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JULY-SEPTEMBER VOLUME 17 NUMBER 3

… And in the Beginning, There was Curiosity

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

"Only the curious have something to find"
- Anonymous

Indeed, there is no rest for the curious.

The PJCD returns with a new set of articles which showcase the inherent curiosity of the PCCP, and they are, individually, little jewels in themselves, as they allow us a glimpse into their author's institution's brand of pulmonary care, providing us with the opportunity to learn from each other in a different way.

For this issue's first article, the Lung Center of the Philippines alerts us as to how the changing landscape of patient demographics and a slew of new and up-an-coming antibiotics reflect the need for PCCP to revisit the current clinical practice guidelines on the management of community acquired pneumonia. It is possible that computed compliance rates across training institutions are not far apart from each other, and this paper suggests that a multicenter study may be the next logical step in further understanding compliance to CPGs.

The Medical City contributes to current practice and knowledge by sharing its experience in the conduct of endobronchial ultrasound-transbronchial needle aspiration (EBUS-TBNA), a technology and expertise not yet recognized as standard local practice. Nevertheless despite the fact that it is an expensive diagnostic option for patients with a variety of pulmonary conditions, its nature as a minimally invasive means of diagnosis makes it an attractive diagnostic tool for many.

Similar to the EBUS-TBNA in The Medical City, the USTH experience reminds us that in many parts of the world, the diagnosis of

pulmonary diseases reaches into the realm of molecular and genetic medicine. Gone are the days when COPD was a disease with a simplistic perspective: it was either from emphysema or chronic bronchitis, their differences made clearer by images of pink puffers and blue bloaters. For this issue, the TNF-α polymorphism is introduced as a tool in furthering our understanding of COPD, albeit in still a small sample of Filipinos. Hopefully, this article will inspire others to take this research to the next level at par with similar researches from Japan, Taiwan and other western countries.

Veterans MMC, on the other hand, shares their experience in using the Multifactorial Risk Index in predicting post-operative pneumonia or respiratory failure. With a multitude of indices available for the bedside clinician, both for diagnostic and therapeutic assessments of patients, VMMC highlights this particular index and presents it to us as a viable option in the pre-operative assessment of patients.

The other articles featured in this issue intend to make us think, and move us into action. Who would have thought of statins for COPD patients—but not for the dyslipidemia that accompany the disease from time to time? And do we routinely offer and encourage our patients to undergo pulmonary rehabilitation, not just as part of post-operative care from lung resection, but for COPD as well?

Indeed, there is no rest for the curious.

These articles demonstrate that research—much like learning—never ends. Our featured papers hope to compel others to continue the work that has been started, and to discover other avenues to improve patient care.

RETROSPECTIVE COHORT STUDY

Impact of Adherence to the Philippine Clinical Practice Guidelines on the Clinical Outcomes of Patients Hospitalized for Community-Acquired Pneumonia at the Lung Center of the Philippines

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ABSTRACT

Background and Objective: This study aims to assess the utilization of the Philippine Clinical Practice Guidelines (PCPG) on Community Acquired Pneumonia (CAP) at the Lung Center of the Philippines in the treatment of CAP and its clinical outcomes.

Methods: This is a retrospective cohort study involving patients > 18 years old admitted at the pay and service wards of the Lung Center of the Philippines from January 2011 to December 2013 with CAP. Using a standard form the following data were collected for each patient as follows: demographic characteristics, coexisting illness, laboratory results including cultures and drug sensitivity of acceptable respiratory and blood specimens, radiographic and physical examination findings. Investigated outcomes include resulting morbidity such as development of respiratory failure; and length of hospital stay.

Results: Among the 1,098 patients included in the study, non-PCPG treatment were given to 603 (54.9%) patients, while PCPG treatment were given to 495 (45.1%). Adherence to PCPG was lower in Moderate-risk CAP (38.1%) than in High-risk CAP (91.1%). Patients with moderate-risk CAP who were not given PCPG treatment demonstrated significant worsening in their oxygen requirement ($p=0.029$), had longer hospital stays ($p<0.001$) and had significantly higher mortality rate ($p=0.02$). In the high-risk CAP population, there was no significant difference in the outcomes for both PCPG and non-PCPG treatment ($p>0.05$) and mortality rates were high both in the PCPG and non-PCPG groups (52.9% and 53.85%). Sputum culture isolates from moderate-risk and high-risk CAP patients were predominantly *Acinetobacter* (37 samples or 16.70% for moderate-risk CAP and 17 samples or 15.6% for high-risk CAP) and Pseudomonas aeruginosa (28 samples or 12.55% for moderate-risk CAP and 19 samples or 17.43% for high-risk CAP). The most common isolate for blood specimens was coagulase-negative *Staphylococcus* for both moderate-risk CAP (51.85%) and high risk CAP (33.33%). Coagulase-negative *Staphylococcus* (41.76%) was also the most common pleural fluid culture isolate in the moderate-risk CAP population.

Conclusion: The overall adherence rate to the CAP treatment guidelines was 45.1%. Adherence was lower in the Moderate-risk than in the High-risk CAP group. Moderate-risk patients who were given non-PCPG antibiotic treatment had higher mortality rates, longer hospital stays and greater tendencies to develop respiratory failure. There was no significant difference in the outcomes for both PCPG and non-PCPG treatment in the High-risk CAP.

INTRODUCTION

Improving the care of adult patients with community-acquired pneumonia (CAP) has been the focus of many different organizations, and most have developed guidelines for management of CAP. The guidelines are intended primarily for use by emergency medicine physicians, hospitalists, and primary care practitioners; however, the extensive literature evaluation suggests that they are also an appropriate starting point for consultation by specialists.[1]

Community-acquired pneumonia (CAP) is a significant cause of morbidity and mortality in adults. CAP is defined as an infection of the lung parenchyma that is not acquired in a hospital, long-term care facility, or other recent contact with the health care system.[2]

The overall rate of community-acquired pneumonia (CAP) in adults is approximately 5.16 to 6.11 cases per 1000 persons per year; the rate of CAP increases with increasing age.[3] Pneumonia and influenza combined is the eighth leading cause of death in the United States and the most common cause of infection-related mortality.[4] In the Philippines, it ranks as the second most common cause of morbidity and fourth most common cause of mortality according to the 2009 Philippine Health Statistics.[5]

Recognizing patients at low risk of complications and therefore suitable for treatment out of the hospital has the potential to reduce inappropriate hospitalization and consequently inherent morbidity and costs. When hospital admission is required, further management is also influenced by the illness severity. Early identification of patients at high risk of death allows immediate initiation of appropriate antibiotic therapy and admission to an intensive care setting where assisted ventilation and other support can be readily initiated if necessary.[6]

The Philippine Clinical Practice Guidelines (PCPG) 2010 update on CAP is based on evidence derived from critical review of the literature. This was drafted to provide the clinician with practical approaches in the resolution of important issues on diagnosis, management and prevention of CAP in immunocompetent adults. The 2010 PCPG update on CAP is specific only for the empiric therapy of immunocompetent adults based on the likely etiology of the pneumonia.

This study therefore aims to assess the utilization of these guidelines among practicing pulmonary medicine specialists at the Lung Center of the Philippines in the treatment of hospitalized patients with community-acquired pneumonia and its effect on clinical outcomes.

METHODS

This is a retrospective cohort study conducted at the Lung Center of the Philippines, a tertiary, specialty medical center. The study involves adult patients who were hospitalized at the pay and service wards from January 2011 to December 2013 with a discharge diagnosis of CAP. Each patient's medical chart was reviewed.

The research protocol was approved by the Research Review Committee of the Department of Pulmonary Medicine and the Institutional Ethics Review Board (IERB). Informed consent was waived due to the retrospective nature of the study.

The inclusion criteria are as follows: (1) age ≥ 18 years; (2) the onset of symptoms having occurred in the community within 24 hours to less than 2 weeks; (3) presence of radiological infiltrate consistent with the diagnosis of pneumonia; and (4) presenting with an acute cough, abnormal vital signs including tachypnea (respiratory rate >20 breaths per minute), tachycardia (cardiac rate >100/minute), and fever (temperature >37.8ºC) with at least one abnormal chest exam finding of diminished breath sounds, rhonchi, crackles, or wheeze. The exclusion criteria are as follows:(1) incomplete charts or data being missing or inconsistent with the diagnosis of CAP; (2) previous hospitalization for the past 90 days; (3) Chronically debilitated, bed ridden patients or those requiring long term home care; (4) History of neoplasm or a history of immunosuppressive

diseases (i.e. HIV/AIDS), or immunosuppressive therapy; and (5) Obstructive pneumonia due to carcinoma or foreign body.

The patients were classified according to the risk stratification that are recommended by the current Philippine CAP guidelines 2010 Update, namely:[6]

(1) Moderate-risk CAP: Patients with any one of the following physical findings: respiratory rate≥30 breaths/minute, pulse rate ≥125 beats/minute, or temperature ≤ 36 C or ≥ 40^{O}C; SBP systolic blood pressure< 90 mmHg and diastolic blood pressure≤ 60 mmHg; those with suspected aspiration; or those with altered mental status of acute onset. Decompensated co-morbid conditions which may aggravate or be aggravated by the pneumonia are included in this category. Patients with radiographic findings of bilateral or multilobar involvement, pleural effusion, or abscess. These patients need to be hospitalized for closer monitoring and/or parenteral therapy.

(2) High-risk CAP: Patients with any of the criteria under the moderate-risk CAP category plus signs of severe sepsis or septic shock or those in need of mechanical ventilation . These patients are warranted admission in the intensive care unit.

The following data were collected for each patient using a standard form: demographic characteristics, coexisting illness, laboratory tests including cultures and drug sensitivity of acceptable respiratory (a gram stain with more than 25 polymorphonuclear leukocytes per low power field and less than 10 squamous epithelial cells per low power field), blood and pleural fluid specimens, radiographic and physical examination findings, and white cell counts (WBC).

Determination of adherence to current (2010) Philippine guidelines for the treatment of CAP was done with the initial antibiotic therapy prescribed. The patients were then categorized into the PCPG group (those who received antibiotics based on the guidelines) and the non-PCPG group (those who received antibiotics not adherent to the guidelines). Patients under the PCPG group received the following antibiotic regimen:[6]

1) For moderate-risk CAP: Intravenous (IV) non-antipseudomonal β-lactam (BLIC, cephalosporin or carbapenem) plus either an extended macrolide or respiratory fluoroquinolone

2) For High-risk CAP with no risk for *Pseudomonas aeruginosa*: IV non-antipseudomonal β-lactam (BLIC, cephalosporin or carbapenem) plus either IV extended macrolide or IV respiratory fluoroquiolone

3) For High-risk CAP with risk for *P. aeruginosa*: IV antipneumococal antipseudomonal β-lactam (BLIC, cephalosporin or carbapenem) plus IV extended macrolide with aminoglycoside OR IV antipneumococal antipseudomonal β-lactam (BLIC, cephalosporin or carbapenem) plus IV ciprofloxacin/levofloxacin (high-dose).

Outcomes including resulting morbidity anddevelopment of respiratory failure, and length of hospital stay were investigated. Data gathered were entered into a computerized data editor. The demographic profile of the patients was presented using frequency counts and percentage for categorical variable. Mean and standard deviation were used to summarize data on age. Comparison of proportion differences based on parameters such as adherence to treatment guidelines and pneumonia classification of patients were determined using Pearson Chi-Square or Fisher's Exact Test. Parameters used to determine the factors influencing adherence or non-adherence to PCPG treatment include the presence of fever, tachypnea, oxygen requirement, laboratory findings such as WBC and clearing of chest radiograph (CXR), and endotracheal intubation and ICU admission for patients with moderate risk CAP, and the presence or absence of respiratory failure for patients with high risk CAP. The mortality rates and the length of stay were also compared between the PCPG and non-PCPG groups. Statistically significant association was considered when the p-value was <0.05.

RESULTS

A total of 1,794 charts were reviewed, 616 were excluded from the study hence, a total of 1,098 CAP patients were included in this study. Demographic and clinical characteristics of the study population were summarized in Table 1.

Out of the 1,098 patients, 563 (51.3%) are females and 535 (48.7%) are males. Majority of the patients (56.2%) are above 65 years old with a mean age of 64.23 ± 18.95 years old. More than half of the patients (69.9%) were under the supervision of private attending physicians. There were 952 (86.7%) patients who were classified as moderate risk CAP and 146 (13.3%) patients were classified as having high risk CAP. In patients with high risk CAP, 45 (4.1%) patients had septic shock and 131 (11.9%) patients required mechanical ventilation.

Table 1. Demographic and Clinical Characteristics of the Study Population (n=1,098)

Characteristic	No.	%
Gender		
Male	535	48.7
Female	563	51.3
Age (Mean and SD : 64.23 ± 18.95)		
18-30 y/o	99	9
31-50 y/o	141	12.8
51-64 y/o	241	21.9
65+ y/o	617	56.2
Attending Physician		
Service	331	30.1
Private	767	69.9
CAP Classification		
Moderate-Risk	952	86.7
High-Risk	146	13.3
With Sepsis	45	4.1
Needed Mechanical Ventilation	131	11.9
Comordities		
COPD	198	22
Bronchial Asthma	94	11
Diabetes Mellitus	151	17
CHF	52	6
Renal Failure	32	4
BXSIS	134	15
PTB	117	10.7
Chronic liver disease	6	1
Neurologic disorder	44	5
CAD	57	6
Previous Use of Antibiotics		
Yes	153	13.9
No	945	86.1

CAP, community-acquired pneumonia; COPD, chronic obstructive pulmonary disease; CHF, congestive heart failure; BXSIS, bronchiectasis; PTB, pulmonary tuberculosis; CAD, coronary artery disease.

Table 2. Distribution of Patients between PCPG and Non-PCPG Adherent Treatment Groups

Class	PCPG No. (%)	Non-PCPG No. (%)	Total N
Moderate-Risk	362 (38.1%)	590 (61.9%)	952
High-Risk	133 (91.1%)	13 (8.9%)	146
Total	495 (45.1%)	603 (54.9%)	1,098

PCPG, Philippine Clinical Practice Guidelines.

The most common comorbidities are COPD (198 or 22%), diabetes mellitus (151 or 17%), bronchiectasis (BXSIS) (134 or 15%), pulmonary tuberculosis (117 or 10.7%), and bronchial asthma (94 or 8.6%), respectively.

A total of 153 (13.9%) patients had previous antibiotic use.

There were a greater proportion of patients who were given non-PCPG treatment than PCPG treatment. The non-PCPG treatment group had 603 (54.9%) patients while PCPG treatment group had 495 (45.1%) patients. For patients with moderate risk CAP, 362 (38.1%) patients were under the PCPG treatment group and 590 (61.9%) patients were under the non-PCPG treatment group. For patients with high risk CAP, the PCPG group had 133 (91.1%) patients while the non-PCPG group had 13 (8.9%) patients. (Table 2)

Outcomes of patients in terms of adherence or non-adherence to PCPG treatment for both moderate and high-risk CAP patients were compared (Tables 3 and 4).

Patients under the moderate-risk CAP, non-PCPG treatment group demonstrated

significant worsening of their oxygen requirement (p=0.029), had significantly higher tendency to have endotracheal intubation (p=0.006), longer hospital stays (p<0.001) and higher mortality rates (p=0.02). Although not statistically significant, these patients seemed more prone to be admitted to the ICU. Comparing the PCPG and non-PCPG groups other parameters such as presence of fever, tachypnea, WBC and clearing of CXR were not statistically significant.

For patients under the high-risk CAP group, there was no noted significant difference in outcomes for both PCPG and non-PCPG treatment groups (p>0.05). Mortality rates were high both in the PCPG and non-PCPG groups (52.9% and 53.85% respectively).

Tables 5 and 6 show the factors influencing the adherence to PCPG treatment among moderate risk and high risk CAP patients. Among moderate risk CAP patients, previous use of antibiotics, presence of COPD and bronchiectasis were significant factors influencing non-adherence to PCPG treatment (p<0.05). There were no factors associated influencing the

Table 3. Clinical and Laboratory Outcomes of Treatment in Moderate-Risk CAP Patients

Outcomes	PCPG (n=362)		Non-PCPG (n=590)		Total	P Value
Clinical Parameters	**No.**	**%**	**No.**	**%**		
Fever						0.527
Worsened	3	0.8%	8	1.35%	11	
Improved	85	23.48%	124	21.02%	209	
Stable	273	75.41%	457	77.45%	730	
Tachypnea						0.632
Worsened	8	2.20%	19	3.22%	27	
Improved	245	67.68%	389	65.93%	498	
Stable	109	30.11%	180	30.5%	289	
Oxygen Requirement						**0.029**
Worsened	13	3.59%	44	7.46%	57	
Improved	241	66.57%	393	66.61%	634	
Stable	108	29.83%	151	25.59%	259	
Laboratories						
WBC count						0.095
Worsened	27	7.46%	78	13.22%	105	
Improved	107	29.56%	197	33.39%	304	
Stable	57	15.75%	91	15.42%	148	
Clearing of CXR						0.72
Clearing	30	8.29%	79	13.39%	109	
Progressive	53	14.64%	112	18.98%	165	
Stable	45	12.43%	104	17.63%	149	
Not Done/Not Repeated	234	64.64%	295	50.00%	529	
Morbidity						
ICU admission	5	1.38%	18	3.05%	23	0.129
Endotracheal intubation	5	1.38%	28	4.75%	33	**0.006**
Hospital Stay						<0.001
< 5 days	131	36.19%	145	24.58%	276	
≥ 5 day	231	63.81%	445	75.42%	676	
Survival						0.02
Alive	359	99.17%	565	95.76%	924 (97%)	
Expired	3	0.83%	25	4.24%	28 (3%)	

CAP, community-acquired pneumonia; PCPG, Philippine Clinical Practice Guidelines; CXR, chest x-ray.

adherence to PCPG treatment for high risk CAP patients.

Table 7 shows the frequency of microorganisms isolated from the collected specimens from patients with moderate and high risk CAP. Among patients with moderate-risk CAP, sputum culture isolates were predominantly *Acinetobacter spp* (37 or 16.70%) and *P. aeruginosa* (28 or 12.55%), then followed by *Klebsiella pneumoniae* (25 or 11.21%), *Enterobacter spp* (23 or 10.31%) and *Moraxella catarrhalis* (23 or 10.31%). Blood culture isolates grew more coagulase-negative *Staphylococci* (CoNS) (51.85%) and *Escherichia coli* (7.4%) species. Pleural fluid isolates also grew predominantly CoNS 2 (33.33%) species. Among high-risk CAP patients, sputum culture isolates were predominantly *P. aeruginosa* (17.43%) and *Acinetobacter* spp (15.6%), then followed by *Enterobacter* spp (13.76%) and *K. pneumoniae* (8.25%). Blood culture isolates were predominantly CoNS (41.67%), then followed by *Streptococcus pneumoniae* (20.83%), *Acinetobacter* (12.5%) and *Enterobacter* (8.33%).

Table 4. Clinical and Laboratory Outcomes of Treatment in High-Risk CAP Patients

Outcomes	PCPG (n=362)		Non-PCPG (n=590)		Total	P Value
Clinical Parameters	**No.**	**%**	**No.**	**%**		
Fever						0.191
Worsened	8	6.01%	2	15.38%	10	
Improved	17	12.78%	4	30.77%	21	
Stable	84	63.16%	7	53.85%	91	
Tachypnea						0.602
Worsened	8	6.01%	1	7.7%	9	
Improved	93	69.92%	10	76.92%	103	
Stable	32	24.06%	2	15.38%		
Oxygen Requirement						0.366
Worsened	18	13.53%	1	7.7%	19	
Improved	67	50.38%	7	53.85%	74	
Stable	48	36.2%	5	38.46%	53	
Laboratories						
WBC count						0.483
Worsened	30	22.56%	4	30.77%	34	
Improved	52	39.1%	4	30.77%	56	
Stable	9	6.8%	2	15.38%	11	
Clearing of CXR						0.962
Clearing	33	24.81%	3	23.08%	36	
Progressive	37	27.82%	3	23.08%	40	
Stable	20	15.04%	2	15.38%	22	
Not Done/Not Repeated	43	32.33%	5	38.46%	48	
Morbidity						0.625
ICU admission	120	90.23%	11	84.62%	131	
Endotracheal intubation	13	9.77%	2	15.38%	15	
Hospital Stay						1
< 5 days	46	34.59%	4	30.8%	50	
≥ 5 day	87	65.41%	9	69.2%	96	
Survival						1
Alive	64	48.1%	6	46.15%	7047.9%	
Expired	69	52.9%	7	53.85%	7652.1%	

CAP, community-acquired pneumonia; PCPG, Philippine Clinical Practice Guidelines; CXR, chest x-ray.

Table 5. Factors Influencing Adherence to PCPG in Moderate-Risk CAP Patients

Factor	PCPG (n=362)		Non-PCPG (n=590)		Total	P-value
	No.	(%)	No.	(%)		
Previous Antibiotic Use						<0.001
No	338	93.37%	477	80.85%	815	
Yes	24	6.63%	113	19.15%	137	
Co-Morbidities						
COPD	46	12.71%	124	21.01%	170	0.001
Bronchial Asthma	31	8.56%	55	9.32%		0.728
Diabetes Mellitus	58	16.02%	77	13.05%	135	0.214
CHF	14	3.87%	29	4.92%	43	0.279
Renal Failure	5	1.38%	21	3.56%	26	0.063
BXSIS	26	7.18%	87	14.75%	113	<0.001
PTB	39	10.77%	67	11.36%	106	0.832
Chronic Liver Disease	3	0.83%	2	0.34%	5	0.374
Neurologic Disorder	9	2.49%	27	4.58%	362	0.116
CAD	18	4.97%	32	5.4%	50	0.881

PCPG, Philippine Clinical Practice Guielines; CAP, community-acquired pneumonia; COPD, chronic obstructive pulmonary disease; CHF, congestive heart failure; BXSIS, bronchiectasis; PTB, pulmonary tuberculosis; CAD, coronary artery disease.

Table 6. Factors Influencing Adherence to PCPG in High-Risk CAP Patients

Factor	PCPG (n=362)		Non-PCPG (n=590)		Total	P-value
	No.	(%)	No.	(%)		
Previous Antibiotic Use						>0.05
No	120	90.23%	12	92.3%	132	
Yes	13	9.77%	1	7.7%	14	
Co-Morbidities						
COPD	23	17.3%	5	38.46%	28	0.131
Bronchial Asthma	5	3.76%	3	23.08%	8	0.124
Diabetes Mellitus	14	10.53%	2	15.38%	16	0.637
CHF	7	5.26%	2	15.38%	9	0.184
Renal Failure	4	3.0%	2	15.38%	6	0.09
BXSIS	20	15.04%	1	7.7%	21	0.693
PTB	8	6.0%	3	23.08%	11	0.06
Chronic Liver Disease	1	0.8%	0	0.00%	1	>0.05
Neurologic Disorder	1	0.8%	7	53.85%	8	0.535
CAD	6	4.5%	1	7.7%	7	0.487

PCPG, Philippine Clinical Practice Guielines; CAP, community-acquired pneumonia; COPD, chronic obstructive pulmonary disease; CHF, congestive heart failure; BXSIS, bronchiectasis; PTB, pulmonary tuberculosis; CAD, coronary artery disease.

DISCUSSION

CAP is one of the most common infectious diseases encountered by physicians. Recognition of patients that needs to be admitted is vital in order to provide optimal and appropriate management. The CAP guidelines addresses the issues on diagnosis, prognostication, management and prevention of CAP. This serves to aid clinicians in the initial diagnosis and management of patients with CAP in order to improve the efficacy and effectiveness of healthcare and patient outcomes.

This study evaluates the utilization of the PCPG 2010 CAP update for the empiric treatment of moderate-risk and high-risk CAP at a tertiary specialty center and addresses the effects of adhering to the guidelines on clinical outcomes and patient care.

The overall adherence rate to the CAP treatment guidelines in this study was 45.1%, which is lower compared to the findings on two previous retrospective studies done in 2001 and 1998 76% and 78% respectively).[7,8] In the moderate risk CAP group, adherence to PCPG treatment guidelines was lower at 38.1%, compared to a higher adherence rate to the guidelines in the high risk CAP population at 91.1%. The factors that had been identified for the poor adherence in the moderate risk CAP group include history of previous antibiotic use and the presence of comorbidities such as COPD and bronchiectasis.

The presence of severe underlying bronchopulmonary disease such as COPD and bronchiectasis and previous use of broad-spectrum of antibiotics (>7 days within the past month) were also known risk factors for infection with Pseudomonas aeruginosa.[6]

Most of the patients in the moderate risk category showed clinical improvement and a lower mortality rate of 3% compared to the previous studies showing a mortality rate of 4-13%.[9,10] However majority of the mortalities were patients who received non-PCPG adherent treatment. These patients also had longer hospital stays and had a higher tendency to have

Table 7. Frequency of Organisms Isolated in Specimen Cultures in Moderate-risk and High-risk CAP Patients

Specimen	Moderate-risk		High-risk	
Sputum	**Organism**	**No. (%) (n=223)**	**Organism**	**No. (%) (n=109)**
	Acinetobacter spp	37 (16.6)	*Pseudomonas aeruginosa*	19 (17.43)
	Pseudomonas aeruginosa	28 (12.55)	*Acinetobacter species*	17 (15.6)
	Klebsiella pneumoniae	25 (11.21)	*Enterobacter* spp	15 (13.76)
	Enterobacter	23 (10.31)	*Klebsiella pneumoniae*	9 (8.25)
	Moraxella catarrhalis	23 (10.31)	*Streptococcus pneumoniae*	7 (6.4)
Blood	**Organism**	**No. (%) (n=27)**	**Organism**	**No. (%) (n=24)**
	CoNS	14 (51.85)	CoNS	10 (41.76)
	Acinetobacter	2 (7.4)	*Streptococcus pneumoniae*	5 (20.83)
	Escherichia coli	2 (7.4)	*Acinetobacter species*	3 (12.5)
	Staphylococcus hominis	2 (7.4)	*Enterobacter*	2 (8.33)
	Enterobacter	1 (3.7)	*Klebsiella pneumoniae*	1 (4.16)
	Streptococcus pneumoniae	1 (3.7)		
	Klebsiella pneumoniae	1 (3.7)		
Pleural fluid	**Organism**	**No. (%) (n=6)**		
	CoNS	2 (33.33)		
	Enterobacter	1 (16.66)		
	Streptococcus pneumoniae	1 (16.66)		
	Streptococcus viridans	1 (16.66)		
	Alkaligenes faecalis	1 (16.66)		

respiratory failure. These can be due to the presence of more comorbid illnesses in this group of patients such as COPD and bronchiectasis that could have contributed to their morbidity. This findings were consistent with the previous study done by Egargo and Idolor (2001) which showed that patients who had PCPG treatment had shorter hospital stays.[7]

On the other hand, despite the adherence to PCPG treatment in the high-risk CAP patients, the mortality rate was still high at 52.9% (versus 53.85% in the non-PCPG group) which was higher compared to literature with a mortality rate of 20-30%.[6] This can be attributed to a more severe baseline clinical condition of patients leading to respiratory failure in the majority of patients and having a less favorable outcome.

The most common bacterial pathogens in sputum specimens for the moderate-risk CAP were *Streptococcus pneumoniae*, *Haemophilus influenzae*, enteric Gram-negative bacilli, and *Moraxella catarrhalis*. For the high risk CAP patients, in addition to the above mentioned microorganisms, Pseudomonas aeruginosa and Staphylococcus aureus were commonly isolated bacterial pathogens.[6] In this study, the sputum culture isolates in the moderate-risk CAP group were predominantly aerobic Gram-negative bacilli such as *Acinetobacter* species, *Pseudomonas aeruginosa*, *K. pneumoniae* and *Enterobacter* which was also reported in some of the community-acquired pneumonia studies.[10,11] Studies that have found a high incidence of Gram-negative organisms as causative agents for CAP included elderly patients and patients with underlying chronic diseases.[13,14] Gram-negative infections was predominant in our study because most of the patients were elderly and had COPD and bronchiectasis as frequent underlying comorbidities. Gram-negative microorganisms were also isolated in the high-risk CAP group and the most common isolates were *P. aeruginosa*, *Acinetobacter* spp., *Enterobacter* spp. and *K. pneumonia*, which conforms to previous literature.[6]

Blood culture specimens, in both moderate risk and high-risk CAP groups showed CoNS, *Acinetobacter* spp., *S. pneumoniae*, *Enterobacter* and *K. pnuemoniae* as the most commonly isolated microorganisms. Isolation of CoNS may suggest contamination of the blood cultures because it is a normal skin flora, and if a true positive culture in the blood it may indicate a nosocomial bacteremia.[15] However, a blood culture must always be taken in the clinical context and never hastily disregarded as being insignificant. The other microorganisms, *Acinetobacter* spp., S. *pneumoniae*, *Enterobacter* and *K. pnuemoniae* were also demonstrated in previous literature.[6]

CONCLUSIONS

The overall adherence rate to the CAP treatment guidelines was 45.1%. Adherence was lower in the Moderate-risk than in the High-risk CAP group. Moderate-risk patients who were given non-PCPG antibiotic treatment had higher mortality rates, longer hospital stays and greater tendencies to develop respiratory failure. There was no significant difference in the outcomes for both PCPG and non-PCPG treatment in the High-risk CAP.

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RETROSPECTIVE COHORT STUDY

Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration in the Philippines: A Preliminary Retrospective Cohort Study on Diagnostic Performance

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ABSTRACT

Background and Aims: Endobronchial ultrasound transbronchial needle aspiration (EBUS-TBNA) is a bronchoscopic technique utilized for staging lung cancer and evaluating mediastinal lymphadenopathy. EBUS-TBNA was introduced during a seminar in the Philippines in 2013 and has been in regular use at our institution since 2014. The objective of this study was to evaluate the diagnostic yield and complications of the procedure, as well as the factors affecting both.

Methods: A retrospective chart and histopathologic review was done on 26 consecutive adult patients who underwent EBUS-TBNA at The Medical City between January 2015 and December 2015.

Results: The overall diagnostic yield of EBUS-TBNA was 85% (22/26); of these, 82% (18/22) were malignant and 18% (4/22) were benign disease secondary to tuberculosis. Subcarinal lymph node location and three or more aspirations per procedure showed a tendency to improve diagnostic yield. No major complications were associated with the procedure.

Conclusion: This preliminary experience in the Philippines showed that EBUS-TBNA is a promising tool for the evaluation of mediastinal lymphadenopathy and lesions, with high diagnostic yield and a good safety profile. Future, larger-scale studies are needed to determine the ways of significantly improving diagnostic performance.

INTRODUCTION

Endobronchial ultrasound transbronchial needle aspiration (EBUS-TBNA) is a bronchoscopic technique that utilizes real-time image guidance to visualize mediastinal structures beyond the airway wall and lumen. Using EBUS-TBNA, lesions in the mediastinum, hilum, and central lung parenchyma may be located and sampled with more precision, reducing the need for mediastinoscopy and thoracotomy. Since it was first described in 1992, EBUS-TBNA has emerged to be at the forefront of lung cancer staging and evaluation of mediastinal lymph-adenopathies, with a diagnostic yield as high as 93%, sensitivity of 94%, specificity of 100%, and accuracy of 94%. Complication rates have also been minimal at 1 to 2%. Since then, numerous published researches have established the safety, diagnostic efficacy, and accuracy of this procedure.

EBUS-TBNA has been utilized for the staging of lung cancer and investigation of mediastinal and hilar lymph node enlargement, both benign and malignant. Staging of lung cancer, particularly non-small cell carcinoma (NSCLC) is vital, as this greatly affects the prognosis and treatment plan for the patient. The most significant treatment decision is to distingu-

ish between those patients who can benefit from surgical resection and those who should receive chemotherapy and/or radiation. EBUS-TBNA is the preferred first step for large, centrally located tumors and for suspicious nodal involvement in the mediastinum. The most recent guidelines of the American College of Chest Physicians and the European Society of Thoracic Surgeons supports the recommendation of EBUS-TBNA as the initial step in the staging of lung cancer.

Mediastinal lymph node staging may be done in a non-invasive or invasive manner. The former is by imaging techniques, the most common of which include computed tomography (CT) scan, magnetic resonance imaging, positron emission tomography (PET), and PET/CT. EBUS-TBNA however has been shown to have a higher sensitivity and specificity than CT and PET scans. In a prospective study by Yasufuku et al, EBUS-TBNA was noted to have a sensitivity of 92.3% and specificity of 100%, compared to those of CT (sensitivity 76.9%, specificity 55. %) and PET scans (sensitivity 80.0%, specificity 70.1%).

Invasive staging techniques are divided into surgical and nonsurgical procedures, which include endoscopic and bronchoscopic techniques. Surgical staging includes mediastinoscopy, anterior mediastinotomy (Chamberlain procedure), and video-assisted thoracoscopic surgery. Mediastinoscopy, deemed the historical gold standard for lung cancer staging, has the limitation of being unable to access the posterior mediastinal and hilar lymph nodes**.** EBUS-TBNA, on the other hand, has been shown to be able to access such stations. Furthermore, numerous published data have shown that EBUS-TBNA has excellent sensitivity, specificity, and negative predictive value that were comparable to those of mediastinoscopy.[9]

In the investigation of mediastinal and hilar lymphadenopathy, EBUS-TBNA has been shown to provide sufficient samples for the diagnosis of most disorders, such as lymphoma and granulomatous inflammation. EBUS-TBNA has also been proven to have a diagnostic yield as high as 94%. In the Philippines, where tuberculosis is endemic, this disease should always be considered as a cause of mediastinal lymphadenopathy.

To the best of our knowledge, Philippine data on the various procedures and techniques for the diagnosis of mediastinal lymphadenopathies and pulmonary lesions are limited. EBUS-TBNA was introduced in the Philippine setting during a bronchoscopy seminar in 2013. Since 2014, it has been made available for public use at The Medical City. To date, only case reports on the use of EBUS in the Philippines are available. With the anticipated increasing use of this technology, there is a need to assess the diagnostic performance of the procedure. Being the first in the country, the authors aimed to evaluate the diagnostic yield and complications of the procedure, as well as the factors affecting both.

METHODOLOGY

This is a retrospective study on consecutive EBUS-TBNA cases that were done at the Center for Endoscopy and Physiologic Studies of The Medical City between January 2015 and December 2015. All patients who underwent this procedure had CT scan findings of mediastinal or hilar mass, mediastinal lymphadenopathy, or both. Written informed consent was obtained from all patients for the performance of the procedure.

EBUS-TBNA procedure

At our hospital, EBUS-TBNA is performed either as an inpatient or outpatient procedure. The patient is placed under moderate to deep sedation with continuous oxygen support by either nasal cannula or nasopharyngeal airway. After preparing the 21-G or 22-G needle (Vizishot NA-201SX-4022-A or NA-201SX-4022-A; Olympus, Tokyo, Japan) and the balloon around the ultrasound probe, a dedicated EBUS-TBNA bronchoscope (BF-UC180F; Olympus, Tokyo, Japan) I s inserted through the oral route and into the tracheobronchial lumen in the usual manner, with intermittent applications of 1-2% lidocaine. The scope with the convex EBUS probe on its tip is then used to scan the area of interest and to look for the pathologic lymph node or lesion and its surrounding

structures. The Doppler capability enables the bronchoscopist to identify adjacent blood vessels that should be avoided during puncture.

Once the pathologic lymph node or lesion has been identified, the bronchoscopist inserts the TBNA needle in the working channel. While the assistant holds the bronchoscope in place, the needle is pushed gently through the tracheobronchial mucosa and into the lesion under simultaneous ultrasound guidance. A cytology and/or histology sample is obtained by passing the needle in and out (how many times? Explain for example that it depends on the bronchoscopist or write the average number of times) through various parts of the lesion. After aspiration, the needle is fully retracted into the sheath and withdrawn through the working channel. After removing the needle, the sample is extruded onto slides for processing. Depending on the case and the discretion of the attending physician, an onsite cytopathologist was sometimes present to comment on adequacy and quality of the specimens obtained.

Outcomes were classified as diagnostic or non-diagnostic. The procedure was labeled as diagnostic if 1) the histopathologic and cytopathologic studies obtained malignant or specific benign findings, such as granulomatous inflammation or 2) the procedure yielded non-specific benign findings and follow-up showed resolution, decrease in size, or stability of the lesion. The procedure was labeled as non-diagnostic if the diagnosis was proven otherwise by a different diagnostic modality. Diagnosis was labeled "unknown" if no follow-up data within the following six months were available; these cases (n = 7) were excluded from the analyses.

Statistical Analysis

In this study, diagnostic performance was procedure-based. A positive result was defined if a specific diagnosis (e.g., carcinoma or tuberculosis) was made without the need for surgical diagnostic intervention. A negative result referred to the need further investigation (e.g., mediastinoscopy or thoracotomy). A false-negative result was defined as no specific diagnosis until further investigation yielded positive findings from the target area or follow-up eventually confirmed a positive diagnostic result in the area of interest. True negative was defined as a biopsy being confirmed as negative after further diagnostic intervention, surgical exploration, or unremarkable follow-up for at least six months. The diagnostic yield and accuracy were calculated. Taking the pathological or microbiological diagnosis revealed by EBUS-TBNA as the gold standard, false positives were assumed to be absent.

Data were presented as mean ± SD or frequencies and percentages. Diagnostic yield was compared according to patient and procedural variables. Factors affecting diagnostic yield success were determined using the Fisher's exact test. A p value of less than 0.05 was considered statistically significant. Statistical analysis was done using Stata SE version 3, StataCorp LP, College Station, Texas, USA.

RESULTS

During the study period, a total of 33 consecutive patients underwent EBUS-TBNA; 7 were excluded because of "unknown diagnoses", as described in the Methods section. Among the 26 patients in the study population, 16 were in-patient and 10 were out-patient procedures; 14 were men and 12 were women; the mean age was 59.8 ± 17.5 years. Thirteen patients had a previous history of smoking, with a median of 15 pack years. Nine had previous underlying malignancies, namely breast, kidney, bladder, oral, and liver. Other characteristics of the population are described in Table 1.

Diagnostic Performance

A total of 40 lymph nodes were sampled in 26 patients (Table 2). The mean number of lymph node site biopsied for each patient was 1.5 ± 0.94 and the mean number of aspirations was 3 ± 0.74 per procedure (Table 3). The overall diagnostic yield of EBUS-TBNA was 85% (22 of 26), among which 18 patients had malignancy, including 10 cases of adeno-

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

Characteristics (N=26)	Mean ± SD or n (%)
Gender	
Male	14 (53.8%)
Female	12 (46.2%)
Age in years	59.8 ± 16.03
Smoking History	
Smoker	13 (50.0%)
Pack-years	15 ± 18.35
Underlying Malignancy	
Breast	5 (19.23%)
Kidney	1 (3.84%)
Liver	1 (3.84%)
Bladder	1 (3.84%)
Oral	1 (3.84%)
Co-morbid conditions	
Hypertension	13 (50.0%)
Diabetes	7 (26.92%)
COPD	1 (3.84%)
Inpatient	16 (61.54%)
Outpatient	10 (38.46%)
Number of lymph node sites biopsied	1.5 ± 0.94
Number of aspirations	3 ± 0.74

Table 2. Diagnostic yield per lymph node station

Lymph Node Station	Lymph nodes (n=40)	Diagnosis established (n, %)
4R	12	10 (83.33)
4L	3	3 (100.0)
7	13	12 (92.3)
10R	2	1 (50.0)
11R	5	5(100.0)
11L	5	4 (80.0)

carcinoma, 3 cases of small cell carcinoma, 1 case of neuroendocrine carcinoma, and 4 cases of metastatic cancer. There were three cases of culture-proven tuberculosis. One patient had chronic granulomatous inflammation on histology and improved on follow-up after Category I treatment for clinically-diagnosed tuberculosis. There were four diagnostic failures; among which, two patients were diagnosed as lung adenocarcinoma by CT-guided transthoracic needle aspiration, one patient was diagnosed as metastatic carcinoma by kidney biopsy, and one patient was diagnosed as lung adenocarcinoma by EBUS with a guide sheath transbronchial biopsy of the peripheral pulmonary lesion. The accuracy for malignancy and tuberculosis were 82% and 100%, respectively (Table 4). As shown in Table 4, analysis of the clinical and procedural factors affecting diagnostic success showed that the subcarinal lymph node location and at least three aspirations per procedure tend to have better diagnostic yield, albeit insignificant.

Complications

All patients underwent the procedure with comfort and excellent compliance. No major complications of pneumothorax, hemorrhage, or infection were noted. Two patients had fever immediately post-procedure and were given prophylactic oral antibiotics. The 16 patients who were admitted for the procedure were discharged the following day. The 10 cases that were done as outpatient were discharged after brief observation, as per institutional protocol.

DISCUSSION

The diagnosis of mediastinal lymph-adenopathy remains a challenge for pulmonary physicians. EBUS-TBNA has been used to diagnose and stage mediastinal lesions and lymphadenopathies, and has been established to have a high diagnostic performance and safety profile. Numerous published data have shown that

Table 3. Diagnosis obtained through EBUS-TBNA

Diagnosis	N=26 (%)
Success	**22 (84.5)**
Malignancy	18
Adenocarcinoma	10
Small cell carcinoma	3
Neuroendocrine carcinoma	1
Metastatic	4
Tuberculosis	4
Failure	**4 (15.38)**

Table 4. Factors affecting diagnostic yield (N=26)

Variables	Accuracy (%)	P value
Age		0.417
< 60 years old	7/7 (100.0)	
≥ 60 years old	15/19 (78.9)	
Sex		0.542
Male	11/14 (78.6)	
Female	11/12 (91.6)	
Smoking		0.417
Non-smoker	12/13 (92.3)	
< 15 pack years	2/3 (66.7)	
≥ 15 pack years	8/10 (80.0)	
Number of lymph node site biopsied		1.000
< 2	11/13 (84.6)	
≥ 2	11/13 (84.6)	
Number of aspirations per procedure		0.408
< 3 aspirations/procedure	2/3 (66.7)	
≥ 3 aspirations/procedure	20/23 (86.9)	
Location of procedure		0.263
Inpatient	13/17 (76.4)	
Outpatient	9/9 (100.0)	
Lymph node station		0.822
Paratracheal (4R/4L)	10/12 (83.3)	
Subcarinal (7)	12/13 (92.3)	
Hilar/Interlobar (10/11)	5/6 (83.3)	
Etiology		1.000
Benign	4/4 (100.0)	
Malignant	18/22 (81.8)	

this procedure was comparable to the historical gold standard of mediastinoscopy for the diagnosis of mediastinal abnormalities.

In this pilot study, all patients who underwent EBUS-TBNA at our institution had suspected malignant or benign mediastinal lesions, or lymphadenopathy of unknown cause. We were able to achieve an overall diagnostic yield of 85%. The accuracy of EBUS-TBNA for malignancy and tuberculosis was 82% and 100%, respectively, analogous with some systematic reviews evaluating its role in diagnosing patients with mediastinal lesions. It is important to note that although EBUS-TBNA has been established in other countries, the procedure is new in the Philippines. Therefore, the members of the bronchoscopy team, including the operator, anesthesiologist, medical trainees, nurses, technicians, and pathologist, have room for improvement along the learning curve.

The reported major predictors of a high diagnostic yield include lymph node size (short axis length >2 cm), presence of abnormal endoscopic findings, subcarinal and right paratracheal location, and the use of histological needle by an experienced bronchoscopist. Furthermore, maximum diagnostic values were achieved in three numbers of aspirations, but plateaued after seven aspirations per lymph node. The AQuIRE Bronchoscopy Registry study reported that smoking status, biopsy of more than two sites, lymph node size, and positive PET scans were factors which significantly affected diagnostic yield. In our study, obtaining three or more samples and biopsy from the subcarinal lymph node station had a tendency towards a higher diagnostic yield, consistent with those mentioned in literature.

The use of EBUS-TBNA with a 22-G needle for sampling under real-time guidance with Doppler mode screening minimizes inadvertent puncturing of blood vessels. This was exemplified by the excellent safety profile demonstrated in our study. All patients who were admitted had a mean length of stay of one day and were discharged without any complications. In addition, the diagnostic yield and absence of complications were the same, whether the patient was admitted to the hospital or underwent the procedure as an outpatient. Unfortunately, the procedural time was not recorded, but was estimated to be around 20 to 60 minutes, depending on the number and location of lesions sampled.

This study had some limitations. Being a new procedure in a single of institution, the number of subjects was relatively few and may have contributed to the lack of statistically significant predictors of diagnostic outcome. Nevertheless, this is only a preliminary report. The retrospective design carried an inevitable

patient selection bias. In our study, diagnostic procedures that were positive for lung cancer by histology were not confirmed by surgical biopsy (the gold standard); therefore, it was not possible to determine the proportion of false positives. Lastly, in this study, there was more than one pulmonologist who performed the procedure; this may have contributed to differences in outcomes due to variations in techniques.

In conclusion, EBUS-TBNA is a safe and efficient approach for the diagnosis of mediastinal lymphadenopathy. This new procedure in the Philippines is a promising tool that can enable clinicians to assess mediastinal lymphadenopathy and lesions in a minimally invasive manner, with high diagnostic yield and safety.

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PROSPECTIVE COHORT STUDY

Concordance of Incidence of Postoperative Pulmonary Complications with Predicted Probabilities Using Multifactorial Risk Index for Postoperative Pneumonia and Respiratory Failure at the Veterans Memorial Medical Center

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ABSTRACT

Postoperative pulmonary complications (PPC) are associated with substantial morbidity and mortality, contributing to nearly 25% of deaths occurring within 6 days postoperatively. The Veterans Memorial Medical Center (VMMC) uses the multifactorial risk index for predicting postoperative pneumonia and respiratory failure.

This study aimed to determine the prevalence of postoperative pneumonia and respiratory failure, identify which clinical characteristics common among surgical patients are associated with the development of postoperative pulmonary complications, determine the distribution of surgical patients among different risk classes, and validate the multifactorial risk index for predicting postoperative pneumonia and respiratory failure.

In this prospective cohort study done at the VMMC (n=1,442), 69 participants developed postoperative pneumonia, and 72 developed postoperative respiratory failure. These figures yield a prevalence of 4.78% and 4.99%, respectively. The clinical variables associated with the development of postoperative pneumonia include age, functional status, weight loss, recent smoking, history of chronic obstructive pulmonary disease (COPD), chronic steroid use, history of cerebrovascular accident, impaired sensorium, transfusion >4 units, type of surgery (ie, upper abdominal, thoracic, extremity, and neurological), general anesthesia, emergency surgery, length of stay, and inpatient mortality. Whereas those associated with the development of postoperative respiratory failure are age, albumin level, functional status, history of COPD, type of surgery, emergency surgery, length of hospital stay, and inpatient mortality. The observed proportion of outcome was concordant with the predicted probability of outcome. The role of preoperative measures in addressing modifiable risk factors and the role of adherence to postoperative care in preventing the said pulmonary complications are yet to be determined.

INTRODUCTION

Postoperative pulmonary complications (PPC) are associated with substantial morbidity and mortality, contributing to nearly 25% of the deaths occurring within 6 days postoperatively.[1] The definition of what constitutes PPC varies greatly: atelectasis, postoperative pneumonia, acute respiratory distress syndrome, and postoperative respiratory failure.[2] Although not as well studied as cardiac complications in the postoperative setting, PPC are as common, as serious, and more costly to manage.[3]

Several risk factors that contribute to the risk of PPC have been previously identified. These are patient-related risk factors, procedure-related risk factors, and laboratory predictors. With these, a number of scoring systems have been devised to predict PPC risk. Arozullah et al have derived and

validated a scoring system to predict the risk for postoperative pulmonary complications, specifically, pneumonia and respiratory failure.[4]

Among the many risk scoring systems, our institution uses the multifactorial risk index for predicting postoperative pneumonia and respiratory failure (Appendix A), which was developed by Arozullah et al and validated in a developed country. Validation of the said index in a developing country such as ours is important to determine whether the predicted risk bespeaks of what is observed in the actual scenario. This would strengthen our preoperative pulmonary evaluation for patients, therefore preventing postoperative pulmonary complications.

Hence, this study aims to validate the multifactorial risk index for predicting postoperative pneumonia and respiratory failure at the Veterans Memorial Medical Center (VMMC). Specifically, it aims to identify which of the clinical characteristics common to surgical patients in VMMC are associated with the development of postoperative pulmonary complications; to determine the prevalence of postoperative pneumonia and respiratory failure among patients who have undergone a surgical procedure and for whom preoperative pulmonary risk assessment was sought, as well as the distribution of surgical patients in each risk class; and lastly, to compare the predicted risk probability to the actual rate of postoperative pulmonary complications.

METHODOLOGY

This prospective cohort study covered a 12-month period, from November 2013 to October 2014, and was conducted at VMMC, a tertiary-care hospital located in North Avenue, Diliman, Quezon City. Participants included all adult patients admitted at the wards and intensive care units; who underwent either emergency or elective surgical procedure under general, regional, or monitored anesthesia care; and for whom preoperative pulmonary risk assessment was secured. Excluded from the study were patients who were intubated preoperatively, had a tracheostomy tube inserted, or had respiratory failure preoperatively. Participants were briefed regarding the study, and written consent was secured. They were followed up for the duration that they were admitted, until a maximum period of 30 days postoperatively. Thirty days was an arbitrary period used in the studies done by Arozullah et al.

For the purpose of this study, *postoperative pneumonia* is defined and diagnosed as nosocomial pneumonia after surgery based on the Centers for Disease Control and Prevention's definition. (Appendix B). *Postoperative respiratory failure*, on the other hand, is recognized as "mechanical ventilation for more than 48 hours after surgery, or reintubation and mechanical ventilation after postoperative extubation," as defined by Arozullah et al.[2]

Sample size computation was based on the incidence of outcomes in each class risk. The incidence of postoperative respiratory failure resulted in a sample size of 82, and including a 20% nonresponse rates will yield a total of 103 participants, with a 95% confidence interval.

The baseline clinical characteristics of the participants and the distribution of patients in each risk class were reported in frequency and percentages. P-values were computed to determine whether a variable showed significant difference between the two groups and to compare the observed proportion of postoperative outcome in every risk class with the standard proportion of outcome.

RESULTS

A total of 1442 participants were enrolled from November 2013 to October 2014. Results are evaluated into those having: (1) postoperative pneumonia complication and (2) postoperative respiratory failure.

For Postoperative Pneumonia

There were 1,442 included patients: 69 (5%)

had postoperative pneumonia, while 1373 (95%) patients did not develop postoperative pneumonia.

Those with postoperative pneumonia were significantly older (70 vs 62 years) with a dependent functional status. Patients developing post-operative pneumonia has chronic obstructive pulmonary disease (COPD), impaired sensorium, >10% weight loss, or had >4 units of blood transfused preoperatively, a recent smoker, and has been using steroids chronically. Postoperative pneumonia likewise developed in patients undergoing upper abdominal (26.09%), extremity (23.19%), neurological (17.39%), and thoracic (14.49%) surgeries (Table 1).

Figure 1 shows the distribution of all the participants into the five risk classes for postoperative pneumonia according to the Postoperative Pneumonia Risk Index (Appendix). Majority of participants (34%) were in risk class III.

Results show that the observed proportion of outcome was not significantly different from the standard proportion of outcome across different risk classes for postoperative pneumonia (Table 2 and Figure 2).

For Postoperative Respiratory Failure

A total of 72 (5%) of the 1,442 study participants had postoperative respiratory failure. Patients developing postoperative respiratory failure were significantly older (69.95 years), with a dependent functional status and has lower albumin levels (36g/L vs 106g/L). These are patients who underwent upper abdominal (25.00%), thoracic (18.06%), neurological (18.06%) and peripheral vascular (8.33%) surgeries (Table 3).

Figure 3 shows the distribution of all this study's participants into the 5 risk classes for postoperative respiratory failure. Majority of the participants (30%) were classified under risk class I.

Results show that the observed proportion of outcome was not significantly different with the standard proportion of outcome across different risk classes for postoperative respiratory failure (Table 4 and Figure 4).

DISCUSSION

Postoperative pulmonary complications have been reported to occur in 5% to 10% of all surgical patients, depending on what type of surgery was performed and how one defines a postoperative pulmonary complication.[1-3] In this study, postoperative pulmonary complications are defined as the development of either postoperative pneumonia or postoperative respiratory failure or both. In our study, the prevalence of having postoperative pneumonia or respiratory failure complications is 5%. This may imply that other factors—such as preoperative measures and postoperative care toward the prevention of such pulmonary complications—need to be looked into.

The mean age of the participants having postoperative pneumonia or respiratory failure was 70 years, older than patients who did not have postoperative pulmonary complications. Although age was considered only a risk factor when associated with multiple co-morbidities. In our study there was no significant gender predominance in those having postoperative pulmonary complications or none.

We also found an association between dependent functional status and the development of postoperative pneumonia, respiratory failure, and weight loss >10%. This finding is consistent with those of previous studies and may be related to limited mobility and acquisition of proper nutrition.[1-4] Low albumin level is significantly associated with the development of postoperative respiratory failure, indicating the importance of nutrition in preventing this complication.[5] The increased risk for pneumonia but not for respiratory failure may be due to immunosuppression in addition to the impact of the underlying disease—such as COPD or rheumatoid arthritis—for which steroid was used.

The proportion of participants who had been recently smoking or had a history of COPD was

Table 1. Demographic and Clinical Characteristics of Participants With and Without Postoperative Pneumonia

	With Postoperative Pneumonia (n=69)	Without Postoperative Pneumonia (n=1,373)	p-value
Age, years ± SD	70.05 ± 14.2	61.5 ± 13.4	<0.001
≥80	20 (28.98%)	177 (12.89%)	
70–79	17 (24.64%)	168 (12.24%)	
60–69	15 (21.74%)	391 (28.48%)	
50–59	14 (20.29%)	381 (27.75%)	
<50	3 (4.35%)	256 (18.65%)	
Male sex	36 (52.17%)	698 (50.84%)	0.828
Albumin (mean g/L ± SD)	30 ± 3	36 ± 8.3	0.932
Albumin <30 g/L	7 (10.14%)	135 (9.83%)	
Functional status			<0.001
Independent	45 (65.22%)	1166 (84.92%)	
Partially dependent	18 (26.09%)	179 (13.04%)	
Dependent	6 (8.70%)	28 (2.04%)	
Diabetes mellitus	18 (26.09%)	262 (19.08%)	0.155
Weight loss >10% in 6 months prior to surgery	9 (13.04%)	25 (1.82%)	<0.001
Disseminated cancer	1 (1.45%)	19 (1.38%)	0.964
Recent smoking	24 (34.78%)	278 (20.25%)	0.004
Chronic Obstructive Pulmonary Disease	20 (28.99%)	121 (8.81%)	<0.001
Chronic heart failure	5 (7.25%)	132 (9.61%)	0.513
Chronic steroid use	3 (4.35%)	19 (1.38%)	0.050
Alcohol >2 drinks/day	3 (4.35%)	25 (1.82%)	0.138
History of cerebrovascular accident	9 (13.04%)	78 (5.68%)	0.012
Impaired sensorium	6 (8.70%)	31 (2.26%)	0.001
Transfusion >4 units	4 (5.80%)	25 (1.82%)	0.022
Blood urea nitrogen (mean mg/dl ± SD)	18.35 ± 10.32	12.38 ± 8.71	
Creatinine (mean mg/dl ± SD)	1.23 ± 1.03	1.11 ± 1.01	
Type of surgery			<0.001
Upper abdominal	18 (26.09%)	279 (20.32%)	
Thoracic	10 (14.49%)	110 (8.01%)	
Peripheral vascular	3 (4.35%)	82 (5.97%)	
Extremity	16 (23.19%)	242 (17.63%)	
Abdominal aortic aneurism repair	0	0	
Lower abdominal	6 (8.70%)	392 (28.55%)	
Neurological	12 (17.39%)	56 (4.08%)	
Back and spine	1 (1.45%)	2 (0.15%)	
Neck	3 (4.35%)	209 (15.22%)	
Dermatologic	0	1 (0.07%)	
General anesthesia	48 (69.57%)	722 (52.59%)	0.006
Emergency surgery	23 (33.33%)	173 (12.60%)	<0.001
Inpatient mortality	26 (37.68%)	41 (2.99%)	<0.001
Length of hospitalization, days	15.9 ± 7	7.50 ± 3	<0.001

Table 2. Observed and Predicted Proportion of Outcome for Postoperative Pneumonia

Risk Class	Participants Having the Outcome	Observed Proportion (%)	Predicted Proportion (%)	p-value
I	0	0	0.2	0.434
II	4	1.3	1.2	0.785
III	29	6.0	4.0	0.260
IV	24	12.6	9.4	0.133
V	12	16.4	15.3	0.787

Figure 1. Distribution of Participants Among the Risk Classes for Postoperative Pneumonia

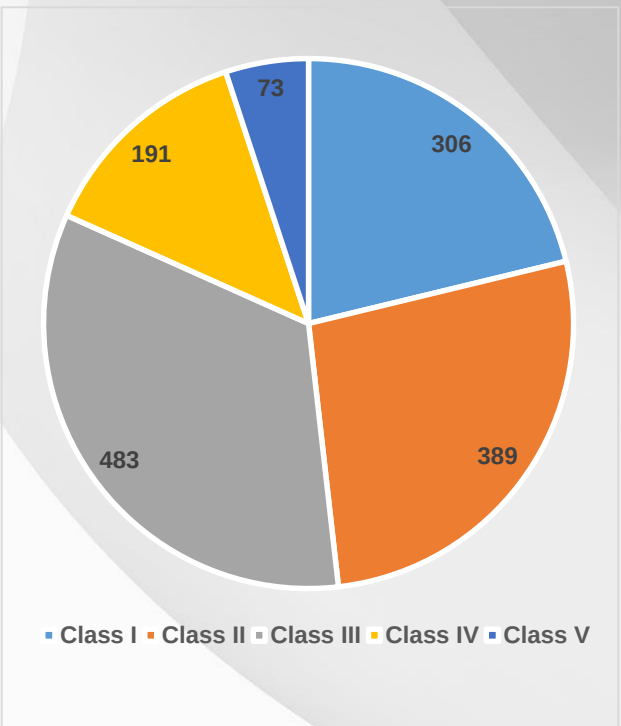
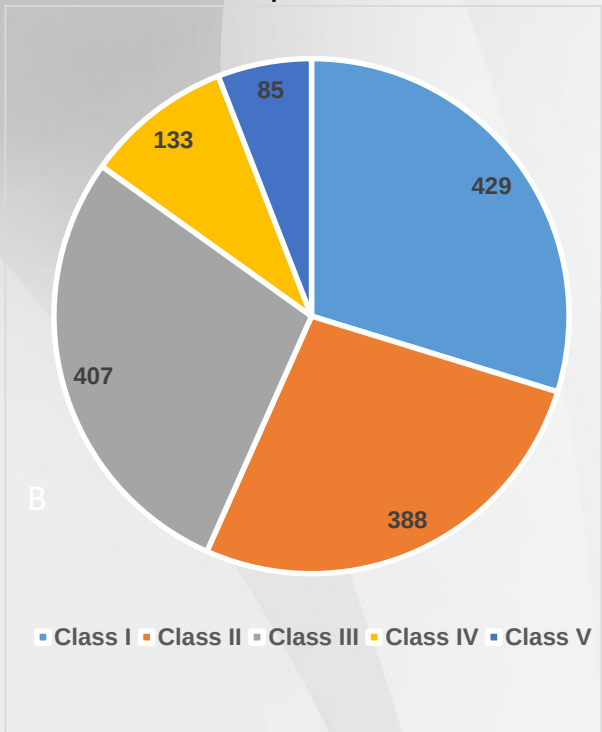


Figure 3. Distribution of Participants Among the Risk Classes for Postoperative Pneumonia



significantly higher in the group with postoperative pneumonia. This is consistent with previous findings that patients who currently smoke have an increased risk of postoperative complications even in the absence of COPD.[1-4] The risk appeared to be highest within the last 2 months of smoking. Those who had quit smoking for more than 6 months had a similar risk as those who did not smoke. The risk for pneumonia remains elevated up to 1 year after quitting—a possible reason why there is a significantly higher proportion of participants with postoperative pneumonia but no significant difference in the proportion of participants with respiratory failure. Patients with COPD were 6 times more likely to have major postoperative complications, consistent with the findings of this study.[6]

Variables pertaining to neurologic status that are associated with postoperative pulmonary complications include impaired sensorium and history of CVA. This could be related to the increased chance of aspiration due to the patients' decreased ability to protect their airways.

Table 3. Demographic and Clinical Characteristics of Participants With and Without Postoperative Respiratory Failure

	With Postoperative Pneumonia (n=69)	Without Postoperative Pneumonia (n=1,373)	p-value
Age, years ± SD	69.95 ± 12.70	61.87 ± 14.6	<0.001
≥80	20 (27.78)	177 (12.92)	
70–79	19 (26.39)	166 (12.12)	
60–69	18 (25.00)	388 (28.32)	
50–59	9 (12.50)	386 (28.18)	
<50	6 (8.33)	253 (18.47)	
Male sex	37 (51.39)	697 (50.88)	0.932
Albumin (mean g/L ± SD)	33 ± 6.8	37 ± 4.9	<0.001
Albumin <30 g/L	36 (50.00)	106 (7.74)	
Functional status			<0.001
Independent	49 (68.06)	1162 (84.82)	
Partially dependent	15 (20.83)	182 (13.28)	
Dependent	8 (11.11)	26 (1.90)	
Diabetes mellitus	14 (19.44)	266 (19.42)	0.995
Weight loss >10% in 6 months prior to surgery	2 (2.78)	32 (2.34)	0.810
Disseminated cancer	1 (1.39)	19 (1.39)	0.999
Recent smoking	15 (20.83)	287 (20.95)	0.981
Chronic Obstructive Pulmonary Disease	23 (31.94)	118 (8.61)	<0.001
Chronic heart failure	6 (8.33)	131 (9.56)	0.729
Chronic steroid use	1 (1.39)	21 (1.53)	0.727
Alcohol >2 drinks/day	1 (1.39)	27 (1.97)	0.727
History of cerebrovascular accident	5 (6.94)	82 (5.99)	0.923
Impaired sensorium	2 (2.78)	35 (2.55)	0.907
Transfusion >4 units	2 (2.78)	27 (1.97)	0.634
Blood urea nitrogen (mean mg/dl ± SD)	23.74 ± 11.91	15.45 ± 8.65	
Creatinine (mean mg/dl ± SD)	1.73 ± 1.41	1.15 ± 0.86	
Type of surgery			<0.001
Upper abdominal	18 (25.00)	279 (20.36)	
Thoracic	13 (18.06)	107 (7.81)	
Peripheral vascular	6 (8.33)	79 (5.77)	
Extremity	7 (9.72)	251 (18.32)	
Abdominal aortic aneurism repair	0	0	
Lower abdominal	6 (8.33)	392 (28.61)	
Neurological	13 (18.06)	55 (4.01)	
Back and spine	1 (1.39)	2 (0.15)	
Neck	8 (11.11)	204 (14.89)	
Dermatologic	0	1 (0.07)	
General anesthesia	38 (52.78)	732 (53.43)	0.914
Emergency surgery	27 (37.50)	169 (12.34)	<0.001
Inpatient mortality	21 (29.17)	27 (1.97)	<0.001
Length of hospitalization, days	22.12 ± 7	7.50 ± 3	<0.001

Surgical site is the most important predictor of pulmonary complications.[7] In our study, the surgical procedures most commonly associated with postoperative pneumonia and postoperative respiratory failure were upper abdominal, thoracic, and neurological surgeries. Following these procedures, patients maintain adequate minute ventilation with lower tidal volume, hence an increased respiratory rate. These breathing patterns, plus the effect of anesthesia, inhibit coughing and decrease mucociliary clearance, thereby contributing to the development of post-operative pneumonia.[6,7]

The proportion of participants who underwent general anesthesia was significantly higher among those who developed postoperative pneumonia, suggesting that the employment of general anesthesia is associated with the development of postoperative pneumonia. This may be associated with changes in respiratory drive, diaphragm and chest wall relaxation, resulting in reduced functional reserve capacity.[5]

The proportion of patients who had preoperative blood transfusion >4 units was signi-

Table 4. Observed and Predicted Proportion of Outcome for Postoperative Respiratory Failure

Risk Class	Participants Having the Outcome	Observed Proportion (%)	Predicted Proportion (%)	p-value
I	0	0	0.5	0.142
II	3	0.77	2.2	0.055
III	26	6.39	5.0	0.198
IV	18	13.53	11.6	0.487
V	28	32.94	30.5	0.625

Figure 2. Comparison Between Observed and Predicted Probabilities for Postoperative Pneumonia

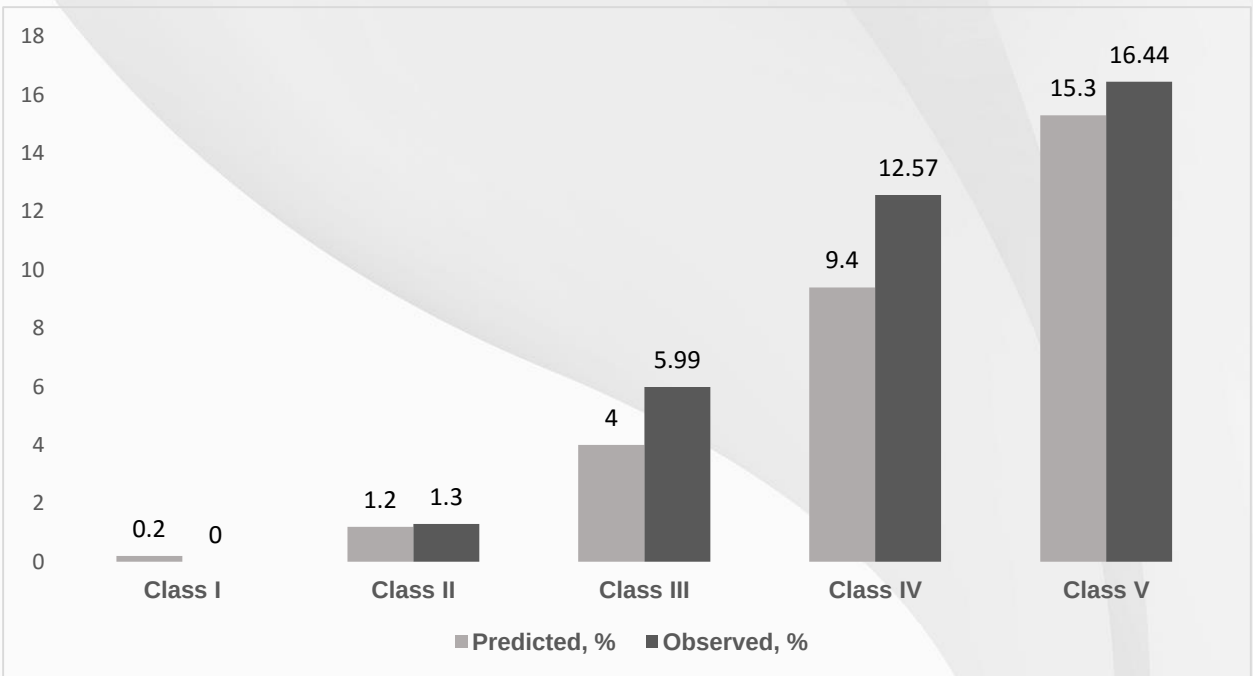
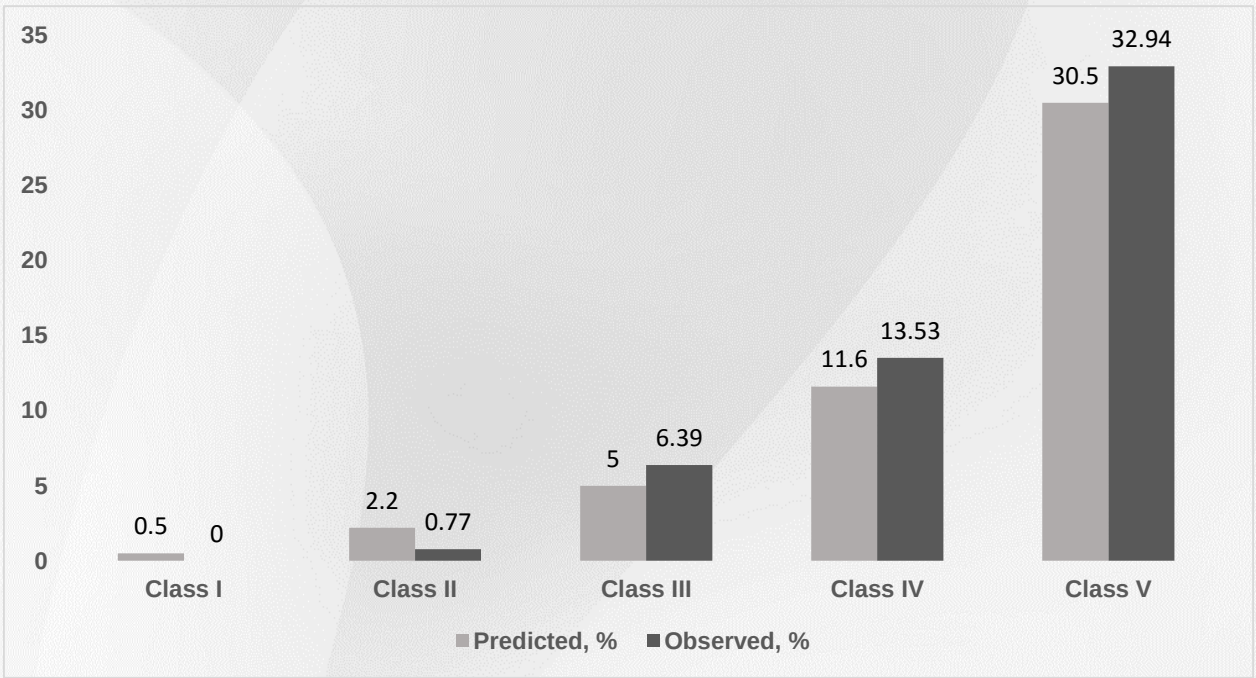


Figure 4. Comparison Between Observed and Predicted Probabilities for Postoperative Respiratory Failure



ficantly higher in the group that developed postoperative pneumonia. Previous studies have linked blood transfusion to the development of postoperative pneumonia.[8,9]

Length of hospital stay and inpatient mortality were significantly higher among patients developing postoperative pneumonia or respiratory failure. This is consistent with the study done by Jin et al.[10] The inpatient mortality for those who developed postoperative pneumonia was at 38%, against 3% mortality for those who did not develop postoperative pneumonia. Arozullah et al found a 21% mortality rate for inpatients with postoperative pneumonia and a 2% mortality rate for those without. This implies that postoperative pneumonia is an important postoperative outcome to prevent because it contributes to the mortality of patients. Postoperative respiratory failure cases in this study yielded an inpatient mortality rate of 29% significantly higher than the 2% rate for those without postoperative respiratory failure. Laso evidenced in the paper by Arozullah et al who found a mortality rate of 27% for those with postoperative respiratory failure and a 1% mortality rate for those without.

Diabetes mellitus (DM) and disseminated cancer compromise the immune system.[11] Therefore, we consider them variables that may be associated with the development of postoperative pneumonia and eventual respiratory failure. However, results revealed no significant differences for these variables between those with and without postoperative pneumonia.

Chronic heart failure poses a risk for pneumonia development due to alveolar flooding, resulting in reduced microbial clearance.[12] It also poses a risk for respiratory failure, especially when the patient is in a state of acute decompensation. We found, however, that chronic heart failure is not significantly associated with the development of postoperative pneumonia and respiratory failure. A possible explanation for this is that patients with

chronic heart failure who underwent surgical procedure were most likely not in a decompensated state.

Using the multifactorial risk index developed by Arozullah et al, the observed proportion of outcome across different risk classes was not significantly different from the standard proportion of outcome for both postoperative pulmonary complications, namely pneumonia and respiratory failure.

In summary, this study found that the clinical variables associated with the development of postoperative pneumonia were older age, a dependent functional status, significant weight loss >10%, recent smoking, history of COPD, chronic steroid use, history of CVA, impaired sensorium, transfusion >4 units, type of surgery (ie, upper abdominal, thoracic, extremity, and neuro-logical) especially on general anesthesia, emergency surgery, and longer hospital stay, and The clinical variables associated with the development of postoperative respiratory failure included older age, lower albumin level, dependent functional status, history of COPD, type of surgery, and a longer hospital stay The observed proportion of outcome for pulmonary complications across risk classes was comparable to the standard proportion of outcome.

Limitations of the Study and Recommendations

In the study, follow-up was limited to inpatient setting, banking on the results of previous studies that report postoperative pulmonary complications as usually manifesting within the first 6 postoperative days. No documentation was done on the outcome of those patients who were discharged apparently well. Also, cases of repair of aortic aneurysm—the type of surgery with the highest point value in computing for the complication—was not observed due to scarcity of the case.

The risk for having postoperative pulmonary complications is multifaceted, with patient- and surgery-related risk factors, laboratory predictors, and modifiable and non-modifiable risk factors.

Preoperative measures to address modifiable risk factors, as well as adherence to postoperative care to prevent development of the said pulmonary complications, are beyond the scope of this study. We recommend that future studies venture on the documentation of this aspect of perioperative management.

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Appendix A

Multifactorial Risk Index for Predicting Postoperative Pulmonary Complications

Risk Factors	Postoperative Pneumonia Risk Index Point Value	Postoperative Respiratory Failure Index Point Value
Type of Surgery		
AAA	15	27
Thoracic	14	21
Upper abdominal	10	14
Neck	8	11
Neurological	8	14
Vascular	3	14
Emergency surgery	3	11
General anesthesia	4	0
Age (years)		
≥ 80	17	6
70–79	13	6
60–69	9	4
50–59	4	0
Functional capacity		
Totally dependent	10	7
Partially dependent	6	7
Independent	0	0
Albumin <3 g/L	0	9
Weight loss >10% within 6 months	7	0
Chronic steroid use	3	0
Alcohol >2 drinks/day	2	0
History of COPD	5	6
Current smoker within 1 year	3	0
Impaired sensorium	4	0
History of CVA	4	0
BUN		
<2.86 mmol/L	4	0
7.85–10.7 mmol/L	2	0
>10.7 mmol/L	3	8
Pre-op transfusion	3	0
Total risk index score		

AAA=abdominal aortic aneurysm; BUN=blood urea nitrogen; CHF=congestive heart failure; COPD=chronic obstructive pulmonary disease; CVA=cerebrovascular accident; SD=standard deviation.

Appendix B
Centers for Disease Control and Prevention's Definition of
Nosocomial Pneumonia After Surgery

Patients should meet one of the following two criteria postoperatively:

1. Rales or dullness to percussion on physical examination of chest AND any of the following:

- New onset of purulent sputum or change in character of sputum
- Isolation of organism from blood culture
- Isolation of pathogen from specimen obtained by transtracheal aspirate, bronchial brushing, or biopsy

2. Chest radiography showing new or progressive infiltrate, consolidation, cavitation, or pleural effusion AND any of the following:

- New onset of purulent sputum or change in character of sputum
- Isolation of organism from blood culture
- Isolation of pathogen from specimen obtained by transtracheal aspirate, bronchial brushing, or biopsy
- Isolation of virus or detection of viral antigen in respiratory secretions
- Diagnostic single antibody titer (IgM) or fourfold increase in paired serum samples (IgG) for pathogen
- Histopathologic evidence of pneumonia

PROSPECTIVE COHORT STUDY

Outcome of Patients Who Underwent Programmatic Pulmonary Rehabilitation Versus Incentive Spirometry Alone After Lung Resective Surgery: A Prospective, Observational, Cross-Sectional, Pilot Study

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ABSTRACT

Objective: To investigate the outcome of patients who underwent programmatic pulmonary rehabilitation (PPR) versus incentive spirometry (IS) alone after lung resective surgery

Methods: This was a prospective, observational, cross-sectional study conducted at a tertiary hospital. It included 52 lung resection patients, with a mean age of 49.48 years in the PPR group, and 50.17 years in the IS group. The main outcome measures were post-operative pulmonary complications such as pneumonia, atelectasis and retained secretions requiring intubation. Length of hospitalization between two groups was also measured.

Results: Post-operative pulmonary complications such as pneumonia, atelectasis and retained secretions requiring intubation is less among patients who underwent PPR as compared to those prescribed with IS as a stand-alone intervention to prevent post-operative pulmonary complications. Likewise, the length of hospitalization in PPR group is shorter compared to the IS group. It was also noted that there is a significant difference (p=0.003) in the length of hospital stay of patients when grouped according to intervention in favour of PPR.

Conclusion: PPR is superior to IS alone in limiting post-operative pulmonary complications. Duration of hospitalization is also shortened in PPR which entails over-all reduction in patient discomfort and hospital cost.

INTRODUCTION

Pulmonary complications are an important cause of post-operative morbidity after lung resection which contributes to an overall increase in hospital costs and length of hospital stay. These include atelectasis, pneumonia, retained secretions requiring intubation and exacerbation of chronic pulmonary disease.[1]

Strategies to reduce the incidence of post-operative pulmonary complications include screening and modification of risk factors, optimizing preoperative status, patient education, intraoperative management and post-operative pulmonary care.[2] Nonetheless, post-operative pulmonary complications remain an important cause of morbidity and mortality after the procedure.[2,3]

Pulmonary rehabilitation has been advocated as an important component in the prevention and amelioration of post-operative pulmonary complications following surgery. However, to date, there have been few studies investigating the effectiveness of pulmonary rehabilitation in patients undergoing lung resection surgery.[4-6]

Jones et al (2007) conducted a prospective observational feasibility study with 20 patients

undergoing lung resection for lung cancer to examine the effects of preoperative pulmonary rehabilitation.[7] Significant improvements were shown in maximal oxygen consumption (VO_2) and 6-minute walk distance (6MWD) between baseline and surgery. Thirty-five percent of the patients had post-operative complications including two post-operative deaths. At post-surgical follow-up (mean of 51 $\pm$ 27 days), VO_2 and 6MWD returned to baseline rather than decreasing below baseline despite lung resection. Other studies have shown reductions of between 12–20% in VO_2 following lung resection without post-operative pulmonary complications or improve gas exchange post-operatively (Vilaplana et al, 1990).[5]

Vilaplana's findings were further supported by Gosselink et al (2000) where patients undergoing lung surgery were randomized into groups receiving physiotherapy alone or, physiotherapy plus incentive spirometry.[8] Physiotherapy interventions were standardized although compliance with the hourly regimens was not measured. The incidence of post-operative pulmonary complications was low (8% following lung resection) and there was no significant difference between treatment and control groups. Given the low incidence of post-operative pulmonary complications, the study was not powered sufficiently to detect a significant difference in post-operative pulmonary complications between groups.

While incentive spirometry is one of the components of programmatic pulmonary rehabilitation (PPR), some centers, including our institution, use it as a stand-alone tool before and after lung resection to prevent pulmonary complications. However, its role in limiting post-operative pulmonary complications and in the recovery of pulmonary function after lung surgery is still unclear because of the lack of conclusive, well-designed clinical trials.[6]

Studies have shown that IS volumes correlated well with measured vital capacity and inspiratory reserve volume and also concluded that IS was a good marker of lung function after lobectomy.[6] However, other studies showed that the addition of IS to a physiotherapy regimen in a small group of pre- and post-thoracotomy patients did not reduce post-operative pulmonary complications.[5] Hence, the usefulness of IS alone for the prevention of clinically relevant post-operative pulmonary complications is controversial.

In line with the above data, this study aims to investigate the outcome of patients who underwent PPR versus IS alone after lung resection surgery at a tertiary hospital.

METHODOLOGY

This was a non–randomized, prospective, observational, cross-sectional study that enrolled patients who had lung resection (lobectomy) due to any cause and underwent PPR or IS alone. Enrolled patients had to have good functional status (European Cooperative Oncology Group class 0-1) on admission, and must have had at least a pre-bronchodilator FEV1 of 1.5 L or more on pulmonary function test prior to surgery. Those who were hemodynamically unstable post-surgery, those who could not follow instructions and hence, unable to perform PPR or IS correctly, and those with unstable co-morbid conditions were excluded.

Patients were classified into two groups depending on the intervention advised by the attending physician (i.e., PPR vs IS). All patients received a standardized surgical approach (posterolateral thoracotomy) and adequate analgesia post-operatively. Demographic, clinical, and surgical data of all patients were prospectively collected and evaluated comparing the two groups.

The rehabilitation team consisted of a chest physician and physical therapists. PPR, which was performed daily, consisted of supervised incremental, symptom-limited muscular and breathing exercises. These specifically include diaphragmatic breathing, IS, coughing, shoulder

exercises, sitting and standing exercises, and scapular and isometric exercises. Those who underwent IS alone were given the IS device and instructed to perform breathing exercises properly using the incentive spirometer. This is done 10 times every hour during waking hours as tolerated by the patient.

Outcome Measurement

Post-operative pulmonary complications such as pneumonia, atelectasis and retained secretions requiring intubation were noted individually from each patient belonging to either group. This is done by reviewing the post-operative chest x-ray/s, complete blood count, vital signs (especially temperature) and the events that transpired after the operation thru chart review. The average length of hospitalization between 2 groups was also noted and compared.

Statistical Analysis

Our data are presented as mean ± standard deviation (SD); frequency count and percentage. Mann-Whitney U test was employed to establish significant difference in the length of hospitalization between two groups. A p-value of <0.05 was considered statistically significant.

RESULTS

From December 1, 2013 to March 31, 2014, 59 patients underwent lung resection for either early-stage non-small cell lung cancer, aspergilloma, or bronchiectasis in our institution. Out of the 59 patients, 57 initially fulfilled the eligibility criteria and hence, were included in the study. Five patients were eventually dropped out from the list because of remarkable peri- and post-operative events: cardiac arrhythmia (n=1), myocardial infarction (n=1), stroke (n=1) and death (n=2).

In total, 52 patients were included in the study from December 1, 2013 to March 31, 2014. Twenty-three (23) patients were prescribed with PPR while 29 patients underwent IS alone as a measure to reduce peri- and post-operative pulmonary complications. Demographic characteristics of patients grouped according to intervention are shown in Table 1. The age of the subjects was comparable between the two groups. Both groups have more males (PPR: 26.9%, IS: 34.6%) than females (PPR: 17.3%, IS: 21.2%) for the total population included in our study. Patients under PPR had a lower incidence of pulmonary complications (pneumonia: 7.7%, atelectasis 5.8%) compared to those in the IS group (pneumonia: 15.4%, atelectasis: 7.7%). None of the patients under PPR was intubated due to retained secretions while 1.9% in the IS group developed such complication. It should be noted the small sample size and even lower event rate for either arm precluded conclusive statistical evaluation.

Table 2 shows the mean hospital days between two groups, counted from the time the patient underwent surgery until the discharge order was given by the attending physician. Patients on PPR had shorter hospital stay (mean: 6.61 days) compared to those patients under IS (mean 8.31 days) (Tables 2 and 3).

DISCUSSION

Following major surgery of the thorax, there are significant changes in lung function and associated clinical manifestations. These changes may be influenced by procedure/patient-related

Table 1. Demographic and clinical data (complications) of included patients

	Intervention	
	PPR	**IS**
Age	49.48 years	50.17 years
Males	14 (26.9 %)	18 (34.6%)
Complications	23 (44.2%)	29 (55.8%)
Pneumonia	4 (7.7%)	8 (15.4%)
Atelectasis	3 (5.8%)	4 (7.7%)
Retained secretions requiring intubation	0	1 (1.9%)

PPR, programmatic pulmonary rehabilitation; IS, incentive spirometry

Table 2. Length of hospital stay (days)

	Intervention	
	PPR	IS
Mean	6.61	8.31
n	23	29
SD	1.44	2.45

PPR, programmatic pulmonary rehabilitation; IS, incentive spirometry

patient-related factors, and occur intra- and/or post-operatively.[1] These post-surgical changes include a characteristic reduction in lung volumes, which is primarily restrictive in nature; a reduction in functional residual capacity predisposing to atelectasis; a slowing of mucociliary clearance; and abnormalities in gaseous exchange.[11-14] These changes are expected and oftentimes transient and self-limiting.

Our observational study suggest that PPR after lung resection limits the incidence of post-operative pulmonary complications such as pneumonia (7.7% vs. 15.4%), atelectasis (5.8% vs. 7.7%) and retained secretions requiring intubation (0 vs. 1.9%) as compared to IS alone. These findings were similar to previous studies that show that pulmonary rehabilitation was an important component in the prevention and amelioration of post-operative pulmonary complications following surgery.[4] Investigations also showed that physiotherapy significantly improve exercise capacity, dyspnea, and health-related quality of life after surgery.[15] Likewise, the study of Gooselink et al revealed that post-operative pulmonary complications were less common in patients who underwent physiotherapy after lung resection, but there is no significant difference when IS was added to the regimen.[8]

Furthermore, this study also demonstrated shorter hospital stays among patients in the PPR group (6.61 days) compared to the IS group (8.31 days) (p=0.003). Previous studies have shown that post-operative pulmonary complications significantly increase intensive care bed days, hospital length of stay and overall health care costs.[15] Although a high level of evidence is scarce, PPR seems to be an appropriate and efficient allocation for resources, as it could lead to shorter hospitalization versus IS. These also suggest that PPR could significantly reduce patient discomfort, resource utilization, and overall hospital costs after lung resection.

CONCLUSION

Based on the results gathered, PPR may provide additional benefit to IS alone in limiting post-operative pulmonary complications. There was also a significant difference in the length of hospital stay of patients in favor of PPR. This result could have an economic impact because of a reduction in overall hospital costs.

Clinicians should be aware that while IS can provide an assessment of lung recovery, a well-organized and regular pulmonary rehabilitation remains the most effective mechanism to augment patient's recovery and limit post-operative pulmonary complications

Table 3. Mann Whitney U test on the length of hospital stay by intervention

Intervention	N	Mean Rank	Sum of Ranks	Mann-Whitney U	P-value
Programmatic Rehab	23	19.70	453.00	177.000	0.003
Incentive Spirometry	29	31.90	925.00		
Total	52				

LIMITATIONS AND RECOMMENDATIONS

The sample size in this study represents a small number of population, and thus a statistically significant difference in relation to post-operative pulmonary complications between the two interventions was not established. Hence, it is recommended that a well-designed larger-scale study with a longer follow-up should be conducted. Additionally, compliance and proper use of IS were not properly documented and should, therefore, be considered in future studies.

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META-ANALYSIS

Meta-analysis on the use of Statins in Chronic Obstructive Pulmonary Disease patients

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ABSTRACT

Background: Chronic obstructive pulmonary disease (COPD) is an inflammatory lung disease characterized by progressive airflow limitation. Statins have anti-inflammatory and immunomodulating properties that could alter inflammation of the airways.

Objectives: To systematically evaluate the effectiveness of adjunct statin therapy in improving exercise tolerance and pulmonary function indices in patients with COPD.

Methodology: This was a meta-analysis on studies involving humans in a randomized control trial in English that examined the effect of statins in COPD

Results: Two articles met the selection criteria that we included in the meta-analysis. These studies combined enrolled 80 subjects. Pooled analysis showed that statin use was associated with a statistically significant improvement in exercise time (treadmill test), with a mean difference of 335.18 seconds (95% CI 253.93 s, 416.43 s] favoring the statin group. It did not show a significant difference between groups in terms of FEV1 (%), total lung capacity and inspiratory capacity. However, statin treatment was associated with a statistically significant improvement in the Borg dyspnea score, with a mean difference of -2.91 in favor of statins (95% CI -3.19, -2.63).

Conclusions: Statin administration to COPD patients showed amelioration in exercise tolerance and dyspnea scores.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is an inflammatory lung disease characterized by progressive airflow limitation. Statins have anti-inflammatory and immuno-modulating properties that could alter inflammation of the airways. HMG-CoA (3-hydroxy-3-methyl-glutaryl-CoA) reductase inhibitors or statins have been used primarily to lower plasma cholesterol and have been shown to prevent cardiovascular disease.[1] In addition to lipid lowering, statins has been shown to shown to have pleiotropic effects, which includes anti-inflammatory, anti-thrombotic, anti-oxidant and immunomodulatory effects. Evidence suggests that these effects may be beneficial to COPD patients.[2,3]

This meta-analysis was conducted to systematically evaluate the effectiveness of adjunct statin therapy in improving exercise tolerance and pulmonary function indices in patients with COPD.

METHODOLOGY

A thorough search was done using Medline and PubMed, with limits set on studies involving humans in a randomized control trial in English that examined the effect of statins in COPD from 2008 to 2012. The evaluated outcomes included improvement in exercise time (treadmill test), 1-second forced expiratory volume (FEV1), total lung capacity (TLC), inspiratory capacity and Borg Dyspnea Score.

All the articles retrieved were appraised separately and independently by two reviewers for its applicability and validity. We evaluated the methodological quality of the randomized control trials by assessing allocation, blinding, and if follow up rate was adequate. Disagreements between the reviewers were resolved by consensus. Randomized, double-blinded, single-blinded or placebo controlled studies were included.

All extracted data from each study included were synthesized and analyzed using Review Manager Version 5.2 for meta-analysis.

RESULTS

Literature search resulted in 9 articles. After appraisal, 2 articles met the selection criteria and we included in the meta-analysis.[4,5] These studies combined enrolled 80 subjects.

The population of COPD patients included in the studies fulfilled the American Thoracic Society criteria for COPD. Their ages ranged from 40 to 80 years old. In general, they had stable COPD for a mean of 3 months on maintenance medications; and had no prior intake of statins.

The two included studies treated the subjects with either pravastatin 40 mg/day or placebo for 6 months.[8,9]

Pooled analysis showed that statin use was associated with a statistically significant improvement in exercise time (treadmill test), with a mean difference of 335.18 seconds (95% CI 253.93 s, 416.43 s) favoring the statin group (Table 1).

The meta-analysis did not show a significant difference between groups in terms of FEV1 (%), with a mean difference of 0.05% (95% CI -4.61%, 4.7%).

The outcome in TLC showed no statistically significant differences between group, although a modest trend towards benefit was appreciated (-0.08 L; 95% CI -0.46 L, 0.30 L).

Similarly, there was no statistically significant differences between groups in terms of inspiratory capacity, but a trend towards benefit was appreciated (0.13 L; 95% CI -0.06 L, 0.32 L).

Finally, statin treatment was associated with a statistically significant improvement in the Borg dyspnea score, with a mean difference of -2.91 in favor of statins (95% CI -3.19, -2.63).

DISCUSSION

Smoking cessation and oxygen therapy in patients with severe COPD has been the primary treatment of patients with COPD, and have provided a clear benefit on prognosis.[1,2] Other therapeutic regimens only provide symptomatic relief. Therefore, new therapies are needed to delay disease progression, improve quality of life and reduce mortality.[1]

Studies show that COPD has a significant inflammatory component.[6,7] In a systematic review by Gan, it was shown that levels of CRP, fibrinogen, leukocytes and TNF-α were significantly increased in individuals with chronic airflow limitation compared to those of healthy controls.[6] These findings indicate that in COPD, systemic inflammation is present and these are persistent even among previous smokers.

In COPD, inflammation follows a pattern starting with neutrophil margination and sequestration from the pulmonary capillaries into the respiratory bronchioles.[3,7] Airway damage subsequently follows when activated neutrophils release neutrophil elastase and myeloperoxidase, and generate reactive oxygen free radicals such as superoxide and hydroxyl free radicals.[3]

Table 1. Exercise Time (Treadmill Test in seconds) of Statins versus Placebo in COPD patients

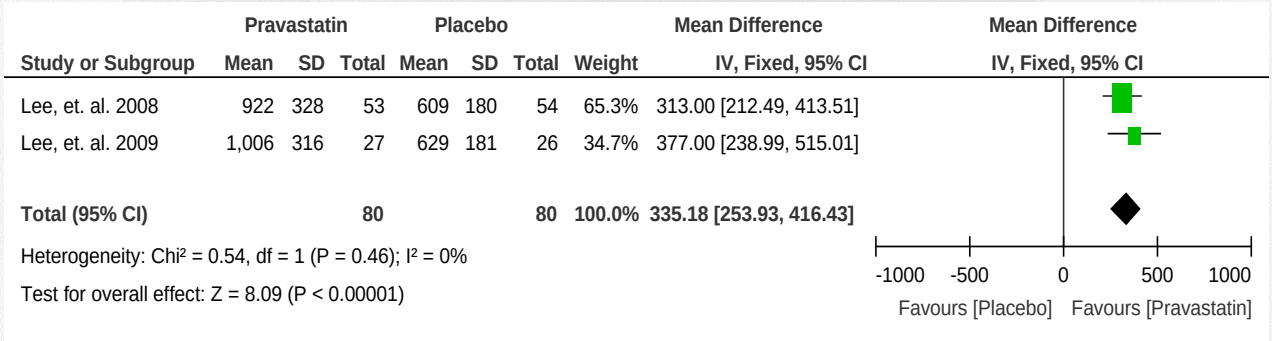


Table 2. FEV1 (%) of Statins versus Placebo in COPD patients

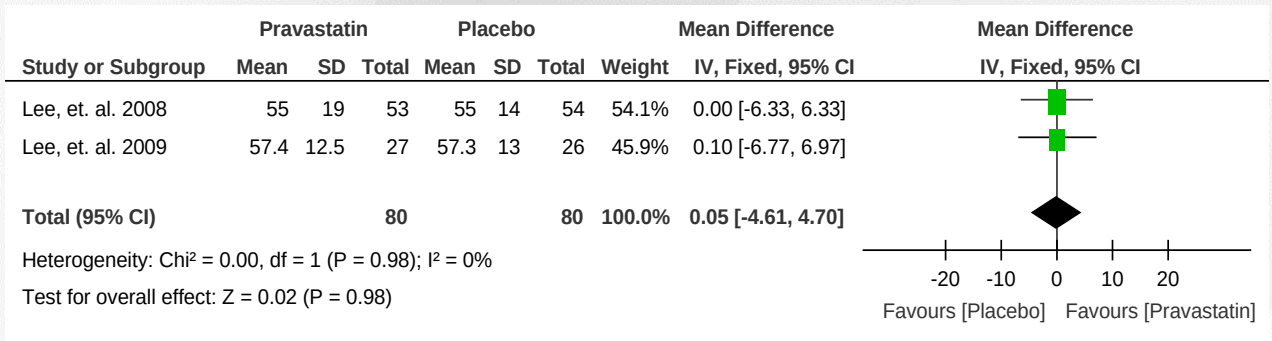
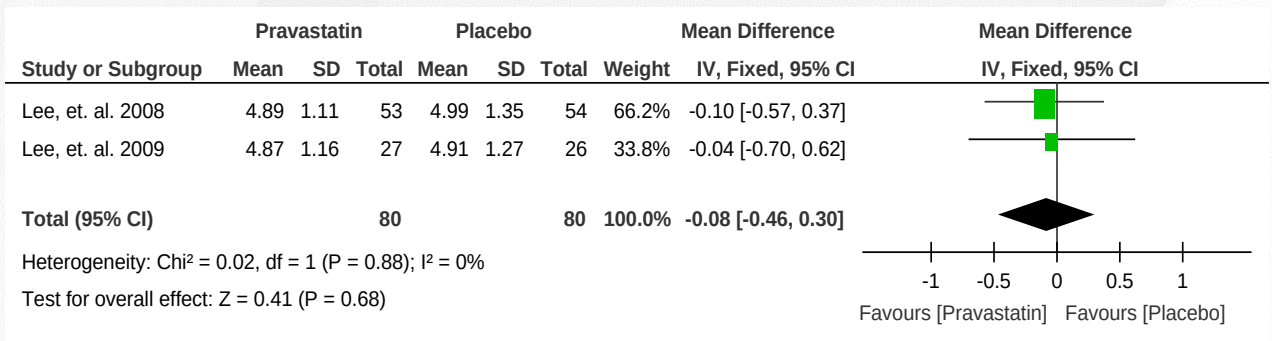


Table 3. Total Lung Capacity (L) of Statins versus Placebo in COPD patients



Smoke exposure also causes release of other inflammatory cytokines which includes interleukin-6, tumor necrosis factor-α, interleukin-1β, transforming growth factor and granulocyte-monocyte colony-stimulating factor.[7]

The presence of systemic inflammation is related to COPD complications which include weight loss, cachexia, osteoporosis and cardiovascular diseases.[6] Individuals with increased systemic inflammatory markers have an accelerated decline in lung function and are at

Table 4. Inspiratory Capacity (L) of Statins versus Placebo in COPD patients

	Pravastatin			Placebo				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
Lee, et. al. 2008	1.33	0.67	53	1.19	0.54	54	68.7%	0.14 [-0.09, 0.37]
Lee, et. al. 2009	1.32	0.72	27	1.21	0.54	26	31.3%	0.11 [-0.23, 0.45]
Total (95% CI)			**80**			**80**	**100.0%**	**0.13 [-0.06, 0.32]**

Heterogeneity: Chi² = 0.02, df = 1 (P = 0.89); I² = 0%

Test for overall effect: Z = 1.34 (P = 0.18)

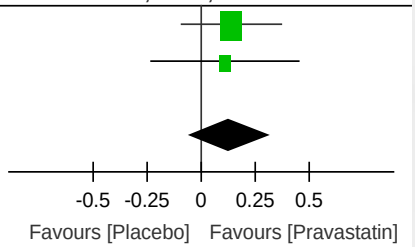
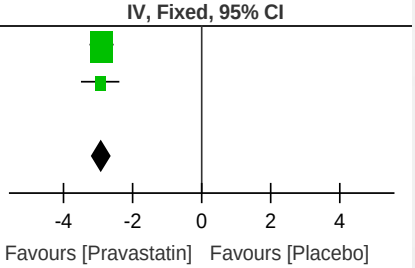


Table 5. Borg Dyspnea Score of Statins versus Placebo in COPD patients

	Pravastatin			Placebo				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
Lee, et. al. 2008	4	0.7	53	6.9	1	54	72.6%	-2.90 [-3.23, -2.57]
Lee, et. al. 2009	3.86	0.7	27	6.8	1.2	26	27.4%	-2.94 [-3.47, -2.41]
Total (95% CI)			**80**			**80**	**100.0%**	**-2.91 [-3.19, -2.63]**

Heterogeneity: Chi² = 0.02, df = 1 (P = 0.90); I² = 0%

Test for overall effect: Z = 20.50 (P < 0.00001)



increased risk of COPD hospitalizations.

Statins may modulate the immune response and manage the cytokine dysregulation which in turn may decrease cellular damage.[4] C-reactive protein levels, which are markers for inflammation which predicts increased cardiovascular events, are shown to be reduced with statin use.[4,7] The reduction in CRP is probably the result of the statins ability to reduce the production of interleukin-6, the cytokine which activates the acute-phase reactant.[7]

Because of its anti-inflammatory effect, statins may reduce the pulmonary inflammation associated with cigarette smoking.[1] Animal studies have shown that statins ameliorated the structural and functional derangement of rat lungs caused by cigarette smoking by suppressing inflammation and matrix metalloproteinase-9 induction and preventing pulmonary vascular abnormality.[1,7]

Lipophilic statins such as atorvastatin and simvastatin have been shown to have much greater anti-inflammatory effect in human and mouse models than the hydrophilic pravastatin.[7]

One additionally proposed mechanism for the anti-inflammatory effect of statins is through the modulation of the cholesterol content, thus reducing lipid raft.[7] The inhibition of lipid raft formation prevents activation of immune cells, prevents the prenylation (i.e., addition of lipids to protein molecules) of signaling molecules, and downregulation of gene expression, thus resulting in reduced expression of cytokines, chemokines and adhesion molecules. Statins reduce IFN-γ production, therefore reducing major histocompa-

tibility complex II-mediated T-cell activation.[6] HMG-CoA (3-hydroxy-3-methyl-glutaryl-coenzyme A) reductase is important in the biosynthesis of isoprenoids, substances that play an important role in the regulation of cell growth, cell secretion and signal transduction through prenylating proteins using covalent links.[7] Thus, another way statins affects inflammation is by inhibition of prenylation.

Statins increase eosinophil apoptosis in humans due to reduction in the cellular expression of CD40.

With the overall results of the study, administration of statins to COPD patients may be helpful as an additional therapy to current medications in improving subjective symptoms of patients, as well as its role in lowering cardiovascular risks. The study of Lawes et al showed a 30% reduction in all-cause mortality at 3-4 years after admission for COPD.[1] This study raises the possibility that statins causes a reduction in death from causes other than CVD since 48% of the known deaths in this study was COPD-related or lung cancer-related deaths.

CONCLUSIONS

Statins already have an established role in treating cardiovascular patients because of their cholesterol-lowering ability, but also has anti-inflammatory and immunomodulatory effects that are beneficial in airway inflammation in COPD.

Statin administration to COPD patients showed amelioration in exercise tolerance, improvement in dyspnea scores and augmentation in pulmonary function indices. Thus, statins may be useful as adjunct to currently available therapies as well as improvement in lipid status.

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CASE-CONTROL STUDY

Association between Tumor Necrosis Factor-α-308G/A Polymorphism and Chronic Obstructive Pulmonary Disease in Patients of the University of Santo Tomas Hospital

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ABSTRACT

Chronic obstructive pulmonary disease (COPD) has been associated with enhanced inflammatory response to noxious particles and irritants. Tumor necrosis factor–α has been observed to be present in elevated levels in COPD patients. Up-regulation of TNF-α production may be a result of mutations in the gene complex coding for its production. Previous association studies between TNF-α -308G/A gene polymorphism with COPD that were conducted on Caucasians and Asians have yielded mixed results. Currently, no studies have been performed on Filipino population. This is a case-control study wherein the occurrence of TNF-α -308G/A gene polymorphism was examined in patients diagnosed with COPD at the University of Santo Tomas Hospital. The recruited participants underwent spirometry likewise COPD assessment test scores were determined. Blood samples were collected for genotyping. Recorded data were then statistically analyzed. Forty-nine percent of the total number of participants were diagnosed with COPD (FEV1/FVC < 70) while 51% were part of the control group (FEV1/FVC > 70). Frequencies of the rare allele (A) were found to be higher (0.11) in the control group compared to the patient group (0.04). Participants with a smoking history are less likely to develop COPD when carrying the heterozygous genotype G/A (OR 0.10, 95%CI 0.01 – 0.79, p=0.021). Within the overall participant population, the occurrence of the rare allele 'A' was higher in the control group (0.12) compared to the patient group (0.7). Heterozygous (G/A) genotype is less likely to have COPD (OR 0.29, 95%CI 0.07-1.21) though disease-SNP polymorphism relationship did not have a strong statistical association (p=0.08).

INTRODUCTION

Chronic Obstructive Pulmonary Disease, commonly known as COPD, is a chronic inflammatory disease of the airways of an individual resulting in the limitation of airflow. Obstruction of the airways was associated with abnormal inflammatory reactions to exposure to various noxious gases such as cigarette smoke.[1] Current standards for COPD diagnosis state that the patient should exhibit chronic cough and sputum production, dyspnea or shortness of breath, rhonchi and prolonged expiration upon physical examination.[2,3]

Current COPD diagnostic standards such as spirometric tests and COPD assessment tests are performed only upon exhibiting the preliminary symptoms of COPD.[3] Studies have delved into the possible usage of genetic biomarkers in COPD risk assessment, diagnosis, and intervention.

One approach in COPD biomarker research is targeting the possible genes that may be involved in the development of chronic inflamma-

tion of the patient's airways. Chronic inflammation, a defining characteristic of COPD, hinders the rate of expiration of air to the point that an individual is unable to release all used air before taking another breath. TNF-alpha is a known inflammation inducing cytokine. It has been linked to numerous inflammatory diseases such as Behçet's disease, Crohn's Disease, other inflammatory bowel diseases, and rheumatic heart disease.[4-7]

Elevated levels of TNF-alpha have been found in the sputum and blood of COPD patients.[8] Studies performed on a Taiwanese population showed a relationship between chronic bronchitis and TNF-alpha gene polymorphism.[9] Similar studies conducted on Japanese and Caucasian populations have also shown a positive association between TNF-alpha gene polymorphisms and COPD.[10,11] However, no studies have been performed in the Philippines regarding the relationship between TNF-alpha polymorphism and COPD. Molecular genetics and epidemiology become important tools in associating the disease with a specific gene. People without the smoking history may develop COPD due to differences in genetic predisposition to the disease. Since COPD results from a gene-environment interaction, the studies and analysis of candidate genes are essential in pathophysiology, risk assessment, diagnosis, and therapy research.

Therefore, it is the aim of this study to determine the relationship between COPD and Tumor Necrosis Factor-α (TNF-α) -308G/A gene polymorphism on selected Filipino population from University of Santo Tomas Hospital (USTH).

METHODOLOGY

Patient Recruitment

Participants were recruited from the UST Hospital – Center for Respiratory Medicine through their attending physician. Consent of the participants in the study was obtained. Consent forms were available in both English and Filipino. All participants recruited were above 18 years of age. Individuals diagnosed to have asthma were not included in the study. A total of 123 participants were recruited for the study.

Phenotyping

Participants underwent spirometry and measurement of their forced vital capacity (FVC) and forced expiratory volume in one second (FEV1) were taken. The ratio (FEV1/FVC) between the two measurements was calculated. Patients with a score of less than or equal to 0.7 FEV1/FVC were classified under the patient group while those scoring higher than 0.7 were assigned to the control group. Participants were also given the COPD assessment test to assess the manifestation or presence of COPD symptoms. General information, such as smoking history, age and gender were collected. Phenotyping of the participants was done by the medical arm of the study.

Sample Collection

The source of genetic material used in the study was blood specimens. Samples were collected by a registered medical technologist or a licensed physician. Consent of the participants was obtained in the early stages of this study. Samples extracted from the participants were immediately frozen to preserve them for future use and analysis. Samples were turned over to the genetics arm of the project without disclosing spirometry and COPD assessment test scores of the sources of the samples, thus eliminating bias in the results.

DNA Extraction

Extraction of the genetic material was done using Wizard Promega DNA extraction kit. First, 900µl of cell lysis buffer was added to 300µL of the sample to release the contents of the cell into the solution. The mixture was allowed to incubate for 10 minutes to ensure complete lysis of all blood cells contained in the sample. Samples were then centrifuged at 13,000 G to

allow separation of heavy intracellular components from hemoglobin. The supernatant was subsequently discarded and 300µL of nuclei lysis buffer was added to the pellet. This would disrupt the nuclear membrane releasing the genetic material into the solution.

The solution was then incubated at 37°C to remove pellet clumps that may have formed in the previous steps. RNAse was then added to the solution to degrade any ribonucleic acid present. The solution was again incubated at 37°C for 15 minutes to allow the maximum activity of the RNAse. The tubes were then immersed in an ice bath to bring the temperature down prior to adding the protein precipitating solution (PPS). The addition of PPS would denature and subsequently precipitate the protein components of the solution and allow its separation from the genetic material via centrifugation.

The resulting brown pellet was discarded and the supernatant was transferred to a tube containing 300µL of isopropanol, a DNA precipitating agent. The mixture was again spun and the supernatant was discarded. Ethanol was then added to the pellet to enhance the precipitation of the DNA. The mixture was again subjected to centrifugation and was air dried. A rehydrating solution was added to the DNA and was left to stand overnight at 4°C.

The quality of the extracted DNA was assessed by using 1% Agarose gel Electrophoresis. Gel was made by heating a mixture of 1.05grams of agarose and 35ml 1x TAE buffer until clear. The mixture was introduced into a caster and was allowed to stand until it solidified. Samples were loaded with EZ loading dye to enable tracking of the movement of the genomic DNA in the gel. The loading dye also increases the density of the DNA sample in order to prevent it from dispersing into the buffer. A DNA ladder was also loaded into the gel to serve as a basis for molecular size and concentration of the genomic DNA in the samples.

Electrophoresis was run at 100 volts to about 50% of the total gel length. The gel was initially stained in ethidium bromide solution for 20 minutes and then destained in sterile distilled water for 5 minutes. The gel was viewed under ultraviolet light and photo documentation was taken using the gel documentation software. Band intensities were compared to the DNA Ladder intensities to assess the concentration of genomic DNA in each extract.

Polymerase Chain Reaction

Polymerase chain reaction was done to isolate a section of the gene of interest. The 5'-region of the TNF- α gene, positions -331 to 14, was amplified using gene specific primers. Primer sequences used were 5'-AGG-CAATAGGTTTTGAGGGCCAT -3' for the forward primer and 5'-GAGCGTCTGCTGGC-TGGGTG-3' for the reverse. Each reaction, with a total volume of 25µL, contained 2.5µL 5x GoTaq Flexi buffer, 2µL 25mM MgCl2, 0.2µL 5units·µL-1 Taq pol, 0.25µL 0.1mM forward primer, 0.25µL 0.1mM reverse primer, 0.25µL 10mM dNTP's, and 6.05µL sterile nanopure water.

PCR was run under the following conditions summarized in Table 1.0

PCR products were subjected to 3% agarose gel electrophoresis at 100 volts to about 80% total gel length. Amplicon size was determined using DNA ladders. Amplicons were sent to a sequencing facility to get the base sequence.

Restriction Enzyme Length Polymorphism

Restriction enzyme length polymorphism (RFLP) was used to determine the presence of the polymorphism in the amplified section of the DNA by means ofthe NcoI restriction enzyme. RFLP reactions consisted of 5µL of PCR product and 0.5µL 20unit/µL of NcoI restriction enzyme. The mixture was then incubated at 37°C for two hours to allow the digestion of the PCR product. Restriction enzyme digests were then subjected to 3% agarose gel electrophoresis run at 100 V

Table 1. Polymerase chain reaction profile

Phase	Temperature	Duration
Initial Denaturation	94°C	3 mins.
Cycles: 35		
Denaturation	94°C	1 min.
Annealing	60°C	1 min.
Extension	72°C	1 min.
Final Extension	72°C	5 mins

to about 60% of the total gel length. The gel was then stained in ethidium bromide solution for 15 minutesand viewed under ultraviolet light. Photo documentation was taken using the gel documentation software. Resulting banding patterns were scored and assessed for the presence of the polymorphism.

Statistical Treatment

The sample population was tested for deviation from the Hardy-Weinberg equilibrium using SNPStat software. Associations of genotype and allele frequencies were tested for association with logistic regression to adjust possible effects of covariates and confounding variables such as smoking history and age.

RESULTS AND DISCUSSION

A total of 123 participants were included in the study with a mean age of 55.23 years. The patient group consisted of 60 individuals diagnosed with COPD. The control group consisted of 63 individuals without COPD. Among these patients a total of 62 participants had a smoking history while 61 did not have any previous history of smoking.

Allele frequencies for the entire population are summarized in Table 2. A higher occurrence of the rare type A-allele was observed in the control population. Participants with smoking history were tested separately for the polymorphism as shown in Table 3.

Heterozygous genotype had a higher occurrence in the control group (COPD=NO) compared to the patient group as summarized in Tables 4 and 5. Participants with a smoking history were less likely to develop COPD when carrying the heterozygous genotype G/A (OR 0.10, 95%CI 0.01-0.79, p=0.021). Within the total participant population, the occurrence of the rare allele 'A' was higher in the control group (0.12) compared to the patient group (0.7). Heterozygous (G/A) genotype is less likely to have COPD (OR 0.29, 95%CI 0.07-1.21) though disease-SNP polymorphism relationship did not have a strong statistical association (p=0.08).

Higher frequency of the rare type allele was observed in control group suggesting that possession of the allele may reduce the risk of developing COPD. The presence of the "A" allele has been previously found to affect the regulation of TNF cytokine production. The polymorphism, located at the promoter sequence of the gene complex, may cause abnormal expression of the TNFα gene leading to anomalous levels of the TNF cytokine. Studies have shown that the -308 region has the ability to bind to certain transcription factors.[12] Variations in such region may change its overall interaction with certain transcription factors leading to either increase or decrease of cytokine production.

The actual mechanism of regulation of TNF cytokine production has not been established.[13] It is more than likely that predisposition to COPD is not hinged on a single gene but an interaction between inflammation-related genes. A meta-analysis showed multiple studies on Asian populations were positive while studies dealing with Caucasian populations were mostly negative for the association.[14,15] This indicates that variations of gene-to-disease relationships may involve ethnicity related genes. Data from this study indicate the presence of a weak association between possession of the rare type allele and COPD. Such findings suggest that the TNF-α gene polymorphism may play a role in susceptibility to COPD.

CONCLUSIONS

Assessment of the allele frequencies is associated with the development of COPD. Smokers bearing the rare allele are less likely to develop the disease as compared to their counterparts bearing the wild-type allele. Genotypes containing the rare 'A' allele (G/A and A/A) are less likely to develop the disease. It is recommended that future studies that delve into COPD epidemiology and the like increase the number of participants to make differences in frequencies more pro-nounced. A matched case–control design is also recommended for this study.

Table 2. Allele Frequencies for the Entire Participant Pool

SNP allele frequencies (n=123)						
	All subjects		COPD=NO		COPD=YES	
Allele	Count	Proportion	Count	Proportion	Count	Proportion
G	227	0.92	112	0.89	115	0.96
A	19	0.08	14	0.11	5	0.04

Table 3. Allele Frequencies for the Participants with Smoking History

SNP allele frequencies (n=62)						
	All subjects		COPD=NO		COPD=YES	
Allele	Count	Proportion	Count	Proportion	Count	Proportion
G	115	0.93	41	0.85	74	0.97
A	9	0.07	7	0.15	2	0.03

Table 4. Genotype Frequencies of the Entire Participant Population

SNP genotype frequencies (n=124)						
	All subjects		COPD=NO		COPD=YES	
Genotype	Count	Proportion	Count	Proportion	Count	Proportion
A/A	5	0.04	4	0.06	1	0.02
G/A	9	0.07	6	0.1	3	0.05
G/G	109	0.89	53	0.84	56	0.93
NA	1	---	1	---	0	---

Table 5. Genotype Frequencies of the Participants with Smoking History

SNP genotype frequencies (n=62)						
	All subjects		COPD=NO		COPD=YES	
Genotype	Count	Proportion	Count	Proportion	Count	Proportion
A/A	2	0.03	2	0.08	0	0
G/A	5	0.08	3	0.12	2	0.05
G/G	55	0.89	19	0.79	36	0.95

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