PaO_2/FiO_2 Ratio (R^2=73.2%) *(Figure 1)*, with an increase in OI corresponding to a 584.59 decrease in PaO_2/FiO_2 Ratio.

Table 2. Average PaO_2/FiO_2 Ratio, OI and OSI for each time interval

Test	ABG	Mean (95% CI)
PaO_2/FiO_2	1 hr	154.94 (112.97-196.91)
	24 hrs	231.21 (168.92-293.5)
	48 hrs	209.62 (161.27-257.98)
	72 hrs	277.58 (155.8-399.36)
	Total	218.34 (181.46-255.22)
OI	1 hr	0.11 (0.07-0.14)
	24 hrs	0.09 (0.05-0.12)
	48 hrs	0.09 (0.06-0.12)
	72 hrs	0.11 (0.07-0.15)
	Total	0.1 (0.08-0.12)
OSI	1 hr	0.11 (0.09-0.13)
	24 hrs	0.09 (0.07-0.11)
	48 hrs	0.09 (0.07-0.11)
	72 hrs	0.11 (0.08-0.13)
	Total	0.1 (0.09-0.11)

ABG, arterial blood gas; PaO2, arterial partial pressure of oxygen; FiO2, fraction of inspired oxygen; OI, oxygenation index; OSI, oxygen saturation index.

OSI was also a significant indicator of PaO_2/FiO_2 Ratio (R^2=58.5%) (Figure 2), but to a lesser degree than OI, with an increase in OSI corresponding to a 683.23 decrease in PaO_2/FiO_2 Ratio. Likewise, OI and OSI are directly correlated with each other, with OI being a significant indicator of OSI (R^2=88.4%). An increase in OI corresponded to a 0.604 increase in PaO_2/FiO_2. The following predictive equation of PaO_2/FiO_2 ratio was derived: PaO_2/FiO_2 Ratio = exp (3.33 + 0.03*[SpO_2] – 9.92*[OSI] – 0.02*[f] + 0.06*[MAP]) (R^2 = 61.41%). Figure 3 shows good correlation between actual and predicted PaO_2/FiO_2 ratio using this formula.

DISCUSSION

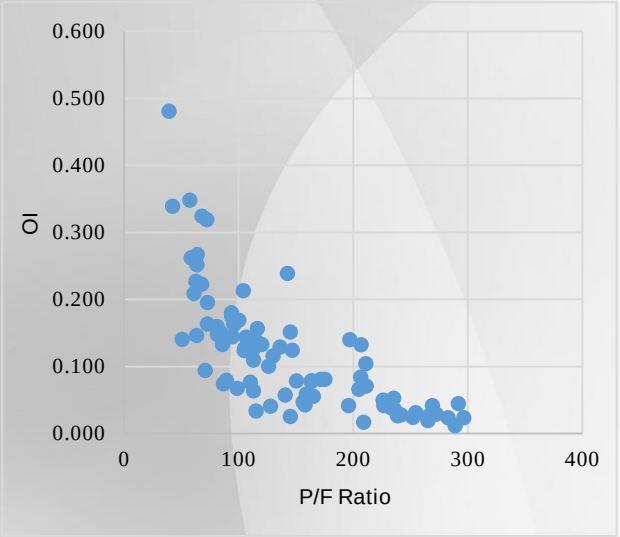
ARDS is a critical illness that needs not only constant clinical assessment, but serial arterial blood gas extractions as well. And the importance of oxygenation monitoring cannot be overemphasized. Unfortunately, due to its financial burden and technical difficulty, particularly in resource limited areas, this is not always practical.

Table 3. Correlation Matrix (ratio) between PaO_2/FiO_2 Ratio, OI and OSI.

	PaO_2/FiO_2	OI	OSI
PaO_2/FiO_2	1	-0.732*	-0.585*
OI	-0.732*	1	0.884*
OSI	-0.585*	0.884*	1

*Correlation is significant at 1% level.

Figure 1. Scatterplot of PaO_2/FiO_2 ratio values versus OI



This study has shown that OSI can be an acceptable alternative to the more expensive PaO_2/FiO_2 Ratio and OSI in determining the oxygenation status of ARDS patients. Of course, it has certain limitations. Artifacts, sunlight, nail polish, improper placement, low perfusion states and presence of dyshemoglobin can give inaccurate OSI results.[10]

Likewise, factors which affect oxygen affinity to hemoglobin, such as changes in carbon dioxide, hydrogen ions, 2-3-diphosphoglycerate and temperature, and presence of carbon monoxide, can influence oxygen saturation.[11] These factors can occur in combination, especially in critically ill patients. Hence, use of the

Table 4. Correlation Matrix (ratio) between PaO_2/FiO_2 Ratio, OI and OSI for each time period.

	After 1 hour			After 24 hours			After 36 hours			After 72 hours		
	P/F	OI	OSI	P/F	OI	OSI	P/F	OI	OSI	P/F	OI	OSI
PaO_2/FiO_2	1	-0.667*	-0.514*	1	-0.631*	-0.552*	1	-0.748*	-0.534*	1	-0.528*	-0.500*
OI	-0.667*	1	0.890*	-0.631*	1	0.922*	-0.748*	1	0.859*	-0.528*	1	0.869*
OSI	-0.514*	0.890*	1	-0.552*	0.922*	1	-0.534*	0.859*	1	-0.500*	0.869*	1

*Correlation is significant at 1% level.

Figure 2. Scatterplot of PaO_2/FiO_2 ratio values versus OSI

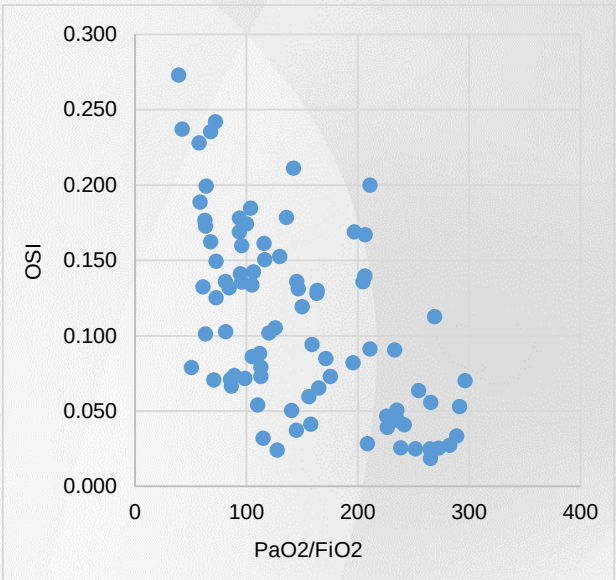
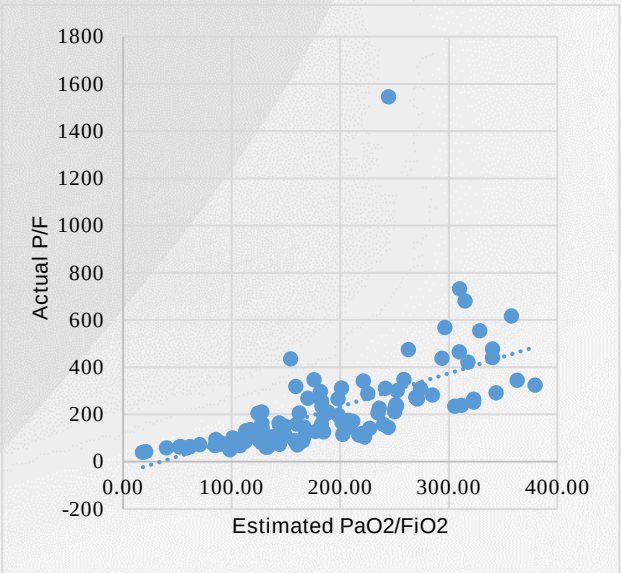


Figure 3. Scatterplot of actual versus predicted PaO_2/FiO_2 Ratios



predictive equation must be interpreted with due consideration of each patient's comorbidities.

Since this is a retrospective study, a prospective study assessing the clinical application of OSI as an alternative to PaO_2/FiO_2 Ratio is recommended.

CONCLUSION

OSI may be a noninvasive surrogate measure of oxygen dysfunction in patients with ARDS. A prospective study is recommended to further assess its clinical application.

REFERENCES

1. Lee WL, Slutsky AS. Acute Hypoxemic Respiratory Failure and ARDS. Murray and Nadel's Textbook of Respiratory Medicine, 6th edition, Edited by Broaddus VC, et al. Philadelphia, Elsevier Saunders, 2015. p 1742.
2. Fanelli V, Vlachou A, Zhang H, et al. Acute respiratory distress syndrome: new definition, current and future therapeutic options. J Thoracic Dis., 2013; 5(3):326-334.
3. Ranieri VM, Rubenfeld GD, Thompson BT et al. Acute respiratory distress syndrome: the Berlin Definition. J Am Med Assoc 2012; 307(23):2526-2533.
4. Chang DW, Hiers JH. Weaning from Mechanical Ventilation. Clinical Application of Mechanical Ventilation, 4th edition, Edited by Chang D. New York, Delmar Cengage Learning, 2014. p522.
5. El-Khatib MF, Jamaleddine GW. A new oxygenation index for reflecting intrapulmonary shunting in patients undergoing open-heart surgery. Chest 2004; 125:592-596.
6. Davies K, Bourdeaux, Gould T, et al. Oxygenation index outperforms the P/F ratio for mortality prediction. Crit Care 2014; 18(Suppl 1): p266.
7. Seeley E, McAuley DF, Kallet RH et al. Predictors of mortality in acute lung injury during the era of lung protective ventilation. Thorax 2008; 63(11):994-998.
8. Agarwal V, Almeida R, Gaurav K, et al. Oxy-

genation Index as a predictor of failure of conventional ventilation and mortality in Acute Respiratory Distress Syndrome. Am J Respir Crit Care Med 2013; 187:A2215.
9. Niehoff J, Delguercio C, LaMorte W, et al. Efficacy of pulse oximetry and capnometry in postoperative ventilator weaning. Crit Care Med 1999; 16(7):701-705.
10. Chop W, Chang D. Monitoring in Mechanical Ventilation. Clinical Application of Mechanical Ventilation, 4th edition, Edited by Chang D. New York, Delmar Cengage Learning, 2014. P259.
11. Powell FL, Wagner PD, West JB. Ventilation Blood Flow, and Gas Exchange. Murray and Nadel's Textbook of Respiratory Medicine, 6th edition, Edited by Broaddus VC, et al. Philadelphia, Elsevier Saunders, 2015. p59.
12. Otekeiwebia A, Ajao O, Ingrid P, et al. Performance of oxygen saturation index among adults with type 1 respiratory failure. Crit Care Med 2014; 42(12 Supp 1): pA1521.

RETROSPECTIVE COHORT STUDY

Turnaround Time for Smear-negative Category I Cases to Initiation of Treatment in District IV of Manila from January 2014 to December 2014

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ABSTRACT

Background: The diagnosis of tuberculosis (TB) requires bacteriologic confirmation through direct sputum smear microscopy to allow early access to treatment. However, smear-negative cases are a commonly experienced diagnostic dilemma. Certification of disease activity from TB Diagnostic Committee (TBDC) is needed to curb unnecessary treatment. Turnaround time starts from the collection of the first sputum sample to the initiation of treatment—this should be within 5 working days based on local guidelines.

Objectives: To determine the mean turnaround time for new smear-negative pulmonary TB (PTB) cases in District IV of Manila referred to the USTH TBDC from January to December 2014.

Methods: A retrospective descriptive study was done to determine the number of days it took for new smear-negative PTB cases to initiate treatment. Demographic data was noted. The intervals between submission of sputum, TBDC certification and the first dose of anti-TB medication were obtained and used for the calculation of turnaround time.

Results: There were 153 patients in the study. The mean total turnaround time was 37.78 $\pm$ 24.62 days, with a mean of 14.30 $\pm$ 18.58 days from sputum collection to follow-up at the health care facility (return of results and referral to TBDC); 12.74 $\pm$ 10.15 days thereafter to TBDC decision to treat; and another 10.69 $\pm$ 15.18 days to initiation of treatment at the health care facility.

Conclusion: There was significant delay in the initiation of treatment among smear-negative PTB cases, mostly observed between sputum collection and TBDC referral. This reflects a poorly functioning default tracing mechanism among Directly Observed Treatment Strategy facilities even at the diagnostic phase, which has negative implications for infection prevention and control.

INTRODUCTION

Tuberculosis (TB) is a major global health problem, ranking as the second leading cause of death from an infectious cause worldwide after the human immunodeficiency virus. Among 9.0 million new TB cases in 2013, there have been 1.5 million associated deaths. Globally, TB mortality rate has fallen by 45% since 1990 and incidence rates have decreased in most parts of the world.[1] However, in the Philippines where TB is the sixth leading cause of morbidity and mortality, the country ranks ninth out of the 22 highest TB-burden countries in the world.[2,3]

Identification and diagnosis of TB cases among individuals with signs and symptoms suggestive of TB entails direct sputum smear microscopy. The National TB Program (NTP) adopts this primary diagnostic method because it provides definitive diagnosis of active TB, it is simple and economical to do, and a microscopy

center could easily be put up in remote areas. The chest x-ray is used to complement bacteriologic testing to arrive at a diagnosis. However, it has low specificity and is unable to differentiate drug-susceptible from drug-resistant disease.[4]

Any person with signs and/or symptoms suggestive of TB or those with chest x-ray findings suggestive of active TB is referred to as Presumptive TB. These patients should undergo direct sputum smear microscopy for two determinations unless he/she is in a situation that prohibits this requirement. If at least one sputum smear is positive for acid-fast bacilli (AFB), the patient is classified as bacteriologically-confirmed pulmonary TB (PTB) and should start treatment. However, if both sputum smears are negative for AFB, the patient may be referred to a Xpert MTB/RIF site for testing. If the patient has no access to Xpert MTB/RIF or could not expectorate, the Directly Observed Treatment, Short-course (DOTS) physician will use his best clinical judgment to decide if a diagnosis of active TB is warranted. Referral to a specialist or a TB Diagnostic Committee (TBDC) may be done to confirm active TB diagnosis. In either case, the patient is classified as clinically-diagnosed TB.[4,5]

In District IV of Manila, patients with two negative sputum AFB smears and chest radiograph findings suggestive of PTB are referred by their respective health centers to the TBDC Center at the University of Santo Tomas Hospital. This committee meets twice a month to discuss each case prior to arriving at a consensus on whether a patient would warrant anti-TB treatment.

Providers must recognize that early and accurate diagnosis is critical in TB care and control.[6] Diagnostic delays result in ongoing transmission in the community and more severe, progressive disease in the affected person.[7]

Turnaround time refers to the time from collection of the first sputum sample to initiation of treatment for TB, which is desired to be within 5 working days.[4] In a systematic review of time delays in the diagnosis of PTB, the average patient delay was 31.7 days and health system delay was 28.5 days for low-income countries.[9] However, there is no published data on the actual turnaround time for patients belonging to smear-negative category 1 up to initiation of treatment. The Philippines, being a high TB burden country, needs to achieve the desired turnaround time to prevent transmission and achieve disease control. This study aimed to determine the turnaround time specifically for smear-negative category 1 cases to initiation of treatment in District IV of Manila.

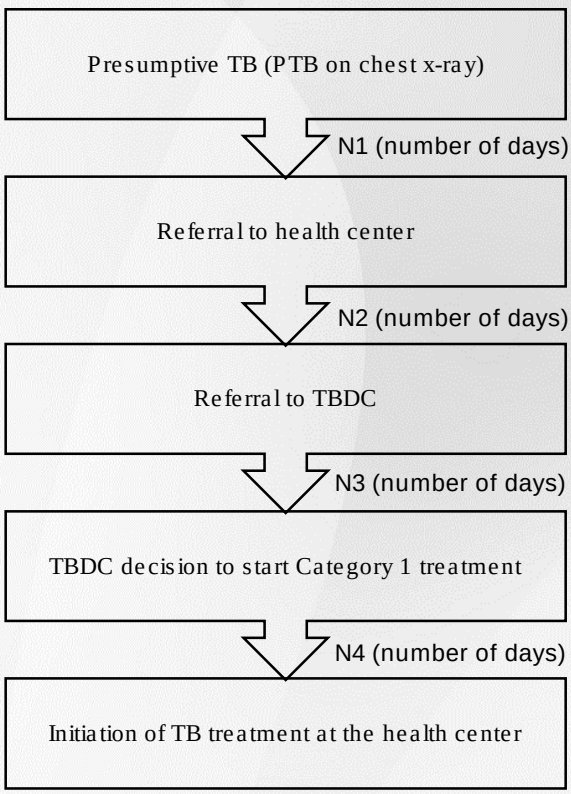
METHODS

This study included all patients of any age and gender from District IV of Manila who are suspected of having presumptive PTB based on chest radiograph findings and had negative sputum AFB smear results and referred to the TBDC of USTH for Category I treatment from January 2014 to December 2014. Patients with incomplete data were excluded.

The following data were then requested from the appropriate health centers of Distric IV of Manila: date of first sputum collection, date the sputum results were brought back to the health center, date the patient was referred to the USTH TBDC, date of TBDC decision to start Category 1 treatment, and date anti-TB medications were initiated at the health center. Demographic data were also obtained. Each patient was then assigned a case number for confidentiality purposes.

Based on the retrieved information, the following information were calculated: the number of days from first sputum collection to the time sputum results were brought back to the health center (N1); the number of days from

Figure. Schema of time intervals assessed in the study



TB, tuberculosis; PTB, pulmonary TB; TBDC, TB Diagnostic Committee.

the return of sputum results to the time of referral to USTH TBDC (N2); the number of days from the time the health center referred the patient to the USTH TBDC to the time the TBDC decides to start Category 1 treatment (N3); and the number of days from TBDC output to the time anti-TB medications were initiated at the health center (N4) (Figure).

The data obtained was listed and tabulated using Microsoft Xcel and the data analyzed using descriptive statistics. Measures of central tendency were used for continuous numerical variables and percentage frequency distribution for categorical data.

RESULTS

There were 153 patients included in the study (55% male and 44% female). The mean age of the population was 36.87 years.

The mean total turnaround time was 37.78 ± 24.62 days, with a mean of 14.30 ± 18.58 days from the first sputum collection to follow-up at the health care facility and TBDC referral (N1+N2); 12.74 ± 10.15 days thereafter to TBDC referral and decision to start treatment (N3) and another 10.69 ± 15.18 days to initiation of treatment (N4) (Table).

Table. Mean turnaround times

Time interval	Time (days)
N1 + N2: From 1st sputum sample to health care facility follow-up (return of results and referral to TBDC)	14.36 ± 18.58 days
N3: From health care facility follow-up to TBDC decision to start treatment	12.47 ± 10.15 days
N4: From treatment decision of TBDC to initiation of treatment at health care facility	10.69 ± 15.18 days
Total turnaround time	37.78 ± 24.62 days

TBDC, Tuberculosis Diagnostic Committee.

DISCUSSION

The TBDC was originally set up by the Department of Health NTP with the advice of the World Health Organisation-Western Pacific Regional Office to help prevent over-diagnosis of PTB using chest x-ray. Its main function is to review symptomatic smear-negative cases with chest x-ray findings suggestive of PTB or referred cases with such radiologic features that may warrant anti-TB treatment. It is composed of an NTP coordinator, a radiologist, a clinician or internist often represented by a pulmonologist or

an infectious disease specialist, and an NTP nurse. Each case is discussed and a consensus among the members is reached regarding the proper management. This decision is mainly recommendatory and is forwarded to the referring physician or unit; however, it must be adhered to if the DOTS services provided by the health center is to be availed.[5]

The turnaround time determined by this study (37.78 $\pm$ 24.62 days) exceeds what has been set by the local guidelines (5 working days). Significant delay of the initiation of treatment among smear-negative PTB cases was mostly observed between the first sputum collection to follow-up at the health care facility and TBDC referral.

In previous studies, the three main reasons for the delay in diagnosing TB are the following: the affected person either does not seek or does not have access to healthcare; the provider does not suspect the disease; and the most commonly available diagnostic test, sputum smear microscopy, lacks sensitivity.[6,8,9] In the study, contributing factors include prolonged processing of direct sputum smear microscopy, poor patient follow-up, and reliance on the TBDC decision for smear-negative cases.

Reducing delay on the part of the person entails providing accessible health care facilities, enhancing community and individual awareness, and active case-finding in high-risk populations.[10] Provider delay is best reduced by increasing provider awareness of the risks and symptoms of TB and of the appropriate and available WHO-approved diagnostic tests in their communities. Rapid molecular tests such as GeneXpert MTB/RIF that increase both the speed and sensitivity of identifying *Mycobacterium tuberculosis* are increasingly available.[7]

Providers must recognize that early and accurate diagnosis is critical in TB care and control.[6] Diagnostic delays result in ongoing transmission in the community and more severe, progressive disease in the affected person.[7]

Patients with sputum smears negative for AFB are considered less infectious than patients who are smear positive. However, they also contribute to TB transmission. In the Netherlands, patients with smear-negative culture-positive TB are responsible for 13% of TB transmission.[11] In the United States, these patients are responsible for 17% of TB transmission.[12] Thus, early diagnosis and initiation of treatment of sputum smear-negative patients is crucial to prevent transmission.

Based on the results of this study, we recommend the improvement in patient follow-up, increased provisions for direct sputum smear microscopy, and training of primary care physicians in the diagnosis of PTB based on clinical and chest radiograph findings. These measures may decrease the turnaround time for the prompt diagnosis and treatment of the disease and prevention of disease progression and transmission.

CONCLUSION

There was significant delay in the initiation of treatment among smear-negative PTB cases, mostly observed during the follow-up visits after sputum collection and interval time to TBDC referral. This reflects a poorly functioning default tracing mechanism among DOTS facilities even at the diagnostic phase, which has negative implications for infection prevention and control.

REFERENCES

1. World Health Organization Global Tuberculosis Report 2014. Geneva: World Health Organization; 2014.
2. Vianzon R, et al. The Tuberculosis Profile of the Philippines, 2003-2011: Advancing DOTS and beyond. Western Pac Surveill Resonse J. 2013 Apr-Jun: 4(2): 11-16.

3. National Tuberculosis Control Program. Manila: Department of Health; 2011.
4. National Tuberculosis Program Manual of Procedures 5th edition: 2014. Manila: Department of Health; 2014.
5. Diagnosis, Treatment, Prevention & Control of Tuberculosis in Adult Filipinos: 2006 Update. Manila: Department of Health; 2006.
6. World Health Organization. Early detection of tuberculosis: An overview of approaches, guidelines and tools. Geneva: World Health Organization; 2011.
7. International Standards for Tuberculosis Care Diagnosis, Treatment, Public Health, 3rd edition; 2014. Geneva: World Health Organization; 2014.
8. Storla DG, et al. A systematic review of delay in the diagnosis and treatment of tuberculosis. BMC Public Health. 2008; 8:15.
9. Sreeramareddy CT, et al. Time delays in diagnosis of pulmonary tuberculosis: a systematic review of literature. BMC Infect Dis. 2009; 9:91.
10. World Health Organization. Integrating community-based tuberculosis activities into the work of nongovernmental and other civil society organization. Geneva: World Health Organization; 2012.
11. Totsmann A, et al. Tuberculosis Transmission by Patients with Smear-Negative Pulmonary Tuberculosis in a Large Cohort in The Netherlands. Clinical Infectious Diseases 2008;47:1135-42.
12. Behr M, et al. Transmission of Myco-bacterium tuberculosis from patients smear negative for acid-fast bacilli. Lancet 1999; 353;444-449.

LONGITUDINAL DESCRIPTIVE STUDY

Neurocognitive outcome of patients with delirium in the intensive care units at a tertiary government hospital

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Introduction: Delirium among patients admitted in intensive care units (ICU) is associated with impairment of cognitive function. This study aims to describe the development of cognitive impairment among patients who developed ICU delirium.

Methods: This is a non-interventional, descriptive, longitudinal study that included patients with ICU delirium. The Montreal Cognitive Assessment Philippine Version (MoCA-P) was used to assess cognitive function. Visual Reproduction (VR) and Logical Memory (LM) subtests of the Wechsler Memory Scale-Fourth Edition (WMS-IV) and the Symbol Search (SS) subtest of the Wechsler Adult Intelligence Scale-Fourth Edition (WAIS-IV) were also performed to further assess the cognitive profile of the subjects.

Results: Out of 39 patients diagnosed to have ICU delirium from November 2014 to February 2015, only 8 subjects were available for evaluation in this follow-up study due to high mortality rate. 6 out of 8 patients (75%) developed cognitive impairment (MoCA-P score <20) 18 months after hospital discharge. Together with the VR and LM subtests of WMS-IV and the SS subtest of WAIS-IV, item analysis showed that the cognitive domains affected are memory, executive function and processing speed.

Conclusions: Critically ill patients who developed delirium during their ICU admission are at high risk for development of long-term cognitive impairment. These findings underline the importance of detection and treatment of ICU delirium as it leads to a high risk of mortality and poor cognitive outcome among survivors.

Keywords: cognitive outcome, dementia, delirium, intensive care unit, critical illness

INTRODUCTION

Current advances in critical care medicine have greatly improved survival in patients admitted to the intensive care unit (ICU).[1] However, cognitive and psychiatric impairments frequently occurs among survivors of critical illness and are associated with development of long-term cognitive complications.[2] Among patients admitted in the ICU, delirium is found to be common during critical illness and is associated with cognitive decline and mortality.[3]

Delirium is an acute brain dysfunction that affects approximately 20% to 80% of ICU patients, depending on the severity of illness.[4] Patients who developed delirium during their ICU admission were three times more likely to have cognitive dysfunction 3 years after discharge.[5] Several other studies report varying incidences of long-term cognitive dysfunction after ICU discharge.[3,6,7] Cognitive impairment among ICU survivors is associated with poor outcomes from rehabilitation and increased risk

of institutionalization, mostly because of inability to fully participate in rehabilitation activities due to impairment in executive function, inability to remember therapy instructions, or deranged implicit and explicit learning ability.[8] In contrast, improvement of cognition may directly improve rehabilitation outcomes.[9]

Currently, most studies focus on the prevalence and risk factors of ICU delirium, with only few studies on the neuropsychological profile of patients with cognitive decline after delirium. This study aimed to describe long-term (18 months) cognitive impairment in critically ill patients who developed ICU delirium at a tertiary government hospital.

METHODOLOGY

This is a non-interventional, descriptive, longitudinal study which included participants who were previously admitted in the medical, neurological, and surgical ICUs of a tertiary government hospital. This is the second part of a prior study that detected delirium in ICU patients. Only patients who developed delirium in the first part of the study were evaluated.

Study Population and Setting

Out of the 196 ICU patients observed in the first part of the study, 39 patients were diagnosed with delirium. Only 20 patients were discharged alive, and of these, two patients died within 6 months of hospital discharge. Of the 18 patients eligible for long-term follow-up, 10 patients were lost to follow-up. Hence, only 8 patients were included in the analysis for the presence of cognitive decline 18 months from hospital discharge.

Informed consent was acquired from the patient or a legal representative before the conduct of any study intervention. Chart review of the 8 patients was done to obtain information related to their admission in the ICU, such as the reason for admission, number of hospital days prior to onset of delirium, onset and duration of delirium, use of sedation, use of mechanical ventilation, number of days on mechanical ventilation, and date of discharge.

Assessment of Cognitive Function

A trained and experienced psychologist who was unaware of the patient's hospital course evaluated the patients in a clinic in our institution to avoid interrater variability in the assessment of cognitive function of the participants. The primary investigators were not allowed to enter the examination room so as not to influence the psychologist in the conduct of the examination.

The Montreal Cognitive Assessment test, Philippine version (MoCA-P) was the standard test used to assess cognitive function. The core domains assessed in this tool include Orientation, Visuo-graphic or visuo-spatial function, Registration, Semantic memory, Sustained attention, Language, and Executive functions. Executive functions were divided into Mental tracking, Cognitive flexibility, Concept formation and Abstract reasoning. A MoCA-P cutoff of 20 was used as a cut-off for the presence of cognitive impairment.

The following tests were also conducted to assess the full cognitive profile of the patients:

1. Visual Reproduction I (Immediate Recall) [VR-1]. This test assessed memory for visual stimuli. The examinee was shown a series of 5 designs one at a time for 10 seconds each. After each design was presented, the examinee was asked to draw this from memory.
2. Logical memory I (Immediate Recall) [LM-1]. This assessed narrative memory under a free recall condition. Two short stories, both of which are Filipino adaptations of the Logical Memory subtest of the Wechsler Memory Scale, 4th Edition (WMS-IV), were presented orally one at a time. The patient was then asked to retell each story from memory immediately after.
3. Visual Reproduction II (Delayed Recall) [VR-2]. The delayed condition assessed long-term visuo-spatial memory with free recall. The examinee was asked to draw the 5 designs shown during the immediate recall phase in any order.

4. *Visual Reproduction-Recognition Phase* [VR-Rec]. The examinee was asked to choose which of 6 designs on a page matches the original design shown during the immediate recall phase.
5. *Logical Memory II* (Delayed Recall) [LM-2]. The delayed condition assessed long-term narrative memory with free recall. The examinee was asked to retell both stories from the immediate recall phase.
6. *Logical Memory-Recognition Phase* [LM-Rec]. The examinee was asked yes/no questions about both stories.
7. *Montreal Cognitive Assessment-Philippines (MoCA-P)* test for Visuospatial/Executive Functioning.
8. The *Symbol Search [SS] subtest of the Wechsler Adult Intelligence Scale – Fourth Edition (WAIS-IV)* is designed to assess processing speed, short-term visual memory, visual-motor coordination, visual discrimination, psychomotor speed, speed of mental operation, attention, and concentration. Working within a specified time limit (i.e., 120 seconds), the examinee scanned a group of symbols and indicated whether one of these matches either of 2 target symbols by marking either the "yes" or "no" box.

The protocol was approved by the institutional technical and ethical review board.

Table 1. Demographic and clinical characteristics of study participants

Variable	Value
Age (years), (mean, range)	59 (36-78)
Gender (n) *Male* *Female*	 5 3
Level of education (years) (mean, SD)	10.88 (3.18)
Diagnosis at ICU admission (n) *Neurologic* *Post-operative care monitoring*	 6 2
Length of ICU stay (days) (mean, SD)	8.62 (6.05)
No. of days in ICU before onset of delirium (mean, SD)	2.00 (2.00)
Duration of ICU delirium (days) (mean, SD)	4.25 (2.82)
MV on admission *Yes* *No*	 4 4
Days on MV (mean, SD) (n=4)	2.62 (3.78)

ICU, intensive care unit; MV, mechanical ventilation.

RESULTS

The study population had a mean age of 59 years, with more males than females, and with an average of 10 years of education (Table 1). Majority of the patients were admitted in the ICU due to neurological diseases, with an average length of ICU stay of 8.62 days. Delirium was diagnosed mostly on the second ICU day with duration of approximately 4 days. There is an equal number of participants who were previously on mechanical ventilation and those who were not during their ICU admission.

Based on the patients' total MoCA-P scores, 6 out of the 8 patients (75%) included in this prospective study have cognitive impairment 18 months after hospital discharge, with total MoCA-P scores $\leq$ 20 (Table 2). Given the small number of participants in the study, the scores of each patient in the different domains of MOCA-P were analyzed using a Boston Process Approach which used an error analysis of their performance per cognitive domain. In this analysis, the participants were classified into three categories (Table 2 and Figure) based on the number of errors committed in the battery: (1) High Performers (n=2), patients who did comparatively better than others in the study group, (2) Typical Performers (n=4), patients who performed like most of the other participants, and lastly (3) Atypical Performers (n=2) who can be regarded as outliers when compared to the rest in the group.

Two participants classified as atypical performers committed errors in 16/17 components

Table 2. Patient performance on neuropsychological battery

Px No.	MOCA-P Total Score	MOCA-P Interpre-tation	Visual Reproduction Interpretation			Logical Memory Interpretation			Symbol Search Interpre-tation (SS)
			Imme-diate Recall (VR-1)	Delayed Recall (VR-2)	Repro-duction Phase (VR-Rec)	Recall (LM-1)	Delayed Recall (LM-2)	Repro-duction Phase (LM-Rec)	
High Performer*									
5	25	N	VS	S	A	A	HA	A	A
8	24	N	A	HA	A	A	A	B	I
Typical Performer*									
1	19	I	LA	LA	I	B	B	A	I
2	12	I	I	I	I	I	I	I	LA
3	13	I	I	I	I	I	I	B	I
4	14	I	I	B	B	B	B	B	I
Atypical Performer*									
6	4	I	I	I	I	I	I	I	I
7	5	I	I	B	I	I	I	LA	I

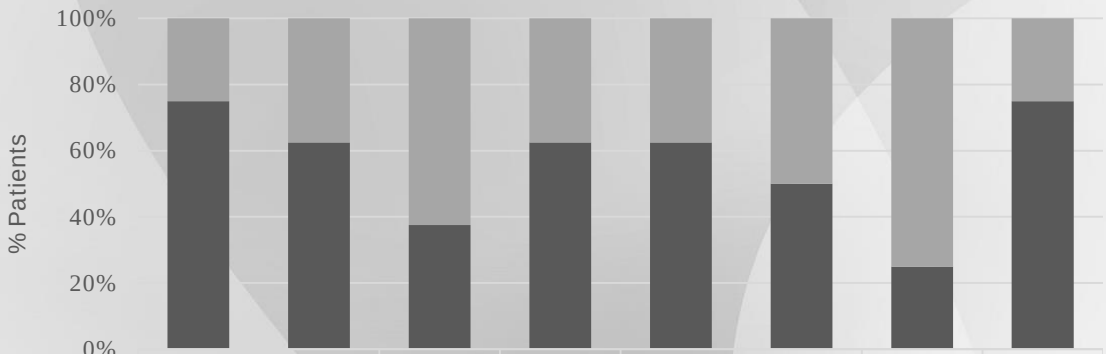
N=Normal; I=Impaired; VS=Very Satisfactory; S=Satisfactory; HA=High Average; A=Average; LA=Low Average B=Borderline.

of MoCA-P. One of these atypical performers presented with aphasia, while the other one presented with florid frontal features. The aphasic patient committed many mistakes, especially on items that required a verbal response. Qualitative analysis revealed that he committed several verbal/semantic paraphasing but seemed to know more than he could display based on the standardized way of administering the MoCA-P. The patient with florid frontal features was difficult to test because words within an instruction or test item would lead the participant to digress. This affected the manner the participant stored the new information on delayed recall. The tangentiality of though also contributed to forgetting more complex instructions. Given these features, the atypical performers were not included in the item analysis for MoCA-P as their inclusion could have an impact on trends that emerged with this small group of patients.

Based on the performance of the high and the typical performers, the components of cognitive function reasonably compromised were memory, executive function and processing speed (Table 3). Specifically, the patients had problems with working memory (i.e., storage/registration, praxis and visual memory, semantic memory and executive functions such as mental tracking, cognitive flexibility and abstract reasoning). On the other hand, the cognitive domains of visuo-graphic/visuo-spatial abilities, sustained attention, naming, concept formation and orientation to place were preserved (Table 4).

Qualitative analysis reveals that storage and retrieval of new visual information (i.e., geometric designs) was more compromised than that with new and complex verbal material (i.e., stories), in part perhaps because the latter is readily meaningful.

Figure. Number of patients with impairment for each neuropsychological test.



	MoCA-P	VR-1	VR-2	VR-Rec	LM-1	LM-2	LM-Rec	SS
Normal/At least average or Borderline	2	3	5	3	3	4	6	2
Impaired	6	5	3	5	5	4	2	6

Table 3. Compromised cognitive domains among high and typical performers (n=6)

Cognitive Domain	Neuropsychological Test	Remarks
Working Memory: Storage / Registration	MoCA-P: Digits Forward	• Half of the patients committed mistakes by interchanging the numbers.
Praxis & Visual Memory	MoCA-P: Word List (Immediate Recall)	• No one was able to succeed during the first learning trial. Only 3/6 were able to mention all 5 words by the second learning trial
Semantic Memory a. Verbal, simple	Visual Reproduction: VR-1, VR-2, VR-Rec	• Most patients (4/6) had low average, borderline and impaired scores.
b. Verbal, complex	MoCA-P: Word List (Delayed Recall)	• The patients needed cueing in remembering the words on the list, especially when the multiple choice format (vs. category cueing) was used.
	Logical Memory: LM-1, LM-2, LM-Rec	• Most patients (4/6) had low average, borderline and impaired scores but with better scores compared to VR tests.
Executive Function a. Mental Tracking	MoCA-P: Serial 7 (plus math computation)	• Most patients made 2-4 mistakes.
b. Cognitive Flexibility	MoCA-P: Trails	• 4/6 did not do well on this, largely due to difficulty switching from one category (i.e., numbers) to the other (i.e., letters).
	MoCA-P: Digits Backwards MoCA-P: Verbal Fluency	• Half of the patients committed mistakes.
c. Abstract Reasoning	MoCA-P: Similarities	• No one was able to generate the minimum 11 words in order to pass. Most patients generated only 3 – 6 words. • 4/6 patients committed mistakes on these items. They instead stated the differences of the objects they were being asked to compare.
Processing Speed	WAIS-IV: Symbol Search	• Most patients (5/6) had low average and impaired scores.

Table 4. Preserved cognitive domains

Cognitive domain	Neuropsychological Test	Remarks
Visuo-spatial Abilities	MoCA-P: copying of a cube, clock face and numbers	• No gross distortions or fragmentations seen. • All patients drew the clock face accurately. • Half of the patients drew some numbers in the wrong quadrant
Sustained attention	MoCA-P: Tap "A"	• Half of the patients did this perfectly while 2/6 patients committed only 1 – 2 mistakes.
Language	MoCA-P: Picture Naming	• 5/6 patients named all 3 pictures. The other patient could just not name the camel but she knew it is found in Saudi Arabia.
Concept Formation	MoCA-P: Clock drawing	• There does not seem to be a problem telling time with this group; they know what the short and hands signify • Clock hands: 3/6 patients had errors, usually because they drew hands of equal length. The errors with the clock hands suggest that they are not attuned enough to the significance of hand length as they were drawing • Clock time: only 1/6 committed an error.

DISCUSSION

Several studies have shown that delirium in the ICU is associated with mortality and long-term cognitive impairment. In this study, 6 out of 8 patients (75%) had cognitive impairment 18 months after hospital discharge. This finding complements those of earlier cohort studies wherein 40% of the patients has cognitive decline after 3 months, while 70% with severe cognitive impairment has persistent cognitive impairment one year after their critical illness.[3,6] One strength in this study is that we evaluated patients from all adult ICUs in our hospital, giving us a diverse population of critically ill patients. Most published studies are small cohort studies limited to a specific disease entity (e.g., post-stroke or post-operative patients).

In a study done by Pandharipande *et al.*, delirium increased the risk of long-term cognitive impairment affecting patients across all ages regardless of the severity of disease at baseline.[6] However, other prospective cohort studies showed that older adults who developed delirium during hospitalization were at 2.4-fold more at risk in developing cognitive impairment.[10,11] In our study, the youngest patient at 36 years old was already noted to have cognitive impairment. Furthermore, more severe illness and longer hospital stay were also associated with faster cognitive decline after hospitalization.[11] In line with previous studies, duration of ICU delirium has significant association with cognitive decline, wherein those with longer duration of delirium were found to have increased risk for long-term cognitive decline. The average length of ICU stay in this group of patients is at 8.62 days, with onset of delirium mostly on the second ICU day with duration of an average of 4.25 days.

While most studies on cognitive decline after critical illness are mainly epidemiologic, focusing on prevalence and the associated risk factors, this study presents a more in-depth analysis on the type of cognitive impairment manifested in this population, which makes it possible to determine a cognitive profile unique to this subset of patients. There are only a few

published papers that thoroughly examined this group of patients using an extensive neuropsychological battery; most studies use only short cognitive screening tools such as Mini-Mental State Exam (MMSE) and MoCA.

In our study, we found that patients with delirium after critical illness show difficulty in memory and executive functions. Problems with sustained attention were also felt to account for poor performance on a speeded clerical task, resulting in subjects working at a slower pace than expected. This is consistent with other studies where they have also shown that attention, memory, executive function, mental processing speed spatial abilities, and general intelligence were most affected.[11] Wilson et al. found that there is a 3.3-fold increase in the rate of cognitive decline on measures of episodic memory while there is a 1.7-fold increase in cognitive impairment on measures of executive function.[10] Multiple cognitive domains are affected, unlike in Alzheimer's disease where delayed memory is usually affected. In another similar on post-stroke patients who developed delirium, the cognitive domains affected were memory, language, visual construction and executive functioning.[12] In our study, language and visuo-spatial abilities were relatively spared.

Impairment on memory tests are always accompanied by impairment in other domains such as semantic fluency and executive function since both domains involve the frontal lobes, frontal subcortical areas and limbic lobe. Frontal features were also evidenced which impacted on semantic memory. These included inattention to details (which led to inaccurate recognition on multiple-choice formats) and cognitive inflexibility (which led to perseverative errors). Studies have shown that neurotransmitter abnormalities, such as reduction in cholinergic activity leading to relative dopamine excess in the central nervous system, and occult diffuse brain injury are important mechanisms that underlies critical illness associated cognitive decline.[13] There is still a need for further neurophysiologic studies to better understand the underlying mechanism behind cognitive decline after ICU delirium and possibly, to determine the effect of early intervention on the cognitive impairment seen in these patients.

There are a number of limitations to our study. First, only a relatively small percentage of patients were evaluated, mainly due to the high mortality during the follow-up period. This underlies the fact that ICU delirium is associated with a high risk of mortality. Second, we only tested the patients at one follow-up period (18 months) without any intermediate assessment. There might be other confounding factors during the time interval which may have affected the patients' cognitive functioning. In addition, we do not know exactly when the cognitive impairment developed in this group of patients. The authors recommend re-assessment of the patients after 6 months to see if there is further decline in the patients' cognition.

CONCLUSION

Long-term cognitive impairment is found in a large proportion of survivors of critical illness who developed ICU delirium during their hospital admission. Patients with longer duration of delirium are more likely to develop cognitive decline which may persist even a year after their critical illness. The components of cognitive function reasonably compromised include memory, executive function and processing speed while visuo-graphic/visuo-spatial abilities, sustained attention, naming, concept formation and orientation to place were relatively spared. These findings underline the importance of detection and treatment of ICU delirium as it leads to cognitive decline. Further periodic evaluation is recommended to monitor the progression of cognitive impairment.

REFERENCES

1. Adhikari NK, Fowler RA, Bhagwanjee S, Rubenfeld GD. Critical care and the global burden of critical illness in adults. Lancet 2010;376:1339-1346.
2. Karnatovskaia L, Benzo R, Gajic O. The Spectrum of psychocognitive morbidity in the critical ill: A review of the literature and call for improvement. J Crit Care 2015;30:130-137.
3. Girard TD, Jackson JC, Pandharipande PP, et al. Delirium as a predictor of long-term cognitive impairment in survivors of critical illness. Crit Care Med 2010;38:1513-1520.
4. Girard TD, Ely W. Delirium in the intensive care unit. Critical Care 2008;12(Suppl 3):S3.
5. Ely E, Jackson J, Tomason J, Truman B, Gordon S, Dittus R, Bernard G. Current opinions regarding the importance, diagnosis, and management of delirium in the intensive care unit: a survey of 912 healthcare professionals. Crit Care Med 2004;32:106-112.
6. Pandharipande P, Jackson J, et al. Delirium as a predictor of long-term cognitive impairment after critical illness. New Engl J Med 2013;369:1306-1316.
7. Hopkins R. Long-term Neurocognitive Function after Critical Illness. Chest 2006;130(3):869–878.
8. Wergin R, Modrykamien A. Cognitive impairment in ICU survivors: Assessment and therapy. Cleveland Clinic J Med 2012;79(10):705-712.
9. Whyte E, Aizenstein H, Ricker J, Butters M. Cognitive impairment in acquired brain injury: a predictor of rehabilitation outcomes and an opportunity for novel interventions. PM R 2011;3 (suppl 1):S45-S51.
10. Hsieh SJ, Madahar P, Hope A, Zapata J, Gong M. Clinical deterioration in older adults with delirium during early hospitalization: a prospective cohort study. BMJ Open 2015; 5: e007496.
11. Wilson R, Hebert L, Scherr P, Dong X, Leurgens S, Evans D. Cognitive decline after hospitalization in a community population of older persons. Neurology 2012;78(13): 950-956.
12. van Rijsbergen M, Oldenbeuving A, Nieuwenhuis-Mark R, et al. Delirium in acute stroke: A predictor of subsequent cognitive impairment? A two-year follow-up study. J Neurol Sci 2011; 306:138-142.
13. Milbrandt E, Angus D. Bench to bedside review: Critical illness-associated cognitive dysfunction - mechanisms, markers, and emerging therapeutics. Critical Care 2006;10:238.

RETROSPECTIVE COHORT STUDY

Prevalence of tuberculosis infection in cancer patients at Veterans Memorial Medical Center

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ABSTRACT

Cancer patients have depressed adaptive cellular immunity, which predisposes them to infections associated with cell-mediated immunity deficiencies such as tuberculosis (TB). Cancer therapy also adds to adaptive cellular immunity dysfunction, further increasing the risk of TB or TB reactivation.

This study retrospectively reviewed charts of histologically diagnosed cancer patients and assessed for TB or TB reactivation prior, during and after cancer specific therapies. The overall computed period prevalence of TB infection in cancer patients was 2.3% or 6 cases per person-years. TB infection developed in 67% of patients prior to cancer-specific therapies, 5% during the duration of cancer-specific therapy and 28% after cancer-specific therapy completion. Cancer therapy was associated with an odds ratio of 15 for TB infection (95% CI 3.10, 77.74; p=0.0009). Among the different cancer types, 12.5% of TB patients developed in lung cancer patients (OR 5.96; 95% CI 1.25, 28.41; p=0.0252). Six percent developed in patients with hematologic and bone malignancy, 2.8% in those with head and neck malignancies, 2.5% in breast cancer patients, 2% in patients with gastrointestinal malignancy and 1.3% in genitourinary malignancy patients. Factors associated with increased odds of TB infections include pulmonary manifestations (OR 4.92; 95% CI 1.52, 15.91; p=0.0077) and history of previous TB infection and treatment (OR 5.80; 95% CI 2.00, 16.66; p<0.0012).

These results show that proper assessment for concurrent TB infection should be done upon cancer diagnosis and prior to initiation, during and after cancer-specific therapies.

Key words: prevalence, cancer, tuberculosis

INTRODUCTION

Patients with depressed adaptive cellular immunity such as those with cancer are at increased risk of tuberculosis (TB) infection or reactivation.[1] Chemotherapy and radiation therapy can further amplify the risk of primary infections and reactivation of chronic indolent infection.[2]

A comprehensive review of TB in cancer patients done from 1989 to 1994 in the US revealed a significant difference from previous years in terms of demographics and cancer therapy. Hematologic malignancies, such as acute leukemia and Hodgkin's lymphoma have higher incidence of TB than solid organ tumors. Leukemia tends to present with disseminated or extrapulmonary disease. Hodgkin's lymphoma appears as focal extrapulmonary disease than disseminated. This is due to the disease itself and its treatment which included radiotherapy, chemotherapy, high dose corticosteroids and bone marrow transplant. Tumor cachexia is also a contributory factor.[3]

Among the solid organ tumors, head and neck, lung cancer and gastrointestinal cancer have the highest incidence of TB infection. It was also found out that cancer patients with comorbidities such as TB and diabetes have high-

er risk of mortality.[3] It has to be noted that since 1970 cancer care has improved with new and more-intensive treatment modalities such as purine analogues, antilymphocyte monoclonal antibodies and hematopoietic stem cell transplantation.[4] These new ways of cancer treatment may have influence the increased risk of TB infection.

From a 1989 to 1994 data, there is an incidence of 90 per 100,000 populations in the United States but most are foreign-born patients (126 per 100,000 population vs. 33 per 100,000 populations).[3] From a 2006 to 2014 data, there is an incidence of 61 per 100,000 populations in India, which is known to have the highest TB burden worldwide.[5]

The Philippines is ranked 9th of 22 countries in the world with the highest TB burden. TB is the 6th leading cause of mortality and morbidity in the country.[6] However, while several studies[7-18] have already described the relationship of TB and cancer, there paucity of local literatures on the frequency of TB infection in cancer patients and its association with cancer therapy in the Philippines and in our institutioe. Therefore, this study was conducted determine the prevalence of active TB infection among diagnosed case of cancer patients at Veterans Memorial Medical Center from January 1, 2011 to December 31, 2013 prior to initiation, during and after cancer-specific therapy

METHODS

This is a retrospective cross-sectional study that included patients with histopathologically diagnosed cancer of any form admitted from January 1, 2011 to December 31, 2013 at Veterans Memorial Medical Center (VMMC). Patients should have histopathologic result released by the VMMC Histopathology Section; had undergone work-up or treatment for pulmonary or extrapulmonary TB prior to initiation of cancer-specific therapy, during cancer-specific therapy, or after cancer-specific therapy completion; and consented to and received cancer-specific therapy. Patients with concomitant human immuno-deficiency virus infection or acquired immunode-ficiency syndrome were excluded. Patient charts of all included patients were reviewed, and the following relevant information were extracted: age, sex, co-morbidities, smoking history; history and outcomes of previous TB diagnosis and treatment; and history and outcomes of previous cancer diagnosis and treatment.

Descriptive statistics were used to describe the population, using means and standard deviations for continuous variables, and frequencies and percentages for standard deviations. The incidence of TB was computed per 1,000 new cancer diagnoses. Cancer-specific TB frequency rate was also computed. Odds ratios were computed to show associated odds.

This study followed the standard operating procedures and guidelines for health research of VMMC. Ethical approval was obtained from the Ethics Committee of VMMC. Confidentiality of patient information were maintained through the use of patient codes.

RESULTS AND DISCUSSION

There were 793 histologically diagnosed cancer patients in VMMC from 2011 to 2013 (Table). Only 63 patients were admitted with a diagnosis of bacteriologically confirmed or clinically diagnosed pulmonary TB (new cases on ongoing intensive or maintenance phase TB treatment; n=10); previously treated TB with work-up for probable TB relapse (n=40), or presumptive TB with work-up to rule out TB (n=13). The rest of the patients either did not receive cancer-specific treatment (n=7), did not receive TB work-up or treatment (n=65), neither TB work-up or treatment nor cancer-specific treatment (n=655), or missing or incomplete data (n=3).

Table 2 summarizes the demographic profile of the 63 patients included in the study, and the computed odds of these characteristics on the development of TB infection. Seventy percent were males. The mean age was 68 ± 15 years and 52% were ≥ 65 years old. Fifty-nine percent had no compounding comorbidities. For patients with

Table 1. Number of admitted patients histologically diagnosed with cancer and cancer types in VMMC from 2011 to 2013

Year	2011	2012	2013	Total
Total number of cancer cases	260	284	249	793
Type of Cancer				
Breast cancer	35	38	46	119
Gastrointestinal malignancy	69	62	72	203
Genitourinary malignancy	56	49	45	150
Gynaecological malignancy	20	43	26	89
Head and neck malignancy	59	69	50	178
Hematologic and bone malignancy	10	17	6	33
Lung and pleura malignancy	9	5	2	16
Skin and soft tissue malignancy	2	1	2	5

Table 2. Baseline demographic and clinical profile of included patients

Variable	Frequency (%)	Mean ± SD	Odds ratio (95% CI)	P value
Sex			1.17 (0.35-3.93)	0.7946
Male	44 (70)			
Female	19 (30)			
Age (years)		68 ± 15	2.15 (0.70-6.57)	0.1792
< 65 years old	30 (48)			
≥ 65 years old	33 (52)			
With comorbidities	26 (51)		0.44 (0.42-1.34)	0.1495
COPD	13		9.10 (2.61-31.70)	0.0005
Diabetes mellitus	10		1.86 (0.46-7.57)	0.3878
ESRD/CKD	3		0.33 (0.02-6.68)	0.4686
Hypertension	32		0.96 (0.32-2.85)	0.9365
With no comorbidities	37 (59)			
Smoking history			0.55 (0.18-1.67)	0.2925
Non-smoker	25 (40)			
Passive smoker	0			
Smoker or previous smoker	38 (60)		3.36 (0.16-68.38)	0.4316
<10-pack years	4 (10)			
>10-pack years	34 (90)			

COPD, chronic obstructive pulmonary disease; ESRD, end-stage renal disease; CKD, chronic kidney disease.

comorbidities, chronic obstructive pulmonary disease, diabetes mellitus, chronic kidney disease or end-stage renal disease, and hypertension were the commonly associated diseases. Sixty percent were previous or current smokers, and 90% had a smoking history of ≥10 pack years.

Sixty percent of patients had no pulmonary symptoms but were worked up due to a history of previous TB treatment (Table 3). Of those who had pulmonary symptoms, cough, dyspnea, anorexia, fever and weight loss were the common manifestations. Only one patient presented with extrapulmonary TB in the form of tuberculous adenitis. All patients underwent sputum acid-fast bacilli (AFB) smear and chest radiography in the diagnosis of TB. Most TB diagnosis were based clinically but three patients had positive sputum AFB smears (two cases of TB relapse and one new case). Of the bacteriologically confirmed cases, one was diagnosed with TB and cancer

Table 3. Tuberculosis-related factors of included patients

Variable	Frequency (%)	Odds ratio (95% CI)	P value
TB diagnosis upon cancer diagnosis			
Probable TB relapse	37 (59)		
Presumptive TB	13 (21)		
New case, on-going treatment	10 (16)		
Retreatment, on-going treatment	3 (4)		
Clinical manifestations	25 (40)	4.92 (1.52-15.91)	0.0077
Fever	4 (6)	0.82 (0.08-8.48)	0.8704
Anorexia	7 (11)	22.00 (2.41-200.78)	0.0061
Cough	19 (30)	3.50 (1.0963-11.1744)	0.0344
Dyspnea	6 (10)	0.47 (0.05-4.34)	0.5059
Weight loss	12 (19)	14.00 (3.15-62.24)	0.0005
Hemoptysis	0		
Night sweats	0		
None consistent with TB	38 (60)		
Site of TB infection			
Pulmonary TB	62 (98)		
Extrapulmonary TB	1 (2)		
TB Diagnostic modality used			
Sputum AFB	63 (100)		
Bronchoscopy	2 (3)		
Chest radiography	63 (100)		
Chest CT scan	4 (6)		
Sputum Gene Xpert	1 (2)		
PCR	0		
PPD	1 (2)		
Tissue biopsy	3 (4)		
Pleural fluid analysis	1 (2)		
Sputum AFB result			
Smear negative	60 (95)		
Smear positive	3 (5)		
TB treatment regimen received			
Previous treatment received (40)		5.80 (2.00-16.66)	0.0012
CAT I	40 (63)		
CAT II	0		
New case, PTB relapse, On-going treatment (15)			
CAT I, intensive	10 (16)		
CAT I, maintenance	4 (6)		
CAT Ia, intensive	0		
CAT Ia, maintenance	1 (2)		
CAT II, intensive	3 (5)		
TB treatment outcome			
Previous treatment received (40)			
Completed	38 (60)		
Defaulted	2 (3)		
New case, PTB relapse, On-going treatment (15)			
Completed	13 (21)		
Defaulted	0		
Treatment outcome unknown	1 (2)		
On-going	1 (2)		

TB, tuberculosis; AFB, acid-fast bacilli; CT, computerized tomography; CAT, category; PTB, pulmonary tuberculosis.

concurrently, and two were diagnosed after cancer-specific therapy. All patients were treated with anti-TB regimen and all but one completed therapy.

The most common cancer type in the cohort was head and neck malignancy (32%); the least common was gynaecological malignancy (3%) (Table 4). The common histologic type was adenocarcinoma (46%) and most patients were in stage II disease (38%). Eighty-four percent (84%) of patients underwent surgery coupled with radiation and/or chemotherapy. Ninety-nine percent (99%) of the patients completed their cancer specific therapy. However, two patients (1%) died prior to completion of cancer-specific therapy; these patients did not develop TB infection.

Overall prevalence. The calculated TB period prevalence from 2011 to 2013 in a population of 793 newly diagnosed cancer patients

Table 4. Cancer-related factors of included patients

Variable	Frequency (%)	Odds ratio (95% CI)	P value
History of previous cancer diagnosis			
Yes	4 (6)		
None	59 (94)		
Type of Cancer			
Breast cancer	5 (8)	0.97 (0.28-3.42)	0.9674
Gastrointestinal malignancy	11 (17)	1.16 (0.37-3.59)	0.7971
Genitourinary malignancy	18 (29)	0.45 (0.10-1.98)	0.2909
Gynaecological malignancy	2 (3)	0.21 (0.01-3.47)	0.2737
Head and neck malignancy	20 (32)	1.13 (0.40-3.21)	0.8196
Hematologic and bone malignancy	3 (5)	2.62 (0.58-11.91)	0.2121
Lung and pleura malignancy	4 (6)	5.96 (1.25-28.41)	0.0252
Histologic type			
Adenocarcinoma	29 (46)		
Squamous cell carcinoma	13 (21)		
Others	21 (33)		
Stage of cancer			
I	5 (8)	1.75 (0.27-11.46)	0.5595
II	24 (38)	0.65 (0.20-2.10)	0.4698
III	17 (27)	0.70 (0.19-2.54)	0.5913
IV	16 (25)	1.75 (0.52-5.84)	0.3631
Grading	1 (2)		
Cancer specific intervention			
Chemotherapy	36 (57)		
Chronic steroid use	0		
Radiation	31 (49)		
Surgery	53 (84)		
Others: Immunotherapy	4 (6)		
Cancer therapy outcome			
Completed	61 (99)		
Interrupted	2 (1)		
Reason for cancer therapy interruption			
Drug adverse effects	0		
Lost to follow up	0		
Death of any cause	2		

in Veterans Memorial Medical Center was 2.3% or rate of 6 cases per 1000 person-years. A bigger study by Kaamboj and Sepkowitz (2006)[11] from 1980 to 2004 with 186,843 population of cancer patients, the computed rate was 55 cases per 100,000 persons. Cancer itself is indeed a risk factor for the development of active TB.[18,19]

Demographic analysis. Pertinent demographic characteristics were noted to have influenced occurrence of TB infection in cancer patients. Patients with concomitant COPD had 9 times increased odds for TB infection (OR 9.10; 95% CI 2.61, 31.70; p=0.0005). Chronic illnesses had long been proven to increase infection risk in cancer patients.[19] Cancer patients with smoking history of ≥ 10 pack had 3 times odds for TB infection but was not statistically significant and with wide range of heterogeneity.

Cancer patients with clinical manifestations like cough, weight loss and anorexia had 5 times odds for TB infection than those without pulmonary clinical manifestations (OR 4.92; 95% CI 1.52, 15.91; p=0.0077). Weight loss and anorexia were manifestations of the malignancy itself that it was noted with wide range of heterogeneity. TB should be included in the differentials of diagnosis in cancer patients with pulmonary manifestations during the course of diagnosis or cancer therapy.

Cancer type and TB infection. The cancer type also is a risk factor for the development of active TB that acute and chronic leukemic, solid organ tumors such as breast, lung, brain, gastrointestinal tract and genitourinary tract malignancies are associated with cellular immune dysfunctions that is why they are predominantly vulnerable to intracellular pathogens associated with cell-mediated immunity deficiencies like *Listeria monocytogenes, Salmonella spp., Nocardia asteroids, Legionella, Cryptococcus neoformans, Histoplasma capsulatum, Coccidioides immitis, Pneumocystis jiroveci, Varicella zoster, Cytomegalovirus, Epstein-Barr* virus, *Herpes simplex*, adenoviruses, *Toxoplasma gondii, Cryptosporidium, Strongyloides stercoralis* and mycobacteria including both *Mycobacterium tuberculosis* and the non-tuberculous mycobacteria.[19]

In this study, among the total number of lung cancer patients, 12.5% developed TB, being the highest among other cancer types. Lung cancer had 6 times odds of TB infection than other cancer type (OR 5.9; 95% CI 1.25, 28.41; p=0.0252). Six percent had TB among the hematologic and bone malignancy patients, 2.8% in patients with head and neck malignancy, 2.5% in breast cancer patients, 2% in patients with gastrointestinal malignancy and 1.3% in genitourinary malignancy patients. Studies had shown that hematologic diseases were the most common malignancy associated with TB infection like Hodgkin's lymphoma. [11,18,20] In this study a case of Non-Hodgkin lymphoma and Ewing sarcoma developed active TB. Among the solid tumors, lung cancer was the most common underlying malignancy and was consistent with the result of this study.[11,18,20]

History of previous TB infection and TB reactivation in cancer patients. In this study, of the 40 patients who had history of previous TB treatment, 37 patients were ruled out for TB reactivation and three had TB reactivation. The mean age was 71 ± 13 years, 75% are males, and 55% had comorbidities of COPD, CKD, diabetes mellitus and hypertension. Forty percent of patients had genitourinary malignancy, 35% had head and neck malignancy, 18% had gastrointestinal malignancy, 5% had breast cancer and 2% had hematologic and bone malignancy. Fifty percent of patients were in the Stage II disease, 20% were in the Stage III and Stage IV disease and 10% were in the Stage I disease. Ninety-five percent of patients completed treatment of previous TB therapy and 5% defaulted. Of the 3 patients that were assessed for TB relapse, two were diagnosed prior to initiation of cancer specific therapy. One patient was bacteriologically confirmed and was considered cured after completing Category II regimen. One other patient was clinically diagnosed and also completed category II treatment. The third patient

was assessed to have bacteriologically confirmed PTB relapse during the duration of cancer-specific therapy, and was considered cured after completing Category II regimen.

Cancer patients previously infected by organisms like *M tuberculosis* are at increased risk of TB reactivation. In a case series, most solid organ malignancy patients had healed scars in their chest radiographs suggesting previous TB, regardless of whether they had anti-TB treatment. The study concluded that the disease was caused by reactivation of latent TB infection. It was observed in the same study that patients not receiving cancer specific therapy were also found to have healed scars and this reactivation may be caused by the immunodeficiency effect of the malignancy itself.[22]

In this study, history of previous TB infection poses a 6 times increased odds for TB reactivation in cancer patients (OR 5.8; 95% CI 2.00, 16.66; p<0.0012). Gastrointestinal malignancy with previous TB treatment has 39 times odds for TB reactivation than head and neck malignancies (OR 38.8; 95% CI 4.51, 333.65; p=0.0009). However, there was a wide range of heterogeneity which may be influenced by many other risk factors. The addition of immunosuppressive therapies should further increase the risk of reactivation. This could explain the fate of the patient who developed bacteriologically confirmed PTB relapse during the course of cancer specific therapy.

Concurrent TB and cancer diagnosis. In this study, 67% had TB diagnosis prior to cancer specific therapies, 5% developed TB during the duration of cancer-specific therapy and 28% developed TB after cancer-specific therapy completion. Of the patients diagnosed with TB prior to cancer-specific therapies, 83% had the TB diagnosis concurrent with cancer diagnosis and 17% were TB relapse cases. The common underlying malignancy were gastrointestinal (25%), followed by genitourinary (17%), breast (17%), lung (17%), hematologic malignancy (17%) and head and neck malignancy (8%).

Of the 10 patients with TB treatment or concurrent TB diagnosis upon cancer diagnosis, 80% in this group were <65 years old, 70% were males and 60% were associated with hypertension, diabetes mellitus and COPD. There were two (20%) cases each of genitourinary malignancy, breast cancer, lung and pleura malignancy and hematologic and bone malignancy. There was one (10%) case each of gastrointestinal malignancy and head and neck malignancy. There were three (30%) cases each of Stage II and Stage IV diseases and two (20%) cases each of Stage I and Stage III diseases. All were pulmonary TB except for one with TB of the lymph nodes. Two were bacteriologically confirmed and the rest were clinically diagnosed PTB cases. Two were already in the maintenance phase of TB treatment upon cancer diagnosis and the rest were in the intensive phase. All cancer patients on TB treatment or concurrent TB infection completed their treatment and the 2 bacteriologically confirmed cases were declared cured after TB treatment completion.

In a study by Kaplan, Armstrong and Rosen,[20] TB developed during the development of the neoplasm in patients with lung and head and neck malignancy as compared to breast and hematologic malignancies. This was seen in our present study, and poses a diagnostic dilemma in lung cancer patients because TB may mimic lung cancer.

Cancer specific therapy and the risk of TB infection in cancer patients. In a series study by Say and Donehan (1974),[21] radiation therapy during the preoperative period increases the risk of infection of two folds in breast cancer patients while postoperative irradiation was not associated with an increased risk. It is theorized that fistula formation, impaired wound healing, and local tissue damage are the negative effects of radiation that predisposes cancer patients to infection and this phenomenon was well described in rectal cancer patients receiving radiation therapy.

Chemotherapy predisposes cancer patients to infection in many ways. It damages anatomical barriers; it causes bone marrow suppression, neut-

ropenia, inhibits bactericidal activity, and alters humoral immunity.[19]

In this study, there is an overall 15 times increased odds for TB infection in cancer patients who underwent cancer specific therapy (chemotherapy and/or radiation therapy and/or immunotherapy) (OR 15; 95% CI 3.10, 77.74; p=0.0009).

The patient that developed TB infection during the duration of cancer therapy was a microbiologically confirmed TB relapse case. The factor that the patient had history of TB infection and the addition of immunosuppressive therapy made him more vulnerable to TB reactivation.

Thirteen patients with no history of previous PTB treatment were worked up upon cancer diagnosis as presumptive TB cases prior or during or post cancer specific therapy. Five patients were diagnosed and treated for active TB infection after cancer specific therapy; four were clinically diagnosed and one was bacteriologically confirmed. Active TB was ruled out in the eight other cancer patients.

In this group, 80% were ≥65 years old, 60% were males, and 80% were associated with hypertension and diabetes mellitus. There were three cases (60%) of head and neck malignancy, one case of gastrointestinal malignancy and one case of breast cancer. Two patients were in Stage IV disease, two in Stage II disease and one in Stage 3 disease. Three patients were diagnosed to have TB infection 2 years after completion of cancer specific therapy, one patient developed TB after 3 years of completion, and one patient developed TB just after completion of cancer-specific therapy.

TB occurring after cancer specific therapy usually occurs in patients with breast or ovarian cancer or hematologic malignancy, while TB occurring during the development of cancer are lung and head and neck malignany.[20] The result of the study is quite different from generalities for head and neck tumors and this maybe a venue for further clinical research.

Mortality rate. There were no reported deaths among cancer patients with TB in the study period. Two deaths were noted in patients without TB infection, and these patients were not able to finish their cancer therapy.

CONCLUSION AND RECOMMENDATION

The overall computed period prevalence of TB infection in cancer patients was 2.3% or 6 cases per person-years. TB infection developed in 67% of patients prior to cancer-specific therapies, 5% during the duration of cancer-specific therapy and 28% after cancer-specific therapy completion. Cancer therapy was associated with an odds ratio of 15 for TB infection (95% CI 3.10, 77.74; p=0.0009). Among the different cancer types, 12.5% of TB patients developed in lung cancer patients (OR 5.96; 95% CI 1.25, 28.41; p=0.0252). Six percent developed in patients with hematologic and bone malignancy, 2.8% in those with head and neck malignancies, 2.5% in breast cancer patients, 2% in patients with gastrointestinal malignancy and 1.3% in genitourinary malignancy patients. Factors associated with increased odds of TB infections include pulmonary manifestations (OR 4.92; 95% CI 1.52, 15.91; p=0.0077) and history of previous TB infection and treatment (OR 5.80; 95% CI 2.00, 16.66; p<0.0012).

The characteristics of cancer patients with TB in this study could serve as guide in the risk stratifications of cancer patients for TB infection. Patients with lung cancer and hematologic malignancy, patients with pulmonary symptoms that may mimic the cancer itself or other bacterial infections, patients with chronic illness like COPD, and patients with previous PTB infection should be screened for concurrent TB infection prior, during and after cancer specific therapy initiation and course. Breast, ovarian, hematologic and head and neck malignancies should be closely monitored for TB infection along and after the course of cancer specific therapies. This study therefore concludes that cancer patients should be carefully assessed for TB infection before, during and after cancer specific therapies.

The use of newer diagnostic modalities like Gene Xpert or interferon-gamma release assays (IGRA) may have an added value in the evaluation

and monitoring of cancer patients with history of previous TB treatment, but this needs further study. The treatment of latent TB in cancer patients with a previous history of TB infection also remains unclear. Due to the limitations of retrospective, single-center studies with limited number of patients, a prospective multicenter study is also recommended to fully characterize the TB risk of cancer patients in the Philippines.

REFERENCES

1. De La Rosa, K., et al. Mycobacterium tuberculosis at a comprehensive cancer centre: active disease in patients with underlying malignancy during 1990-2000. European Society of Clinical Microbiology and Infectious Diseases. 2004; 10: 749-772.
2. Ramon AE Jacobs, Ping Gu and Abraham Chachoua. Reactivation of pulmonary tuberculosis during cancer treatment. Int J Mycobacteriol. 2015; 4: 337-340.
3. Libshitz HI et al. Tuberculosis in cancer patients: an update. J Thoracic Imaging. 1997; 12(1): 41-6.
4. Hadir A. El-Mahallawy et al. Tuberculosis in cancer patients: Role of new techniques in relation to conventional diagnostic methods. Journal of Advanced Research. 2010.
5. Amupama Dutt Mane et al. Clinical characteristics and outcome of cancer patients with tuberculosis. J Clin Oncology. 2015; 33.
6. Manual of Procedures for the National TB Control Program. 5th Edition. 2013. Department of Health.
7. ME Falagas et al. Tuberculosis and malignancy. Quarterly J Med. 2010; 103: 461-487.
8. Luis Anibarro and Alberto Pena. Tuberculosis in patients with hematologic malignancies. Mediterranean J Hematol Infect Dis. 2014; 6(1).
9. Silva FA et al. Risk factors for and attributable mortality from tuberculosis in patients with hematologic malignancies. Haematologica. 2005; 90:1110-5.
10. Chen CY et al. Clinical characteristics and outcomes of Mycobacterium tuberculosis disease in adult patients with haematological malignancies. BMC Infect Dis 2011; 11:324.
11. Mini Kamboj and Kent A Sepkowitz. The risk of tuberculosis in patients with cancer. Clinical Infectious Disease. 2006; 42: 1592-5.
12. Antonis Christopoulos et al. Epidemiology of active tuberculosis in lung cancer patients: a systematic review. Clin Respir J 2014;8:375-381.
13. Lonnroth K et al. Systematic screening for active tuberculosis: rationale, definitions and key considerations. Int J Tuberc Lung Dis. 2013; 17(3):289-98.
14. Canadian Tuberculosis Standards. 7th edition. Quebec: Public Health Agency of Canada; 2013.
15. NICE Clinical Guidelines CG117. London: NICE; March 2011.
16. Barbara Rybacka-Chabros, Beata Gryglicka and Janusz Milanowski. Coexistennce of lung cancer and active pulmonary tuberculosis. 2013. National Cancer Research Institutute.
17. Chia-Jen Liu et al. Risk and impact of tuberculoiss in patients with chronic myeloid leukemia: A nationwide population-based study in Taiwan. International Journal of Cancer. 2015: 136; 1881-1887.
18. Fujita T, et al. Mycobacterium tuberculosis infection in cancer patients at a tertiary care center in Japan. J Infect Chemother. 2013: 1-4.
19. Teresa R. Zembower. Epidemiology of infections in cancer patients. Cancer Treatment and Research 2014; 161:43-89.
20. Kaplan M, Armstrong D, Rosen P. Tuberculosis complicating neoplastic disease. A review of 201 cases. Cancer. 1974;3:850-858.
21. Say CC, Donegan W. A biostatistical evaluation of complications from mastectomy. Surg Gynecol Obstet 1974;138(3):370–376.
22. Kim HR, et al. Solid-organ malignancy as a risk factor for tuberculosis. Respirology 2008; 13: 413-419.

CROSS-SECTIONAL STUDY

Prediction of Pneumonia Based on Signs and Symptoms in Patients Presenting with Cough at the Veterans Memorial Medical Center

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ABSTRACT

Objective: This study aims to identify the association between pneumonia's signs and symptoms and its radiographic findings among patients with cough.

Method: All adult patients (18 years old and above) who consented for the study; coming from the outpatient department, Medical Ambulatory Care Clinic, and emergency room of the Veterans Memorial Medical Center from 2013 to 2014; complaining of cough were interviewed by their attending physicians who utilized the standardized history and physical examination checklist. All patients underwent chest radiography, posteroanterior view.

Results: Gender distributions were the same among the patients with and without pneumonia. Most of the patients with pneumonia were around the ages of 50 to 69. Among the symptoms, sputum production obtained the highest sensitivity (89%) and bloody sputum obtained the highest specificity (100%). Rhinorrhea and sore throat turned out to be negative predictors of pneumonia. Among the different physical examination findings, rales showed the highest sensitivity (75%) and local dullness had the highest specificity (97%). A pulse rate >100 beats per minute, a respiratory rate >25 cycles per minute, or a temperature >37.8°C were also associated with an increased probability of pneumonia.

Conclusion: Chest radiography should not be requested for all patients presenting with cough. It should be reserved for patients with signs and symptoms associated with a high probability of pneumonia.

INTRODUCTION

A 2010 report from the US Centers for Disease Control and Prevention states that the third most common reason for physician visits is cough.[1] Among the distinguishable diseases that present with acute cough, pneumonia represents 5% of consultations, and it is the fifth most common diagnosis following bronchitis, upper respiratory tract infection, asthma, and sinusitis.[2] Pneumonia entails a specific course of treatment and follow-up, unlike other types of acute respiratory infections, which only require expectant management. Primary care physicians must rely on the patient's medical history and physical examination, with or without a radiologic evaluation, to diagnose pneumonia.

Accurate diagnosis of pneumonia in primary care is difficult because it is not feasible to obtain chest radiographs from all patients with lower respiratory tract infection. The British Thoracic Society guidelines discourage performing a chest radiograph on every patient presenting with cough, because the cost of the procedure can be high and patients may be exposed to unnecessary radiation.[3,4]

The physician's concern about the possibili-

ty of pneumonia (ie, the presence of acute infiltrate on chest radiographs) appears to be the chief reason for obtaining chest radiography and prescribing unnecessary antibacterial drugs that cause the worldwide problem of antibiotic resistance.[5]

A disease-specific checklist that measures the probability of pneumonia may facilitate the diagnosis and treatment of such patients.

This paper aims to determine—through the combination of symptoms, patient history, physical examination results, and radiologic evidence—the statistical likelihood of diagnosing pneumonia in patients who present with acute cough. We sought to identify the correlation between symptoms in a patient presenting with acute cough and findings of pneumonia on chest radiography.

METHODOLOGY

This is a cross-sectional study that included all adult patients (18 years old and above) who came from December 2013 to December 2014 to the Veterans Memorial Medical Center outpatient department, MACC, and emergency room with a cough less than 2 weeks in duration and who consented to participate the study. Patients with a pulse rate ≥160 bpm, a temperature ≥40 °C, or a systolic blood pressure <90 mmHg were excluded from the study.

Patients were interviewed by the attending physician using the standardized history and physical examination checklist (Appendix A). All patients underwent chest radiography, postero-anterior view.

Radiology residents or staff radiologist consultants who interpreted the chest radiographs were not allowed any access to the patients' history except for history of cough less than 2 weeks in duration.

The principal investigator secured the patients' accomplished forms and correlated the findings with the chest radiography results (as interpreted by the radiologist for the confirmation of presence or absence of pneumonia). Data used for statistical analysis were descriptive (ie, frequency, proportion, sensitivity, and specificity) as well as inferential (ie, logistic regression).

We used Power Analysis and Sample Size (PASS) 2008 software to compute the minimum sample size requirement with the following parameters for logistic regression analysis: alpha (α)=0.05, power (1-β)=80%, P0 (percent of pneumonia among patients without tachypnea)=0.26, and P1 (percent of pneumonia among patients with tachypnea)=0.02. Except for alpha and power levels, which were set by the researchers, all the parameters were taken from literature. The computed 161 minimum sample size was increased to 194 to account for a possible 20% nonresponse.

RESULTS AND DISCUSSION

Gender distribution overall was 48% for males and 52% for females. Among patients without pneumonia, the gender distribution was 54% male and 46% female. In terms of age, the average for patients with pneumonia was 68 years old; for those without pneumonia, 65 years old. Most of the patients were within the age bracket of 50 to 69; specifically, 55% of those with pneumonia and 63% of those without pneumonia 63% fell within this age group (Table 1).

Among the different symptoms that were presented, sputum production obtained the highest sensitivity (89%), while sore throats and night sweats turned out to be the least sensitive. Bloody sputum obtained the highest specificity scores of 100%, while sputum production and chronic cough has the lowest of specificity of 57% (Table 2).

Only the following symptoms significantly affected the presence or absence of pneumonia: rhinorrhea ($p<0.001$), sore throat ($p<0.001$), sputum production ($p<0.001$), and fever ($p<0.001$). The relative risks of rhinorrhea and sore throat were both <1. This suggests that the presence of

rhinorrhea or sore throat is a negative predictor for pneumonia. However, as indicated by these factors' low sensitivities, very few patients had findings with these two factors, suggesting that this may be a chance result. On the other hand, the resulting relative risks >1 for sputum production and fever suggest that the presence of these symptoms increase the probability pneumonia. Results also showed that the other acceptable predictors of pneumonia were not significantly related to the occurrence of pneumonia.

Among the different physical examination findings, rales obtained the highest sensitivity (75%), while cachexia turned out to be the least sensitive (1%). Local dullness obtained the highest specificity score (97%) while temperature, rales, and rhonchi had the lowest (86%).

Among the different possible clinical findings, results showed that only the following

Table 3. Physical Examination Findings Associated with Pneumonia

	With Pneumonia (%) n=92	Without Pneumonia (%) n=69
Sex		
Male	44 (48)	37 (55)
Female	48 (52)	32 (46)
Age (years)		
Mean, SD	67.9 (14)	64.9 (14)
13–19	0	0
20–29	0	0
30–39	1 (1)	1 (1)
40–49	5 (5)	5 (7)
50–59	24 (26)	20 (29)
60–69	27 (29)	24 (35)
70–79	10 (11)	5 (7)
≥80	25 (27)	14 (20)

significantly affected the presence or absence of pneumonia: pulse rate >100 bpm (p<0.001), respiratory rate >25 cpm (p<0.001), temperature >37.8°C (<0.001), rales (<0.001), and local dullness (p=0.02). The relative risk of all these 4 significant factors exceeds 1. This denotes that presence of any of them increases the probability of pneumonia (Table 3).

When a patient presents with cough associated with fever and sputum production together with clinical findings of tachycardia, tachypnea, and rales, the probability of diagnosing pneumonia is high. In this study, however, 45% of our 161 patients with cough did not have pneumonia, and we found that those with rhinorrhea and sore throat were less likely to have the disease. Differential diagnosis can save patients from unnecessary exposure to radiation, as well as reduce healthcare costs that come from the prescription of empiric antibacterial treatments given for pneumonia.

One limitation of this study is that it observed mostly elderly patients, many of whom had comorbidities that may have predisposed them to pneumonia. These comorbidities include chronic obstructive pulmonary disease, which were not among the parameters we analyzed. Furthermore, the association between signs and symptoms and atypical pneumonia were not included in this data analysis; these can be included in a future study.

Based on our observations, we recommend that chest radiography be reserved for patients with cough associated with signs and symptoms that seem to be significant predictors for the occurrence of pneumonia. It is for this group, too, that more aggressive management, such as (empirical) antibiotic treatment for pneumonia, should be considered.

CONCLUSION

Chest radiography should not be requested for all patients presenting with cough. It should be reserved for patients with signs and symptoms

associated with a high probability of pneumonia. These include those with fever and sputum production and clinical findings of tachycardia, tachypnea and rales.

Table 2. History Findings Associated with Pneumonia

History Findings	Sensitivity	Specificity	Relative Risk	P-value
Chronic cough	53.26	56.52	1.18	0.219
Pleuritic chest pain	11.96	95.65	1.43	0.076
Night sweats	2.17	92.75	0.49	0.121
Rhinorrhea	5.43	65.22	0.26	<0.001
Sore throat	2.17	72.46	0.15	<0.001
Sputum production	89.13	56.52	3.59	<0.001
Smoker	29.35	75.36	1.10	0.507
Chills	3.26	89.86	0.51	0.073
Alcoholic	8.70	92.75	1.08	0.738
Bloody sputum	3.26	100.00	1.78	0.488
Fever	51.09	76.81	1.62	<0.001

Table 3. Physical Examination Findings Associated with Pneumonia

Physical Findings	Sensitivity	Specificity	Relative Risk	P-value
Pulse rate >100	22.83	95.65	1.69	<0.001
Respiratory rate > 25	51.09	88.41	2.01	<0.001
Temperature >37.8°C	54.35	85.51	2.00	<0.001
Local dullness	13.04	97.10	1.58	0.020
Rales	75.00	85.51	3.11	<0.001
Asymmetric respiration	2.17	94.20	0.57	0.217
Cachexia	1.09	92.75	0.28	0.052
Rhonchi	9.78	85.51	0.81	0.250

REFERENCES

1. Center for Diseases Control and Prevention. National ambulatory medical care survey: 2010 summary tables. Available at: https://www.cdc.gov/nchs/data/ahcd/namcs_summary/2010_namcs_web_tables.pdf.
2. Metlay JP, Kapoor WN, Fine MJ. Does this patient have community-acquired pneumonia? Diagnosing pneumonia by history and physical examination. JAMA. 1997;278(17):1440–5.
3. Paula Diehr, Robert Wood, James Bushyhead. Prediction of pneumonia in outpatients with acute cough—a statistical approach. J Chronic Dis. 1984;37(3):215–25.
4. Lim WS, Baudouin SV, George RC, et al. British Thoracic Society guidelines for the management of community acquired pneumonia in adults: update 2009. Thorax. 2009;64(Suppl 3):iii1–55.
5. Costelloe C, Metcalfe C, Lovering A, et al. Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: systematic review and meta-analysis. BMJ. 2010;340:c2096.

PROSPECTIVE COHORT STUDY

A Retrospective Study Comparing Young and Old Patients Diagnosed with Primary Lung Cancer

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ABSTRACT

Background: Lung cancer is the second most common cause of cancer-related deaths in the Philippines. While lung cancer is predominantly a disease of the elderly, an increasing trend among young patients has been reported. Nevertheless, local data comparing the characteristics of young and old lung cancer patients are sparse. This study aims to determine whether the demographic and clinicopathologic characteristics of Filipino lung cancer patients <50 years old differ from those of older patients.

Methodology: This retrospective study includes all patients admitted at a tertiary hospital, from January 2011 to December 2013, with a histologic or cytologic diagnosis of primary lung cancer. The participants, identified by chart review, were grouped into young (<50 years old) and old (≥50 years old). Demographic and clinicopathologic data were obtained. Comparisons were made using the chi-squared test.

Results: Two hundred fifty-one patients had a diagnosis of primary lung cancer. Twenty-eight (11%) patients were <50 years old, with a median age of 44; 223 (89%) were ≥50 years old, with a median age of 65. The gender (p=0.336) and smoking habits (p=0.310) of the 2 groups did not significantly differ. Coughing was the most frequent initial symptom, and majority of the patients (69%) were at stage 4 at the time of diagnosis. Adenocarcinoma was the most common histologic type observed in both groups. The overall 1-year survival rate was 79%. No significant differences appeared in clinicopathologic characteristics between the young and old patient groups.

Conclusion: While lung cancer patients in the young group were mostly females, nonsmokers, with advanced-stage adenocarcinoma, and presented with cough and upper lobe lesions, their profile, including treatment modalities and survival, did not differ significantly from the older group.

INTRODUCTION

Lung cancer is a modern-day disease afflicting a steady number of men and women worldwide since the turn of the twentieth century. Today, it has become the second most commonly diagnosed cancer for both sexes and the most common cause of cancer death. It is projected to claim 1.67 million lives by year 2015 and 2.2 million by the year 2030.[1,2] In the Philippines, the age-standardized incidence and mortality rates for the world population of lung cancer are 50.2 and 46.4, respectively, per 100,000 males; 13.2 and 12.6, respectively, per 100,000 females.[3]

Predominantly considered as a disease of the elderly (with median age-at-diagnosis of 70 years old), lung cancer is rare among young adults. It has a reported incidence of 1.2% to 6.2% for those under 40 years,[4,5] 5.3% for those under 45 years,[6] and 13.4% for those under 50 years old.[7] However, other studies have shown

trends of increasing incidence rates among young patients.[8,9] Recent studies suggest that younger patients with lung cancer are often female nonsmokers who (1) present with advanced-stage disease that is predominantly adenocarcinoma, (2) are more likely to receive aggressive treatment, and (3) have survival rates similar to older patients.[10,11,12] However, other reports have shown different results with regard to responses to treatment. Also, survival rates vary depending on the regions the studies were made and the ethnicities of the patients involved.[13]

This study aims to describe the clinical characteristics of young and old lung cancer patients admitted at a tertiary hospital. The results of this study could establish baseline local clinical data that would improve our understanding of the Filipino lung cancer patient.

METHODS

This retrospective study covering the period of January 2011 to December 2013 was conducted in a 660-bed privately owned tertiary care facility. It included all Filipino patients admitted into the hospital with a diagnosis of primary lung cancer based on (1) histologic examination of surgical or biopsy specimens or (2) cytologic examination of bronchial washing or brushing, lymph node aspiration, or pleural effusion. Non-Filipino patients and patients whose clinical diagnosis of lung cancer was not proven by histologic or cytologic examinations were excluded.

Patients with a diagnosis of primary lung cancer, lung mass, or malignant pleural effusion were identified from charts in the Medical Records section using the International Classification of Diseases version 10 coding system. Patients <50 years old were classified as "young," while those ≥50 years old were classified as "old." Clinical data—including age, gender, smoking habits, comorbid illnesses, family history of cancer, presenting symptoms, radiologic findings, cytologic or histologic diagnosis, treatment modalities and 1-year survival—were recorded.

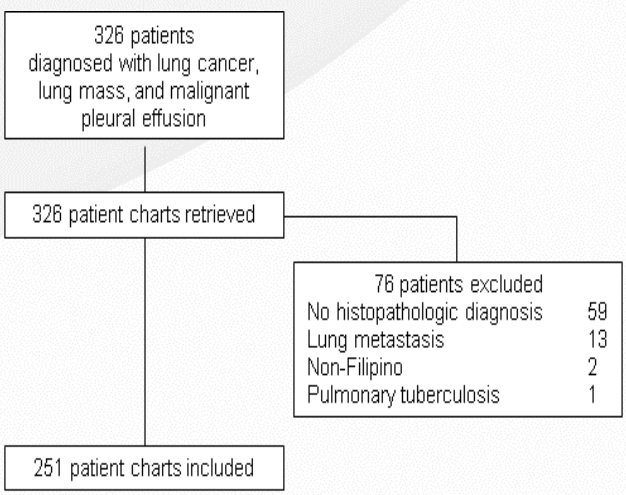
For categorizing according to smoking habits, current smokers were defined as patients who reported smoking ≥100 cigarettes in their lifetime and who, at the time of admission, smoked either every day or some days; former smokers were those who reported smoking ≥100 cigarettes in their lifetime but did not smoke at time of admission; and never smokers were those who reported smoking <100 cigarettes in their entire lifetime.[14]

Data were recorded using Microsoft Excel and analyzed using MedCalc statistical software. Qualitative variables were summarized as proportions. A 2-tailed chi-squared test determined whether there was significant difference between the 2 groups. *P*-value ≤0.05 was deemed statistically significant.

RESULTS

Review of charts at the Medical Records section generated 326 patient charts that contained diagnoses of lung cancer, lung mass, and malignant pleural effusion. After applying the criteria for inclusion and exclusion, 75 charts were excluded and 251 were included in the study (Figure 1).

Figure 1. Flowchart of included and excluded patients



The 251 included patients represented a 3% incidence of lung cancer among admitted patients. Twenty-eight patients (11% of cohort) were <50 years old, and 17 (61%) of this subcohort were females (Table 1). Two hundred twenty-three (89%) patients were ≥50 years old; this group was predominantly male. The young group had a median age of 44, while the old group had a median age of 65.

One hundred thirty-seven (55%) of the lung cancer patients were never smokers. The differences in gender and smoking habits between the two groups were not statistically significant (Table 1).

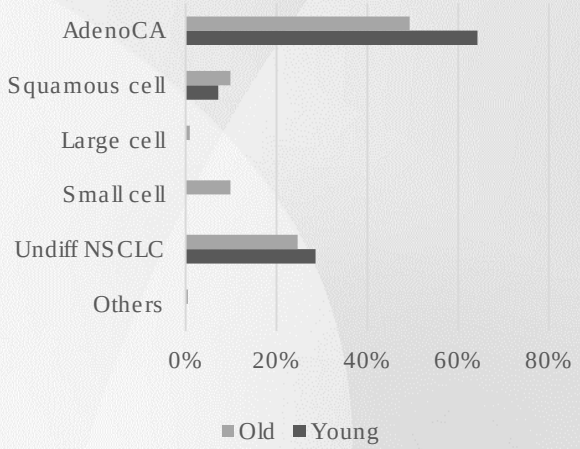
Hypertension was the most common comorbid condition identified in each group. Six patients in the old group (3%) and 1 in the young group (4%) had a prior history of cancer elsewhere. A family history of gastrointestinal cancer was identified in 17 (7%) of all included patients, while lung cancer was identified in only 5 (2%). Most of the patients (87%) did not have a family history of cancer (Table 1).

Adenocarcinoma was identified in 130 pat-

Table 1. Clinical and demographic profile of included patients

	Young (<50 years)	Old (≥50 years)	P-value
No. of patients	28 (11%)	223 (89%)	
Median age, y (range)	44 (31–49)	65 (50–98)	
Gender			0.336
Male	11 (39%)	125 (56%)	
Female	17 (61%)	98 (44%)	
Smoking status			0.310
Current	8 (28.6%)	97 (43.5%)	
Former	1 (3.6%)	8 (3.6%)	
Never	19 (67.8%)	118 (52.9%)	
Comorbidities			0.382
Hypertension	9 (32.1%)	107 (48.0%)	
Diabetes mellitus	2 (7.1%)	60 (26.9%)	
Asthma	3 (10.7%)	17 (7.6%)	
COPD	0	12 (5.4%)	
Pulmonary TB	2 (7.1%)	15 (6.7%)	
Cancer	1 (3.6%)	6 (2.7%)	
Family history of cancer			0.196
Lung	2 (7.1%)	3 (1.3%)	
Gastrointestinal	1 (3.6%)	16 (7.2%)	
Breast	1 (3.6%)	10 (4.5%)	
Genitourinary	1 (3.6%)	2	
Hematologic	1 (3.6%)	1 (0.4%)	
Thyroid	1 (3.6%)	1 (0.4%)	
None	25 (89.3%)	194 (87.0%)	

Figure 2. Histologic type of lung cancer (%)



ients (52%) and was the most common histologic type of lung cancer in both the young and old groups. It was followed by undifferentiated non–small cell lung cancer (NSCLC), found in 64 (25%) patients (Figure 2). Of those with NSCLC, 174 (75%) were at stage 4 upon diagnosis. Sixteen (70%) of those with small cell lung cancer presented with extensive disease (Table 2).

The three most common symptoms at time of diagnosis for both age groups were cough, dyspnea, and back pain. Younger patients did not present with hemoptysis, lymphadenopathy, body malaise, or weight loss. Radiologic findings showed that the upper lobe was the most common location of primary lesions in both age groups (Table 2).

Patients with metastatic disease mostly had involvement of one metastatic site at the time of diagnosis. The three most common sites for metastases were the pleura, bone, and lymph nodes (Table 3).

One hundred thirty-three (53%) patients did not undergo treatment at the time of diagnosis. Most of those who underwent single-treatment modality were subjected to chemotherapy. There was no significant difference between the 2 groups in terms of initial treatment approach (Table 4).

One hundred ninety eight (79%) patients were alive one year after the diagnosis of lung cancer. The 1-year survival rate for patients diagnosed with small cell lung cancer was 100% (Table 5).

DISCUSSION

This study showed a 3% incidence of lung cancer among admitted patients at our institution. Eleven percent of those with the disease were <50 years old at the time of diagnosis. Lung cancer in the young is considered rare, with incidence rates ranging from 1% to 12%, as in this study.[4,5,15,16,17,18] Other reports, however, have shown increasing incidence trends.[8,9,19] It is difficult to make interstudy comparisons because there is no definite age cutoff to define young patients: some investigators set the cutoff at <40 years old,[4,5] while others set it as <45 years old or <50 years old. [6,7,13,20-23] Since the incidence of lung cancer has been shown to increase rapidly after 50 years of age, we used 50 years as cutoff age in our study.[24]

The Surveillance, Epidemiology, and End-Results (SEER) Cancer Statistics Review shows that the median age for the diagnosis of cancers of the lung and bronchus is 70 years.[24] In this paper, the young group had a median age of 44, while the old group had a median age of 65. A similar pattern was noted in the study of Gadgeel et al.[23]

Females dominated the young group, while 56% of the old group were males. This is comparable to other studies, which observed a higher female-to-male ratio in younger lung cancer patients, thus suggesting a probable higher susceptibility to lung carcinogens among women.[4,6,25]

The association between cigarette smoking and the development of lung cancer has long been established. While the predominant cause of this disease is now known, other factors that may independently or synergistically increase risk—such as air pollutants, human occupational causes, micronutrients in the diet, and preexisting lung disease (eg, tuberculosis)—are

Table 2. Cancer-related baseline characteristics (time of diagnosis)

Variable	Young (<50 years)	Old (≥50 years)	P-value
Disease stage			
Non-small cell lung cancer			0.617
1	0	7 (3.1%)	
2	0	1 (0.4%)	
3	3 (10.7%)	47 (21.1%)	
4	25 (89.3%)	149 (66.8%)	
Small cell lung cancer			0.296
Limited	0	7 (3.1%)	
Extensive	0	16 (7.2%)	
Presenting symptom			0.795
Cough	18 (64.3%)	131 (58.7%)	
Dyspnea	4 (14.3%)	44 (19.7%)	
Back pain	5 (17.9%)	27 (12.1%)	
Neurologic	1 (3.6%)	15 (6.7%)	
Hemoptysis	0	14 (6.3%)	
Body malaise	0	5 (2.2%)	
Weight loss	0	5 (2.2%)	
Lymphadenopathy	0	3 (1.3%)	
Superior vena cava syndrome	0	1 (0.4%)	
Asymptomatic	1 (3.6%)	11 (4.9%)	
Radiologic finding			0.651
Upper lobe	8 (28.6%)	78 (35.0%)	
Lower lobe	7 (25%)	56 (25.1%)	
Right middle lobe	3 (10.7%)	31 (13.9%)	
Hilar	5 (17.9%)	38 (17.0%)	
Massive effusion	5 (17.9%)	20 (9.0%)	

also being investigated.[26]

A case control study in the Philippines by Ngelangel et al associated lung cancer with smoking and a positive family history of lung cancer.[27] Interestingly, in this study, only 5 patients had a positive family history of lung cancer, and 137 (55%) patients were never smokers. These findings suggest that other environmental and genetic factors may be at play in the development of the disease.

Adenocarcinoma is the most common histologic type of lung cancer worldwide.[24] Data also show that it is the most common subtype found among younger patients.[10-13,28] This study found adenocarcinoma to be the most predominant subtype in both groups. Although the incidences of each histologic type do not significantly differ between the young and old

Table 3. Metastatic sites

Variable	Young (<50 years)	Old (≥50 years)	P-value
No. of sites			0.127
1	20 (71.4%)	141 (63.2%)	
2	5 (17.9%)	34 (15.2%)	
>2	3 (10.7%)	5 (2.2%)	
Specific sites			0.671
Pleura (effusion)	12 (42.9%)	64 (28.7%)	
Bone	8 (28.6%)	53 (23.8%)	
Lymph nodes	14 (50%)	46 (20.6%)	
Brain	6 (21.4%)	26 (11.7%)	
Lung (nodules)	5 (17.9%)	11 (4.9%)	
Liver	1 (3.6%)	11 (4.9%)	
Adrenal	2 (7.1%)	9 (4.0%)	
Pancreas	0	1 (0.4%)	
Peritoneum	0	1 (0.4%)	
Spinal cord	0	2 (0.9%)	

Table 4. Treatment strategy

Treatment	Young (<50 years)	Old (≥50 years)	P-value
Single			0.244
Surgery	1 (3.6%)	16 (7.2%)	
Chemotherapy	11 (39.3%)	49 (22.0%)	
Radiotherapy	1 (3.6%)	16 (7.2%)	
Combined	3 (10.7%)	21 (9.4%)	0.514
None	12 (42.9%)	121 (54.3%)	

Table 5. One-year survival

Variable	Young (<50 years)	Old (≥50 years)	P-value
Overall	24 (85.7%)	174 (78.0%)	0.464
By stage			0.415
Non-small cell			0.234
1	-	5 (2.2%)	
2	-	1 (0.4%)	
3	3 (10.7%)	38 (17.0%)	
4	21 (75%)	113 (50.7%)	
Small cell			
Limited	-	6 (2.7%)	
Extensive	-	11 (4.9%)	
By cell type			
NSCLC	24 (85.7%)	157 (70.4%)	
Small cell	-	17 (7.6%)	

patient groups, large cell and small cell cancer were not found to occur in the young group in this small study.

Symptoms associated with lung cancer are usually nonspecific and occur late. As a result, majority of patients are diagnosed during the advanced stage of the disease. In the United States, for instance, only 16% of patients have localized disease at the time of diagnosis.[24] In this study, 174 (75%) patients with NSCLC were at stage 4 by the time their cancer was diagnosed, while 16 (70%) of those with small cell lung cancer presented with extensive disease. No significant difference in terms of staging was noted between the 2 groups, in contrast to the claims of several reports that younger patients present with more advanced disease than older patients.[13,18,29,30]

Most of those with metastatic disease had involvement of 1 metastatic site at the time of diagnosis. The 3 most common sites for metastases were the pleura, bone, and lymph nodes.

Patients commonly presented with cough, dyspnea, and back pain in both groups. Hemoptysis, weight loss, and body malaise were not noted in the young patients on presentation. A number of older patients were also noted to be asymptomatic at the time of diagnosis. This is similar to the findings of Bourke et al, who noted that younger patients had less hemoptysis and fewer of them were asymptomatic upon presentation. However, Bourke et al observed that younger patients had higher incidences of chest and shoulder pain, fever, and neurologic symptoms.[13]

Lung cancer occurs most frequently in the upper lobes,[31] and radiologic findings reveal that the upper zone is the most involved area, followed by the middle lobe, and then the lower lobes. Lower lobe lesions were more frequently noted among younger patients.[13] In this study, the primary tumor was most commonly observed in the upper lobe, followed by the lower lobe, and then the right middle lobe in both age groups.

Data from the SEER registry and other previous studies have shown that younger patients with lung cancer were more likely than older patients to receive anticancer treatment, including combined-modality therapy. In addition, despite presenting with more advanced-stage disease, younger patients were more likely to undergo cancer-directed surgery.[13,23,24] These, however, were not noted in this study as we found no significant difference between the old and young patient groups in terms of initial treatment approach. This study also showed that 133 (53%) of the patients did not undergo treatment at the time of diagnosis, while most of those who underwent single-treatment modality were subjected to chemotherapy. This is in conjunction with the finding of a high percentage of patients presenting with stage 4 upon admission.

The 1-year relative survival rate for lung cancer is currently estimated at 44%, which is higher than the 37% of 1975–1979, perhaps largely due to improvements in surgical techniques and combined therapies. However, the 5-year survival rate for all stages combined is only 16%. The 5-year survival for small cell lung cancer (6%) is lower than that for NSCLC (18%).[2]

In this study, 194 (79%) of all patients were alive 1 year after the diagnosis was made, and patients with small cell lung cancer had a 100% 1-year survival rate. Other studies have shown varying survival rates according to tumour histology,[2] which was not made in this study.

In summary, lung cancer still remains a significant global health burden, accounting for the most number of cancer-related deaths. Most epidemiologic studies have shown that although lung cancer is predominantly a disease of the elderly, younger patients may also be affected. Reports show that patients aged <50 years old are more commonly female, nonsmokers; they more often have adenocarcinoma than squamous cell carcinoma, present with advanced disease, and have better or similar overall survival rates

when compared with older patients.[10,11,12,23] In this study, patients in the young group were mostly females, nonsmokers, with advanced-stage adenocarcinoma, and presented with cough and upper lobe lesions. However, the characteristics of this group—including treatment modalities and survival—did not differ significantly from the older group.

This being a retrospective study, one must take into account the limitations inherent to the study design when interpreting the findings. The results reported here should be validated using a prospective study design.

CONCLUSION

The incidence of lung cancer among admitted patients in a tertiary hospital was 3%. Eleven percent of the patients were <50 years old. Females dominated the young group, while more males were noted in the older group. Most of the patients were nonsmokers; presented with cough, dyspnea, and back pain; and had a primary tumor located in the upper lung zone on radiologic imaging. Adenocarcinoma was the most common histologic type observed in both groups. Seventy-five percent of the patients had advanced-stage disease, often with metastatic lesions to the pleura, bone, and lymph nodes. Most of the patients did not undergo treatment at the time of admission. The 1-year relative survival rate was 79%.

REFERENCES

1. World Health Organization. Projections of mortality and burden of disease, 2002–2030. http://www.who.int/healthinfo/global_burden_disease/projections2002/en/. Accessed on September 18, 2013.
2. American Cancer Society. Cancer Facts & Figures 2013. Atlanta: American Cancer Society; 2013.
3. Medina V, Laudico A, Redaniel MTM, et al. Incidence trends 1980–2002. In: *Cancer in the Philippines*, vol. IV, part 2. Manila: Philippine Cancer Society; 2011.
4. Subramanian J, Morgensztern D, Goodgame B, et al. Distinctive characteristics of non-small cell lung cancer (NSCLC) in the young: a surveillance, epidemiology, and end results (SEER) analysis. J Thorac Oncol. 2010;5(1):23–8.
5. Liam CK, Lim KH, Wong CM. Lung cancer in patients younger than 40 years in a multiracial Asian country. Respirology. 2000;5(4):355–61.
6. Zhang J, Chen SF, Zhen Y, Xiang J, Wu C, Bao P, Luketich J, Hu H, Zhou X, Yao S, et al: Multicenter analysis of lung cancer patients younger than 45 years in Shanghai. Cancer. 2010;116(15):3656–62.
7. Ak G, Metintas M, Metintas S, Yildirim H, Erginel S, Alatas F. Lung cancer in individuals less than 50 years of age. Lung. 2007;185(5):279–86.
8. Strand TE, Malayeri C, Eskonsipo PK, Grimsrud TK, Norstein J, Grotmol T. Adolescent smoking and trends in lung cancer incidence among young adults in Norway 1954–1998. Cancer Causes Control. 2004;15(1):27–33.
9. Marugame T, Yoshimi I, Kamo K, et al. Trends in lung cancer mortality among young adults in Japan. Jpn J Clin Oncol. 2005;35(4):177–80.
10. Chen KY, Chang CH, Yu CJ, Kuo SH, Yang PC. Distribution according to histologic type and outcome by gender and age group in Taiwanese patients with lung carcinoma. Cancer. 2005;103(12):2566–74.
11. Capewell S, Wathen CG, Sankaran R, Sudlow MF. Lung cancer in young patients. Respir Med. 1992;86(6):499–502.
12. Skarin AT, Herbst RS, Leong TL, Bailey A, Sugarbaker D. Lung cancer in patients under age 40. Lung Cancer. 2001;32(3):255–64.
13. Bourke W, Milstein D, Giura R, et al. Lung cancer in young adults. Chest. 1992;102(6):1723–9.

14. Centers for Disease Control and Prevention. State-specific secondhand smoke exposure and current cigarette smoking among adults – United States, 2008. MMWR Morb Mortal Wkly Rep. 2009;58(44):1232–5.
15. Schottenfeld D. Epidemiology of lung cancer. In: Pass HI, Mitchell JB, Johnson DH, et al (Eds). *Lung Cancer: Principles and Practice*. Philadelphia, PA: Lippincott-Raven, 1996;305–21.
16. Jung KW, Park S, Kong HJ, et al. Cancer statistics in Korea: incidence, mortality and survival in 2006–2007. J Korean Med Sci. 2010;25(8):1113–21.
17. Liu NS, Spitz MR, Kemp BL, et al. Adenocarcinoma of the lung in young patients. Cancer. 2000;88(8):1837–41.
18. Green LS, Fortoul TI, Ponciano G, et al. Bronchogenic cancer in patients under 40 years old. The experience of a Latin American country. Chest. 1993;104(5):1477–81.
19. Kim L, Kim KH, Yoon YH, et al. Clinicopathologic and molecular characteristics of lung adenocarcinoma arising in young patients. J Korean Med Sci. 2012;27(9):1027–36.
20. Roviaro GC, Varoli F, Zannini P, Fascianella A, Pezzuoli G. Lung cancer in the young. Chest. 1985;87(4):456–9.
21. Kyriakos M, Webber B. Cancer of the lung in young men. J Thorac Cardiovasc Surg. 1974;67(4):634–48.
22. Kreuzer M, Kreienbrock L, Gerken M, et al. Risk factors for lung cancer in young adults. Am J Epidemiol. 1998;147(11):1028–37.
23. Gadgeel S, Ramalingam S, Cummings G, et al. Lung cancer in patients < 50 years of age: the experience of an academic multidisciplinary program. Chest. 1999;115(5):1232–6.
24. Howlader N, Noone AM, Krapcho M, et al (Eds). SEER Cancer Statistics Review, 1975-2010, National Cancer Institute. Bethesda, MD; 2013.
25. Kuo CW, Chen YM, Chao JY, Tsai CM, Perng RP. Non-small cell lung cancer in very young and very old patients. Chest. 2000;117(2):354–7.
26. Youlden D, Cramb S, Baade P. The international epidemiology of lung cancer: geographical distribution and secular trends. J Thorac Oncol. 2008;3(8):819–31.
27. Ngelangel CA, Javelosa MA, Cutiongco-de la Paz EM; Philippine Cancer Genetics Study Group. Epidemiological risk factors for cancers of the lung, breast, colon-rectum & oral cavity: a case-control study in the Philippines. Acta Medica Philippina. 2009;43(4):29–34.
28. Hsu CK, Chen KY, Shih JY, et al. Advanced non-small cell lung cancer in patients aged 45 years or younger: outcomes and prognostic factors. BMC Cancer. 2012; 12:241.
29. Neuman HW, Ellis FH Jr, McDonald JR. Bronchogenic carcinoma in persons under forty years of age. N Engl J Med. 1956; 254(11):502–7.
30. Antkowiak JG, Regal AM, Takita H. Bronchogenic carcinoma in patients under age 40. Ann Thorac Surg. 1989;47(3):391–93.
31. Byrd RB, Carr DT, Miller WE, Payne WS, Woolner LB. Radiographic abnormalities in carcinoma of the lung as related to histological cell type. Thorax. 1969;24(5): 573–5.

NOTES

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