PHILIPPINE JOURNAL OF CHEST DISEASES

Volume 19 Number 3
July-September 2018

IN THIS ISSUE:

- TB in the private sector
- NUTRIC vs Modified SGA
- Prediction of extubation success
- Bronchoscopic lung cancer detection
- IPC vs pleurodesis in malignant pleural effusion
- Osteoporosis in COPD

AN OFFICIAL PUBLICATION OF PHILIPPINE COLLEGE OF CHEST PHYSICIANS

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

Address all communication and manuscripts for publication to the following: The Editor, Philippine Journal of Chest Diseases, 84-A Malakas St., Pinyahan, Quezon City. Email: secretariat@philchest.org. Phone: (+632) 924 9204.

INSTRUCTIONS TO AUTHORS

The Philippine Journal of Chest Diseases publishes scientific papers in the field of pulmonary medicine. These papers may be in the form of collective and current reviews (state of the art, meta-analyses), original investigations, case reports, editorials or letters to the editor. All manuscripts must be submitted electronically to secretariat@philchest.org. Manuscripts should be single spaced and left-justified, including references. Use 10-point type, approximately 1-inch margins, and format for 8 ½ x 11 paper. The editorial staff requires files that can be opened and manipulated in Word 2004-2009, PowerPoint or Excel.

Accepted manuscripts become the property of the Philippine College of Chest Physicians and are published with the understanding that they are not for publication elsewhere without approval. These manuscripts are subject to editorial modification.

Generally, write using the first person, active voice; for example, "We analyzed data," not "Data were analyzed." The Abstract and acknowledgments or disclaimers are the exceptions to this guideline, and should be written in the third person, active voice; "The authors analyzed," "The authors wish to thank."

Supply a title page as the first page of the manuscript with the following information:

1. The manuscript's full title which should provide sufficient information regarding the contents of the manuscript.
2. All authors should provide their complete names, professional titles, and institutional affiliations. Include an author byline that lists all authors' full names and academic degrees above a Masters; for example, "Juana Cruz, MD, PhD, and Juan Ramos, MD". Also include sentence-style bios for each author than list position(s) or title(s) and institutional affiliation(s); for example, "Dr. Cruz is assistant professor, Section of Pulmonary Medicine, Department of Internal Medicine, State University College of Medicine".
3. Contact information (address and email address, plus telephone and/or fax) for the corresponding author.
4. Disclosure of funding received for this work from any organization or company.
5. State if the paper has been presented in any convention and whether any awards have been conferred on the paper.

Abstract. The abstract should not be longer than 250 words. It should contain a summary of what was done in the study, including objectives, study design, important results and conclusions. Only findings restricted to the study should be mentioned in the abstract. For research reports only, abstracts must be in the structured form of four paragraphs, with headings Purpose, Methods, Results, and Conclusions; and must include the year of the study. The authors should also provide three key words under which the article can be indexed.

Headings

For all manuscripts. Use main headings and short subheadings as needed. Do not create a heading at the very top of the manuscript (e.g., "Introduction"), since layout constraints make such headings unworkable. Text should be set in Times New Roman font, 10 point in size, and single-spaced. The main heading of the online-only text should be in 12 point and boldface; subheadings should be in 10-point and boldface. If subheadings are used, two or more such headings must be used, as in outline style.

For research reports. Structure the body of the manuscript using the headings Introduction, Methods, Results, and Conclusions. At least a full paragraph of text must precede the Introduction heading, for layout reasons.

For articles. Create headings that are substantive and interesting and that will give readers a sense of the article's organization. Make headings as short as is feasible. At least a full paragraph of text must precede the initial heading, for layout reasons.

Text. Formal scientific or technical style shall be followed in writing the manuscripts. All abbreviations should be spelled out when used for the first time. For standard terminology, such as chronic obstructive pulmonary disease

(COPD) or forced vital capacity (FVC), only standard abbreviations should be used. Information or data that is best described in tables should be presented as such. Tables which duplicate information provided in the text shall be removed. Generic names of drugs shall be used except in instances where trade names are vital, such as in clinical trials.

Tables and Figures. Only tables cited in the text should be included. All tables should be called out in the text and shall be numbered in ascending order depending on the sequence they were referred to in the text. A different order for tables and figures is to be used. Symbols are * † ‡ § ¶.

A single table or figure with the appropriate labels should be printed on a single page. The text and data in online tables should be Arial font, 10 point in size, and single-spaced. The table title should be set in Arial font 12 point, and bold. Headings within tables should be set in 10 point bold.

Explanatory notes or legends should be written at bottom of the table or figure. Table titles should make the table sufficiently understandable independent of the manuscript. Typically, include type of data, number and type of respondents, place of study, year of study. Titles should be placed directly above the table, not in a data cell. Columns should be clearly labeled, including unit of measure.

Footnotes: If information is needed to make the table understandable that won't easily fit into the table title or data cells, create one or more footnotes. Table footnotes should be set in 8 point and single-spaced. Place footnotes at the bottom of the table, not in a data cell. All abbreviations should also be explained.

Figures. Only figures (or pictures) cited in the text should be included. All figures should be called out in the text and shall be numbered in ascending order depending on the sequence they were referred to in the text. A different order for tables and figures is to be used.

Figures are acceptable as Excel, PowerPoint or Word 2004-2009 files. All files supplied must be "live" figures that can be opened and formatted. PDFs and JPGs are not accepted. Figures should be two-dimensional; black-and-white or grayscale; and without gridlines or background shading. X and Y axes, if present, must be labeled.

Figure legends should make the figure sufficiently understandable independent of the manuscript. Legends should be placed on the last page in the manuscript. All figures should be separated from the text file, yet bundled into a common file, if possible, with individual figures separated by page breaks.

The editorial staff reserves the right to determine whether the graphical instruments are appropriate for the information being imparted and modify or request modification/s for inappropriate illustrations. The editorial staff reserves the right to generate illustrations compatible with the professional standards of the journal.

References. Authors are responsible for the accuracy and completeness of their references and for correct text citations. All references should be identified at the appropriate parts of the text using Arabic numerals enclosed in parentheses. All references should then be typed double-spaced at the end of the manuscript and numbered according to the order they were cited in the text. Journal references should include the names of all the authors and inclusive page numbers. Abbreviations of names of journals should conform to those used in the Index Medicus.

For world wide web citations, follow the following format: <author's name> <title of document> <<URL>> <date of document> (accessed <date accessed>). You may break URLS across lines, but if possible, arrange for breaks to occur only at punctuation separators (but not on hyphens, and don't ever add hyphens).

Samples of the style to be followed in the listing references are enumerated below:

JOURNAL ARTICLE: Tanchuco JQ, Young J. Normal standards for spirometric tests in Filipino children. Chest Dis J 1989. 16:93-100.

BOOK: Kelley MA, Fishman AP. Exercise Testing. In: Pulmonary Diseases. 2 edition. Fishman AP, (ed.). McGraw-Hill Book Co.; 1989. pp.2525-2532.

WORLD WIDE WEB: Horton M, Adams R. Standard for interchange of USENET messages Request for comment s 1036, Network Working Group. <ftp://ftp.demon.co.uk/pub/doc/rfc/rfc1036.txt> Dec.1987 (Accessed 19 June 1995)

Personal communications, unpublished data or manuscripts in preparation should not be used as numbered reference. Instead, these may be cited in parentheses or as a footnote on the page where they are mentioned. Authors assume responsibility for verifying the accuracy of their cited reference.

Advertisements. All requests for rates should be add-ressed to: The Business Manager, Philippine Journal of Chest Diseases, PCCP Secretariat, 84-A Malakas St., Brgy. Pinyahan, Diliman, Quezon City (Telephone No. 924-9204 and Fax No. 924-0144). The journal also accepts announcements from institutions or professional invitations to forthcoming symposia or convention for publication at minimal cost depending on available space.

Reprints. Requests for additional reprints of individual articles should be addressed to: The Editor-In-Chief, Philippine Journal of Chest Diseases, PCCP Secretariat, 84-A Malakas St., Brgy. Pinyahan, Diliman, Quezon City (Telephone No. 924-9204 and Fax No. 924-0144). Author/s of each manuscript are entitled to 25 copies of the article. These shall be sent to the major author. Requests for reprints should be addressed to the senior author. Reprints of entire issues may be provided at cost, depending on availability of copies.

Subscriptions. All requests for subscriptions should be addressed to: The Business Manager, Philippine Journal of Chest Diseases, PCCP Secretariat, 84-A Malakas St., Brgy. Pinyahan, Diliman, Quezon City (Telephone No. 9249204 and Fax No. 924-0144. E-mail address secretariat@philchest.org. One issue (P120.00). Back issues (depending on availability P120.00).

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

TABLE OF CONTENTS

JULY-SEPTEMBER 2018 VOLUME 19 NUMBER 3

1 **Editorial**

3 **Private Sector in the Philippines: Knowledge, Attitudes and Practices in TB and Drug-resistant TB**
Maria Imelda Quelapio, Tauhidul Islam, Catharina van Weezenbeek, Maridel Borja, Camilo Roa, Jubert Benedicto, Lalaine Mortera, Roentgene Solante, Rosalind Vianzon

12 **Predictive Value of NUTRIC vs the Modified SGA Nutritional Assessment Tools for 28-Day ICU Mortality**
Enrik John Aguila, MD, MBA; Anne Kimberly Lim, MD; Kristine Reyes, MD; Ma. Janeth Samson, MD, FPCP, FPCCP

21 **Diaphragm muscle thickness and rapid shallow breathing index (RSBI) as predictors for successful extubation among critically ill adult patients**
Geraldine Garcia, MD; Jose Gil Archie Causing, MD; Judy Lin-Ong, MD, Mary Joy P. Ordanza, MD; Chito Paulo A. Sistoza, MD

30 **Lung cancer detection rates of conventional bronchoscopic techniques: bronchial brushing, endobronchial biopsy, bronchial lavage and bronchial washing**
Marlo P. Bagano, MD, FPCP; John Clifford E. Aranas, MD, FPCP, FPCCP; Martiniano C. Zanoria, MD, FPCP, FPCCP

36 **A Meta-analysis on Indwelling Pleural Catheters versus Pleurodesis in the Management of Malignant Pleural Effusions: A Modern Dilemma**
Anjuli May Jaen, MD; Ralph Elvi Villalobos, MD; Irene Rosellen Tan, MD; Ruth Divinagracia, MD

45 **Screening for Osteoporosis in Male COPD Patients treated with or without Long-term Inhaled Corticosteroid at the Lung Center of the Philippines**
Mari Chris H. Mercado, MD, FPCP; Glynna Ong-Cabrera, MD, FPCP, FPCCP

"Predictions" in pulmonology

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

"Those who have knowledge, don't predict. Those who predict, don't have knowledge"
- Lao Tzu

There's something to be said about predicting diagnoses based on objective and subjective information provided by a patient. Physicians study many years to reach even a differential diagnosis, and at times the quality of patient information is poor, so much so that doctors have to muddle through mounds of data every single day only to still end up with a "probability", a "possibility" and a "prediction".

Of course patients are not to know that doctors essentially predict (or "guess") diagnoses. But that's fundamentally what is done. And so of course, it goes without saying that the more information is made available to physicians, the more accurate a diagnosis will be, and the less likely the diagnosis will end up being just a "guess".

Unfortunately, clinching a diagnosis is not just a matter of collecting information and putting them together. Oftentimes, doctors have to deal with misleading information, useless information, and incorrect information. The physician then has to transform into a detective, needing to navigate through all these, awaiting for that eureka moment when the proverbial light bulb goes on in the mind.

Unfortunately, speed and timeliness of the diagnosis can be compromised in the quest for an accurate diagnosis. However, "slowly but surely" cannot be the physician's mantra. Just take the everyday emergency room, where life-saving decisions have to be made in seconds, and history-taking is extremely abbreviated.

Enter scoring systems, predictive values, baseline data and comparative analyses. They are meant to fast track decision making processes and make the "guessing" more systematic. Most often, they also require a leaner set of diagnostic information than what convention dictates.

The PJCD here, in this issue, presents studies which generated relevant data to the pulmonary physician, in aid of diagnosing and managing common conditions: nutritional assessment tools

in relation to ICU mortality, diaphragm muscle thickness and RSBI in relation to successful extubation, detection rates of the various specimen collection techniques during bronchoscopic procedures.

Indeed, the element of time in managing patients remain crucial in achieving successful patient outcomes. However, let it not also be said that patients were diagnosed and managed based only on scoring systems, Likert scales and computed values. No calculator can yet approximate the human mind, nor the human heart. As there have yet to be numerical equivalents for “gut feel” and “expert opinion”.

And that is always the way things must be.

“Prediction is not just one of the things your brain does. It is the primary function of the neo-cortex, and the foundation of intelligence.
- Jeff Hawkins

CROSS-SECTIONAL STUDY

Private Sector in the Philippines: Knowledge, Attitudes and Practices in TB and Drug-resistant TB

Maria Imelda Quelapio,[1] Tauhidul Islam,[2] Catharina van Weezenbeek,[3] Maridel Borja,[4] Camilo Roa,[5] Jubert Benedicto,[6] Lalaine Mortera,[7] Roentgene Solante,[8] and Rosalind Vianzon[9]

[1]Independent consultant, Philippines; [2]World Health Organization - Papua New Guinea; [3]KNCV Tuberculosis Foundation, The Hague, Netherlands; [4]College of Medicine, University of the Philippines; [5]Philippine Tuberculosis Society, Inc.; [6]Philippine College of Chest Physicians; [7]Philippine Coalition Against TB (PhilCAT); [8]Philippine Society of Microbiology and Infectious Disease; [9]National TB Program, and Department of Health, Philippines

Corresponding author: Maria Imelda Josefa D. Quelapio, 1402 The Malayan Plaza, ADB Ave. cor Opal Road, Ortigas Center, Pasig City, Philippines
Contact details: mameldquelapio@gmail.com

ABSTRACT

Setting: The Philippines has had a long history of Public-private Mix Directly observed treatment short-course (PPMD) for the care of tuberculosis (TB) patients.

Objective: This study aimed to document the knowledge, attitudes and practices (KAPs) of private physicians on TB and multidrug-resistant TB (MDR-TB).

Design: This cross-sectional study interviewed 118 private physicians.

Results: Private Medical Doctors (MDs) have a mixed practice in the diagnosis and treatment of TB and MDR-TB. Some referred patients to fellow providers, while managing other patients in their own clinics. Ninety-six percent of MDs requested microscopy for presumptive TB patients; however, only 36% utilized DOTS microscopy centers; 66% requested culture, with 59% utilizing PMDT facilities. Management in MDs' own clinics was higher for presumptive patients with no obvious risk of drug resistance compared to those with a drug resistance risk (95% vs. 58%), and it was higher for TB patients compared to MDR-TB patients (92% vs. 6). Standard treatment regimens were prescribed correctly by 82% MDs for new TB cases, and by 72% for retreatment cases. A quarter of MDs did not advise supervised therapy for patients. Knowledge on TB/MDR-TB case definitions was demonstrated by 83%-99% MDs; by 93%-100% on TB outcomes, and 50%-67% on MDR-TB outcomes. Eighty-six percent were willing to collaborate with government for MDR-TB control.

Conclusion: This study revealed positive knowledge and practices in the private sector on TB/MDR-TB management, with much interest and openness for collaboration. The WHO framework for PPM MDR-TB needs to be urgently explored for implementation in the Philippines.

Keywords: KAPs, public-private mix, PPM, MDR-TB

INTRODUCTION

The role of the private sector in tuberculosis (TB) control cannot be ignored. While directly observed treatment, short-course (DOTS) began in the 1990s within National TB Programs (NTP), the private sector emerged to be a key provider of TB services in many settings, becoming the rationale underlying public-private mix DOTS (PPMD).[2] The Philippines, a high TB burden country and one of the 30 high multidrug-resistant TB (MDR-TB) burden countries, has over 15,000 private physicians. The 2011 drug resistance survey estimated 8,500 new MDR cases annually (2% among new; 21% among retreatment). In 2013, 3,962 (47%) rifampicin-resistant/MDR-TB cases were detected, with 57% treated using second-line drugs (SLD).[3]

The Philippine NTP initiated DOTS in 1996, a time of disunity in TB care between the public and private sectors. One study revealed only 13% of private physicians were using smear microscopy; another showed 4% sole reliance on smear, and 55% on both chest x-ray (CXR) and smear, and a hundred regimen variations prescribed. Among 1,355 private doctors interviewed, 88% solely relied on CXR; 89% prescribed inappropriate regimens; 98% did not follow-up patients; and only 24% knew the NTP policies. [4]

In 1994, even prior to DOTS, motivated private specialists had established the Philippine Coalition against Tuberculosis (PhilCAT) as a "unifying force" among stakeholders. The 1997 Nationwide TB Prevalence Survey documented that most TB symptomatics sought care in the private sector even with free government services, urging the NTP to formally adopt the PPMD strategy in 2002, designating PhilCAT to systematically engage private physicians and institutions through DOTS referral, and establishment of PPMD units. DOTS became countrywide in 2003; in 2011, engaged non-NTP providers contributed 11.7% TB cases to the NTP. The programmatic management of drug-resistant TB (PMDT) was piloted by a non-governmental PPMD unit, the Tropical Disease Foundation, mainstreamed into the NTP with guidance from the Green Light Committee. PMDT is now nationwide, with all regions accessing MDR-TB diagnosis and treatment.

Despite the country's long PPMD experience, strategic information regarding TB management outside the NTP remains lacking. TB ceased to be a reportable disease in 2001. A report on four countries, including the Philippines, showed huge relative anti-TB sales volumes in private markets; Philippine procurement data derived a sales volume enough to treat 2.4 times the NTP caseload. This concluded that even after PPMD adoption, an enormous drug quantity continues to be channeled and used massively outside the NTP.

This paper aimed to assess the knowledge, attitudes and practices (KAPs) of private physicians in TB and MDR-TB care.

METHODOLOGY

A cross-sectional study on the KAPs of hospital-based private physicians in five major cities in the Philippines on TB and MDR-TB management was conducted between June-December 2012. The National Capital Region (NCR), Regions III, IVA, VII and XI, were selected for their relatively large and urbanized populations. From 194 government-licensed private facilities, 93 hos-

pitals were randomly selected: all 8 large (>300 beds), all 35 medium (101-300 beds) and 30% of 50 small (1-100 beds) hospitals. Among the 93, 76 participated in the study, with non-participation coming from facilities not dealing with TB patients, and those with competing activities during the study.

Three affiliated medical doctors (MDs) from each large hospital, two from medium, and one from each small hospital, nominated by the Hospital Director, were interviewed. Of 144 targeted physicians, 82% (118) participated in the study.

A Technical Working Group representing the NTP, the National TB Reference Laboratory, and the World Health Organization (WHO) was convened. An advisory group from three prominent medical societies solicited buy-in for the project and contributed technical inputs; six pulmonologists served as study interviewers. After consent, one-on-one MD interviews were conducted using a semi-structured questionnaire. Editing and verification were made to ensure consistency of responses; output frequencies were generated for selected categorical data.

The study protocol was approved by the WHO-Western Pacific Region Ethical Review Board. Informed Consent Forms were signed by the Hospital Directors, and MDs. Data were kept confidential and restricted to the study team.

RESULTS

Among the 118 MDs, 74% were >40 years old, 56% males, 67% from NCR, 58% pulmonologists, 13% infectious disease (ID) specialists, 10% other sub-specialists and internists, and 19% others **(Table 1)**. Three-fourths were affiliated with private hospitals only; the remaining with both private and government facilities. TB practice was, on average, 17 years; 70 MDs (59%) had undergone training for DOTS Referring Physicians, 59 (50%) involved in TB work within the last five years, through DOTS referral, implementation, advocacy or research.

Table 1: Profile of respondents

Characteristics	Value (n, %)
Age: >40 years	87 (74%)
Sex: Males	66 (56%)
Area of practice	
NCR	79 (67%)
Region III	4 (3%)
Region IV-A	12 (10%)
Region VII	11 (9%)
Region XI	12 (10%)
Specialization	
Pulmonology	68 (58%)
Infectious Diseases	15 (13%)
Other sub-specialties* and Internal Medicine	12 (10%)
Others*	23 (19%)
Affiliation	
Private hospital(s) only	88 (75%)
Private and public hospitals	30 (25%)
No. of hospital affiliation	
1 only	28 (24%)
2-3	59 (50%)
4-6	31 (26%)
Ave. duration of TB practice (years)	17 (range: 2-50)
Involvement in TB	
Trained in DOTS	70 (59%)
TB work	59 (50%)

- *Sub-specializations other than Pulmonology and Infectious Disease*
- *** General medicine, family medicine, paediatrics, surgery, obstetrics-gynecology, otolarrhyngology*

PRACTICES

Referring and managing

The average number of *presumptive TB cases* seen was seven patients weekly, and five *confirmed TB patients*. *Presumptive DR-TB patients* numbered one to two weekly, with zero to one *confirmed MDR-TB patient*.

Most physicians had mixed practice, sometimes referring certain patients to other providers, while managing others in their own clinics. **Figure 1** shows only 31% MDs referred *presumptive TB patients* to other providers, compared to 73% referring *presumptive DR-TB cases*; 69% referred *TB patients*, while 96% referred *MDR-TB patients*. Consistently, **Figure 2** shows 95% MDs managed *presumptive TB cases* in their own clinics vs. 58% managing *presumptive DR-TB cases*; 92% managed *confirmed TB patients* vs. 6% managing *MDR-TB patients*. The two figures indicate that the practice of clinic management was more for patients with no drug resistance, or known DR-TB risk, while the practice of referring was more for patients that harbored MDR-TB, or DR-TB risk.

Utilization of recommended facilities and tools

Among those who referred patients for TB care, utilization of DOTS and PMDT facilities was 85%-94% **(Figure 3).** The rest referred to fellow physicians, mostly pulmonologists and ID specialists regarded as TB/MDR-TB experts.

Ninety-six percent of MDs managing presumptive TB cases in their clinics requested for diagnostic smear; 66% MDs managing presumptive DR-TB cases, for culture; and 51% for drug susceptibility test (DST), as recommended by the national guidelines.

Thirty-six percent MDs utilized DOTS facilities to perform microscopy; and 59% utilized PMDT facilities to do culture/DST. The rest utilized private, or public laboratories of unknown quality.

Treatment and use of recommended regimens

Clinic treatment of cases was 92% (108) for new cases, 73% for retreatment, 21% for chronic, 18% for presumptive DR-TB, and 6% for MDR-TB patients (**Figure 4**). Among the 108, 82% claimed to prescribe the NTP standard regimen for new cases, 2HRZE/4HR (H=isoniazid, R=rifampicin; Z=pyrazinamide, E=ethambutol);[13] the remaining would use three non-standard regimens, majority prolonging E throughout the continuation phase, and a few using three instead of four drugs during the intensive phase.

Seventy-two percent (61) would prescribe the NTP standard retreatment regimen, 2HRZES/1HRZE/ 5HRE (S=streptomycin); the remaining would use 12 non-standard regimens, majority simply repeating first-line drugs for varying durations, or adding a fluoroquinolone, including ciprofloxacin despite recommendations against its use. For chronic cases, 72% also repeated first-line drugs, or added a fluoroquinolone. For confirmed MDR-TB patients, six added a fluoroquinolone to first-line drugs including H and R; two added amikacin, and one added clarithromycin. The injectable duration was 2-6 months; the entire treatment duration ranged 12–24 months.

Supervised therapy

Among those who treated TB patients in their clinics, 75% (81) claimed they advised

Figure 1. Doctors who referred patients

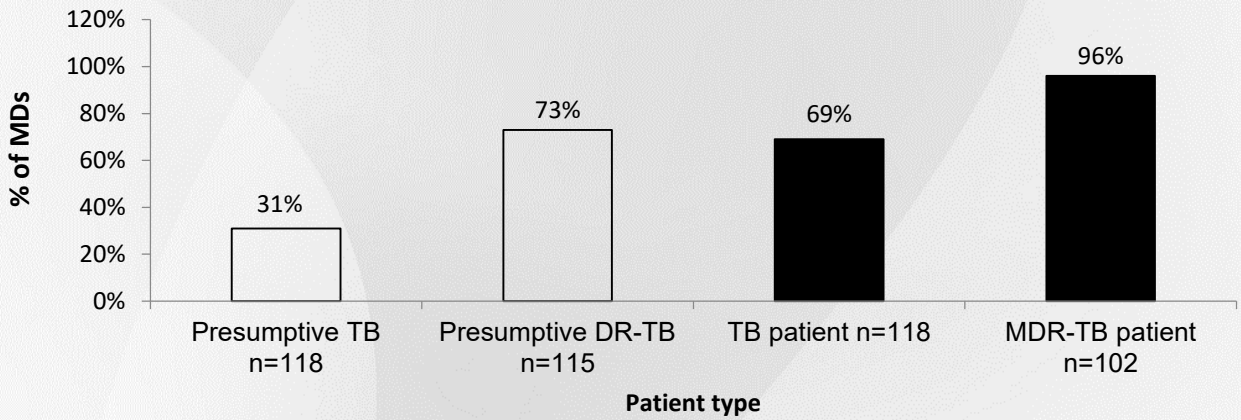


Figure 2. Doctors who managed patients in their clinics

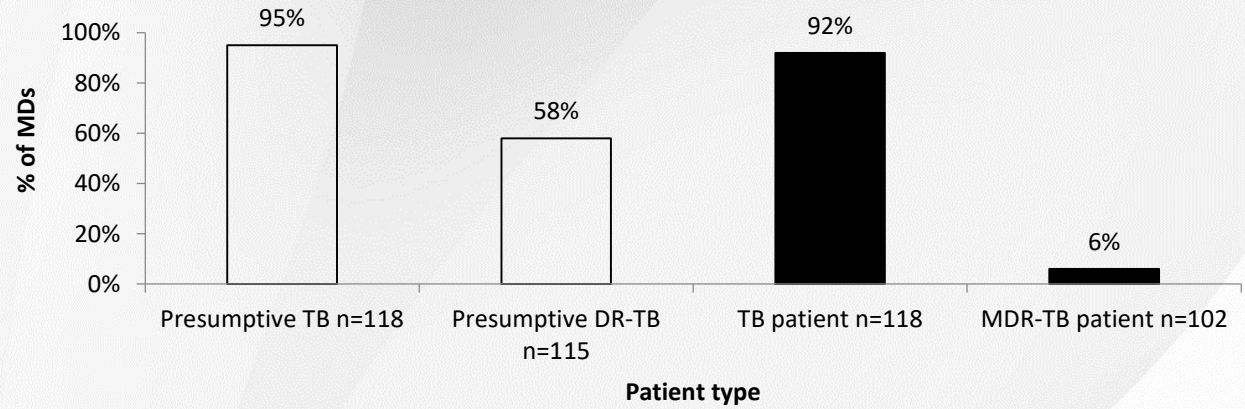
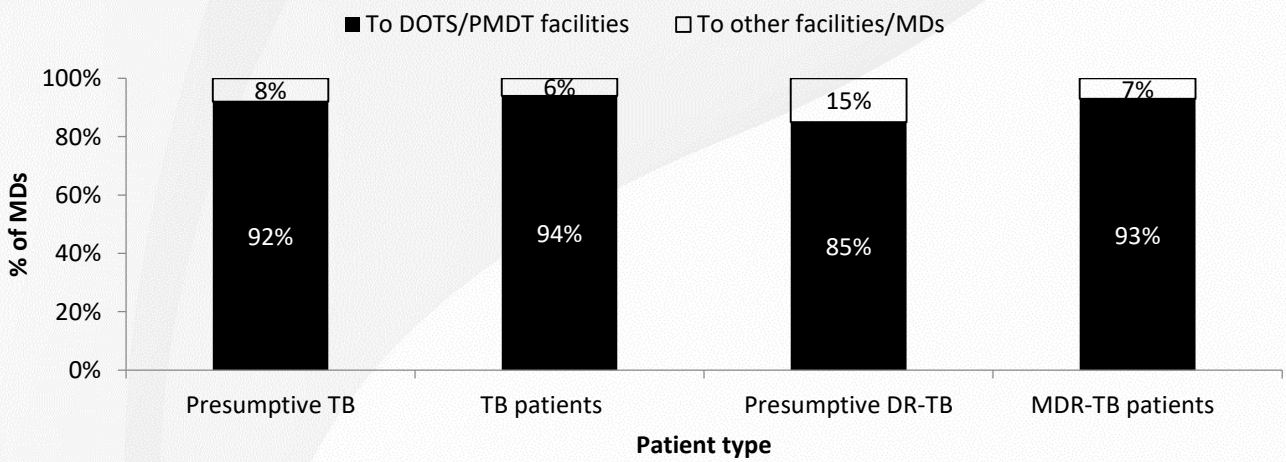


Figure 2. Doctors who managed patients in their clinics



supervised treatment; 23% (25) did not; two gave no response. Among the six MDs who treated MDR-TB patients, four advised supervised therapy, while two did not. The choice of a treatment partner was a family member, a volunteer or a public health care worker. However, there was no mechanism to ensure actual treatment supervision.

KNOWLEDGE

To gauge knowledge in this study, MDs were asked to provide case definitions for presumptive and confirmed pulmonary TB/MDR-TB cases. Essential definition elements contained in national guidelines [13, 14] were identified, including cough of >2 weeks for *presumptive TB*, positive acid-fast bacilli smear for *TB patients*; previous treatment, DOTS non-conversion, MDR-TB contact, or TB/HIV for *presumptive DR-TB*; and HR resistance for *MDR-TB*. MDs' mention of the essential element was considered a satisfactory response. MDs with satisfactory responses ranged from 83%-99% across all patient types **(Figure 5)**.

MDs who treated TB/MDR-TB patients were asked to provide definitions of treatment outcomes. Considered essential elements for "*successful TB*, and *MDR-TB treatment*" based on the national Guidelines [13, 14] were completion of the recommended treatment course, and/or conversion to negative smear, and/or negative culture, respectively. Essential elements for "*unsuccessful TB*, and *MDR-TB treatment*," were non-conversion to negative smear, and/or culture, respectively, death, and loss to follow-up. Mention of essential definition elements was considered satisfactory. MDs with satisfactory responses on TB outcomes ranged from 93%-100%, and 50%-67% on MDR-TB outcomes **(Figure 6)**.

ATTITUDES

Asked regarding willingness to collaborate with the government in MDR-TB control, 86% MDs responded affirmatively, with 10% expressing time constraints**.** Perceived areas for collaboration included advocacy in 79%, DOTS and PMDT referral in 76%, participation in MDR-TB training in 75%, research in 52%, and providing treatment in 38%. It is noteworthy that four MDs were willing to set up a hospital DOTS clinic, and three hospital-based DOTS MDs were eager to set up a PMDT clinic.

DISCUSSION

This study on private physicians' KAPs in TB/MDR-TB has revealed remarkable transformation in the public-private situation in the Philippines. Sound diagnostic and prescribing habits in majority of MDs, their participation in programmatic TB work, further interest and availability to collaborate with government, and the knowledge on the NTP's technical standards are striking. Moreover, the high utilization rate of NTP-supported facilities for care is proof of trust in government-run facilities.

More efforts, though, are needed to address the low DOTS uptake for certain patients, and the low utilization of quality assured facilities for diagnosis. Recognized DOTS impediments include health system weaknesses, e.g., lost patients along the referral pathway, communication breakdown between referring physicians and TB facilities; logistics and financial factors, e.g., inconvenient and costly daily facility visits, and issues in private MDs' reimbursement schemes; and social factors, like stigma associated with TB facilities. It is essential to carefully pinpoint and address the reasons why MDs prefer clinic management, despite an insufficient DOT infrastructure, and innovate treatment supervision schemes that consider both private patients and MDs' preferences. Strengthening linkages among referring providers, patients and accredited facilities, using regularly updated directories of equipped centers, and inte-

Figure 4. Treatment rate among doctors for different types of TB

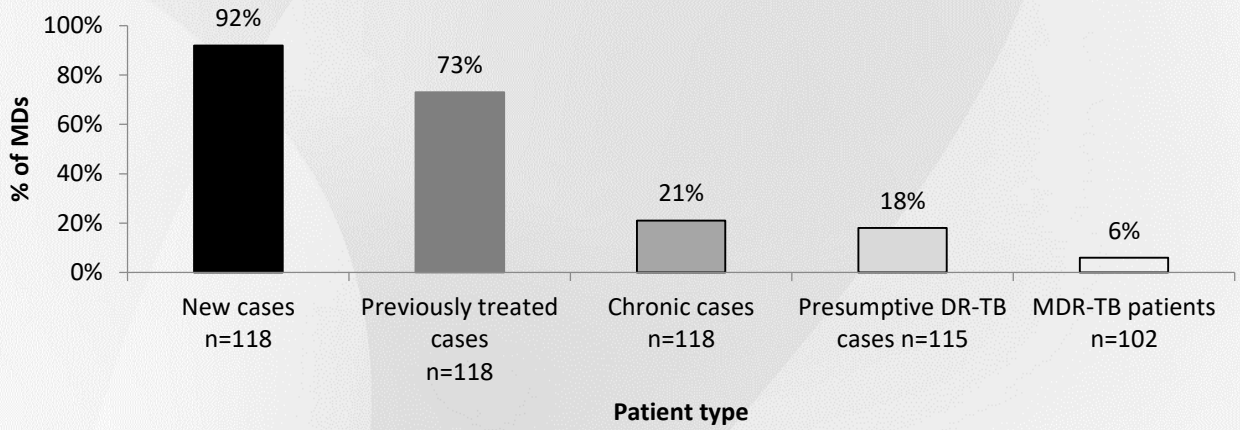


Figure 5. Knowledge on case definitions of patient types

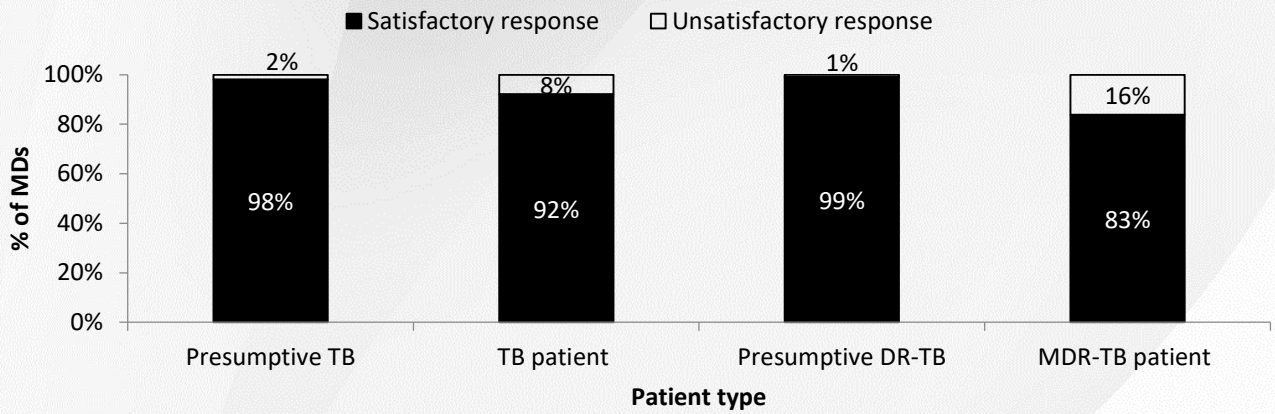
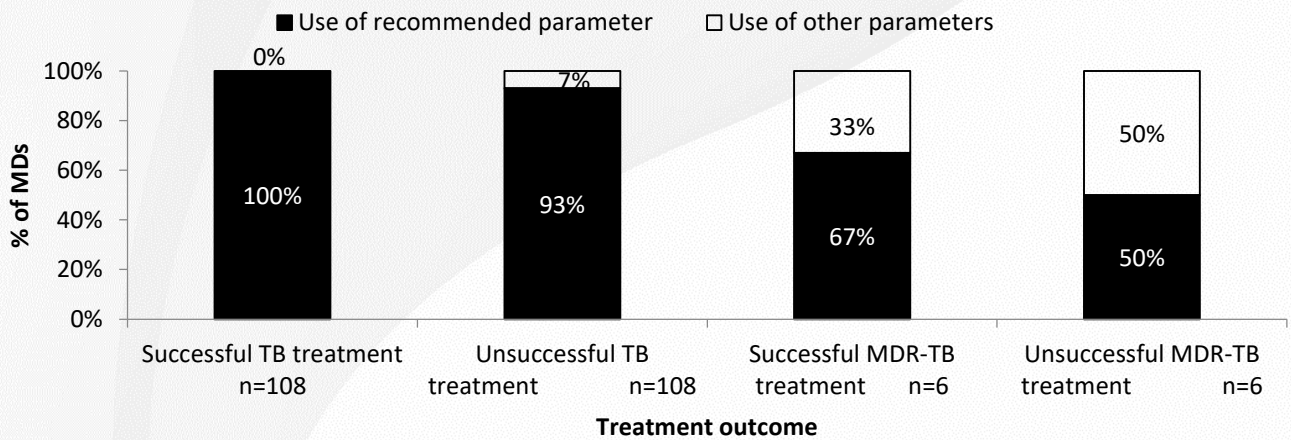


Figure 6. Knowledge on treatment outcomes of TB and MDR-TB



grating patient-centered care in implementation are critically needed. PhilHealth, viewed as the key to the country's TB program through its TB Out-patient Package, must ensure a commensurate and convenient reimbursement to MDs for a more enduring partnership.

Private laboratories of unknown quality should be included in ongoing quality assurance programs, both to avoid serious repercussions of inaccurate or late diagnosis, and widen workload distribution. Similarly, clinicians perceived as TB/MDR-TB "experts" should be invited to guidelines-based discussions and trainings, encouraging rational use of TB drugs, exposing them to programmatic involvement, such as referral, research, advocacy, etc. The practice of adding fluoroquinolones and/or amikacin to a failing regimen, under-treatment using less drugs, or shortened treatment durations with no supervised therapy, must be halted to prevent resistance amplification, and extensively drug-resistant TB. As anti-TB medicines remain widely available countrywide, the effectiveness of these SLDs needs to be preserved, being the core agents in new shorter regimens, and reliable companion drugs to the new medicines, bedaquiline and delamanid. Fortunately, the roll-out of Xpert MTB/RIF in all regions of the country is providing less and less reason for empiric SLD treatment.

WHO-Geneva recently published a framework for the engagement of all health care providers and partners in DR-TB management, presenting different approaches for various functions, such as clinical care, patient care, advocacy, funding mobilization, research, etc., allowing individuals and organizations to fit in with appropriate roles, depending on experience, interest, and capacity. These approaches provide unique win-win prospects for general practitioners, specialized physicians, patients and organizations.

PPMD in the Philippines has generated valuable lessons for PPM DR-TB expansion. NTP readiness to respond to the demands of this potential advancement is crucial, including ensuring a sustainable budget, supporting capacity assessment and building, monitoring and supervision, and scale up. Not to be ignored is the finding of 2.4% more cases managed outside the NTP,[12] underscoring the need to restore mandatory notification by non-NTP providers to allow measurement of additionality to the NTP. Stakeholders mapping, conducting dialogues with the enthusiastic private sector are some of the first steps worth considering by the NTP.

This study was limited to hospital-based practice and did not include stand-alone practice. Participants were mostly specialized doctors, who comprise a smaller proportion than general practitioners. Hence, the results are non-generalizable to all private physicians, and areas not represented in the study. Additionally, no structured observations validated responses about clinical practice.

CONCLUSION

This study has seen, beyond doubt, marks of behavior change that have evolved over the last 15 years. This era of much interest and openness in the private sector for collaboration in TB control must be seized. The framework for the systematic engagement of the private sector in PMDT needs to be urgently studied, implemented, and tailored to the Philippine setting.

Authors' contributions: Islam T, van Weezenbeek C and Vianzon R made substantial contributions to conception and design; Quelapio MID, Roa C, Borja M made substantial contribution to acquisition of data, analysis and/or interpretation of data; Quelapio MID drafted the article; Islam T, van Weezenbeek C, Roa C, Borja M, Vianzon R provided critical revisions for intellectual content. All authors provided final approval of the version to be published.

Acknowledgements: This study was funded by the USAID through the World Health Organization, Western Pacific Regional Office. All authors have no conflict of interest. The authors thank all the 76 private hospitals through their Medical Directors, and 118 private MDs; and Shane Boiser, Chariza Halun, Lerma Malabag, Jennifer San Luis, Andre Tanque, and Ma. Philina Villamor who served as study consultant-interviewers.

REFERENCES

1. Uplekar M, Pathania V, Raviglione M. Private practitioners and public health: weak links in tuberculosis control. Lancet 2001; 358:912-6.
2. Uplekar M. Involving private health care providers in delivery of TB care: global strategy. Tuberculosis 2003; 83:156-64.
3. Global Tuberculosis Report 2017. Geneva, World Health Organization, 2017 (WHO/HTM/TB/2017.23).
4. Portero JL and Rubio M. Private practitioners and tuberculosis control in the Philippines: strangers when they meet? Tropical Medicine and International Health, 2003; 8(4):329-335.
5. Auer C and Lagahid J. Diagnosis and management of tuberculosis by private practitioners in Manila, Philippines. Health and Policy, Jul 2006; 77(2): 172-181.
6. Manalo MF, Pineda AC, and Montoya JC. Knowledge, attitudes and practices for tuberculosis among Filipino family physicians: a comparative analysis by practice setting and location. Phil J Microbiol Infect Dis, 1998;27(1):6-12.
7. Engaging all health care providers in TB control: Guidance on implementing public-private mix approaches. Geneva, World Health Organization, 2006 (WHO/HTM/TB/ 2006.360).
8. Tupasi TE, Radhakrishna S, Co VM, et.al. Bacillary Disease and health-seeking behavior among Filipinos with symptoms of tuberculosis: implications for control. Int J Tuberc Lung Dis, 2000; 4(12):1126-32.
9. Vianzon RG, Garfin AMC, Lagos A, and Belen R. The tuberculosis profile of the Philippines, 2003–2011: advancing DOTS and beyond. WPSAR Vol 4, No 2: 11-16, 2013 | doi: 10.5365/wpsar.2012.3.4.022.
10. Quelapio MID, Mira NRC, Tupasi TE, et. al. Responding to the multidrug-resistant TB crisis: mainstreaming programmatic management to the National Tuberculosis Programme. Int J Tuberc Lung Dis, 2010; 14 (6):751-57.
11. Wells WA, Ge Colin Fan, Patel N, et. al. Size and patterns of private TB drug markets in the high burden countries. PLoS ONE, 2011 May 6(5):1-9.
12. Islam T, van Weezenbeek C, Vianzon R, et. al. Market size and sales pattern of tuberculosis drugs in the Philippines, Public Health Action (The Union) 2013:3(4):337-341
13. National TB Program Manual of Operations. Manila, Philippines. Department of Health, 2006.
14. Administrative Order No. 2008-0018. Guidelines for the implementation of programmatic management of drug-resistant TB. Manila, Philippines, Department of Health, 2008.
15. Guidelines for the programmatic management of drug-resistant tuberculosis: 2011 update. Geneva, World Health Organization, 2011 (WHO/HTM/TB/2011.6).
16. K Lonroth, E. Corbett. J Golub, et. al., Systematic Screening for active tuberculosis: rationale, definitions and key considerations. Int J Tuberc Lung Dis, 2013; 17 (3):289-298.
17. Framework for the engagement of all health care providers in the management of drug−resistant Tuberculosis. Geneva, World Health Organization, 2015. (WHO/HTM/ TB/2015).

PROSPECTIVE STUDY

Predictive Value of NUTRIC vs the Modified SGA Nutritional Assessment Tools for 28-Day ICU Mortality

Enrik John Aguila, MD, MBA; Anne Kimberly Lim, MD; Kristine Reyes, MD; Ma. Janeth Samson, MD, FPCP, FPCCP

Institute of Pulmonary Medicine, St. Luke's Medical Center-Quezon City

ABSTRACT

Objective: To determine the predictive value of using modified NUTRIC and modified SGA for clinical outcomes namely the 28-day ICU mortality, length of mechanical ventilation days, and length of ICU stay among adult ICU patients.

Methods: This was a single center, prospective cohort study on adult patients aged 19 years and above admitted at the SLMC – QC ICU from July to November 2017. All patients were assessed upon admission using both the modified NUTRIC and modified SGA, which were correlated with clinical outcomes.

Results: A total of 114 patients were included in the study. All 114 patients (100%) were classified as SGA-high risk, while 40 (35%) and 74 (65%) had low and high NUTRIC scores, respectively. The low NUTRIC score group had a significantly shorter length of ICU stay (3 days versus 7 days, p=0.0003) and a lower overall mortality rate (5% versus 31%, p=0.001). There was a direct and moderate correlation between NUTRIC score and length of ICU stay (p=0.0001). Modified NUTRIC scoring had good sensitivity (92%) and poor specificity (42.7%) to predict ICU mortality.

Conclusion: The modified NUTRIC scoring system is predictive of 28-day ICU mortality. High NUTRIC scores are associated with longer length of ICU stay.

Keywords: Modified NUTRIC, modified SGA, ICU mortality, mechanical ventilation days, length of ICU stay.

INTRODUCTION

Nutrition plays a significant role in a patient's recovery. This is particularly true most especially in the critical care setting. Malnutrition has been associated with increased morbidity and mortality, impaired respiratory and cardiac function, decreased immune function, and increased length of hospital stay.[1] Hence, it is important to address nutrition-related issues as it highly predicts a patient's course of recovery from his illness.

Nutritional screening serves a paramount role in the initial stages of patient care. With an effective nutrition screening process, necessary nutritional support can be planned and carried out for a patient's optimal care.[2] However, traditional screening tools are often limited due to their subjective nature.[3] Hence, there is a need to study on better tools that can assist in the identification of critically ill patients most likely to benefit from nutrition therapy. Among the nutritional assessment tools used include the Nutrition Risk

in the Critically Ill (NUTRIC) and the Subjective Global Assessment (SGA).

SGA uses a subjective approach based on seven criteria: intake prior to admission, presence of GI symptoms, weight loss, physical assessment, presence of edema or ascites, functional assessment and the stress caused by the disease in relation to nutritional requirements. On the other hand, NUTRIC is designed to quantify the risk of critically ill patients in developing adverse events that may be modified by aggressive nutritional therapy and is based on age, number of comorbidities, days from hospital to ICU admission, and APACHE II and SOFA scores from admission. NUTRIC helps in identifying critically ill patients most likely to benefit from optimal nutrition considering subsequent clinical outcomes.[4,5]

At St. Luke's Medical Center – Quezon City, a validated modified SGA has been widely used since 2013 for all admitted patients. The tool had a sensitivity of 94.7%, a specificity of 95.2%, a positive predictive value of 95.7% and a diagnostic accuracy of 95%.[6] ICU-admitted patients were similarly assessed using SGA; however NUTRIC has been determined to be more appropriate in this setting. Hence, this study aimed to determine the predictive value of a modified NUTRIC and modified SGA for 28-day intensive care unit (ICU) mortality among adult patients admitted at the ICU of St. Luke's Medical Center – Quezon City.

METHODOLOGY

A single-center, prospective cohort study was conducted on all eligible adult patients aged 19 years and above admitted at the Jonathan Y. Dy Intensive Care Unit of the St. Luke's Medical Center Quezon City, a private tertiary hospital from July to November 2017. The following patients were excluded: discharged from ICU against medical advice during the 28-day study period; with signed waivers modifying or restricting medical/nutritional management against medical advice during the 28-day study period; with do-not-resuscitate (DNR) directives upon admission to ICU who died during the course of the 28-day study period; those transferred to hospital of choice within the 28-day study period; and those who were readmitted to the ICU within the 28-day study period.

All patients included in the study were assessed using both the modified Subjective Global Assessment, accomplished by the Clinical Nutrition Service dietitian, and the modified NUTRIC scoring system, accomplished by the Medical Resident on Duty (MROD) within the 1st 48 hours of ICU admission.

SGA is a screening tool with a subjective approach to identify the nutrition status of the patient based on history and physical examination.[9] SGA grade was based on seven criteria and each of these criteria was stratified as either normal/mild, moderate or severe. Anthropometric measurements, including weight changes before and during the illness are recorded, as well as the nutritional history, which includes the appetite, intake and gastrointestinal symptoms. The healthcare professional also assesses the patient's physical appearance such as subcutaneous fat loss and muscle loss, presence or absence of edema/ascites. Existing medical conditions are also noted. The patient's SGA grade and anthropometric data (height, weight, and BMI collected from the electronic medical record) were graded from 0-3 and the total score was used to determine the patient's nutrition risk level. For the purpose of analysis, patients who scored at least 1 (moderate or high risks) were classified as malnourished.

The modified NUTRIC classifies patients at nutritional risk using objective variables: age, comorbidities, APACHE II, SOFA score, days from hospital to ICU admission.[7] Patients were given points corresponding to the parameters met in the qSOFA. If the patient only met 1 parameter, he was given 1 point. If he met 2 or all the parameters, he was given a total of 2 points. From the existing laboratory results from medical record,

the modified NUTRIC score was computed using the score sheet. The modified NUTRIC score was calculated for each patient using several parameters. Necessary data were obtained from the chart and the *St. Luke's Healthcare System Application* online. Modified NUTRIC scores were calculated without using interleukin (IL)-6 values; the creators of the tool allowed exclusion of this variable when not clinically available. Patients were classified as having a high score if the sum was 5 or greater; these patients were classified as having a higher risk of malnutrition. Each patient was assigned a 3-digit numerical patient code and data collection forms were accomplished per subject.

Nutritional assessment were done to all patients upon admission regardless of their primary admitting diagnosis as recommended by the European Society of Parenteral and Enteral Nutrition (ESPEN) and Philippine Society of Parenteral and Enteral Nutrition (PHILSPEN) guidelines. Demographic data and clinical variables were gathered solely from the chart. There was no point of contact with the patient and their relatives.

The dietitian, MROD and the researchers who determined the modified SGA and modified NUTRIC scores were blinded of the results of each.

Clinical outcomes such as length of ICU stay, length of mechanical ventilation days, and 28-day ICU mortality of patients included in the study were determined accordingly. The Acute Physiology and Chronic Health Evaluation (APACHE) II and Sequential Organ Failure Assessment (SOFA) scores were computed. The APACHE II and SOFA scores were used to assess severity of illness calculated on the first day of ICU admission. For the APACHE II, tympanic temperature was used in lieu of rectal temperature since the former was the one measured at the Jonathan Dy ICU.

The primary outcome was the all-cause mortality during the first 28 days from the time of ICU admission until ICU discharge, transfer to regular room or step down from unit. A non-mortality outcome was considered if a patient was discharged within 1 month from ICU admission. Secondary outcomes included length of mechanical ventilator days (invasive and/or non-invasive) and length of ICU stay.

The Clinical Protocol and all relevant documents were reviewed and approved by the SLMC Institutional Ethics Review Committee.

All study data were recorded and investigators were responsible for the integrity of the data. Patient confidentiality were respected by ensuring anonymity of patient records. A 3-digit code was used for each patient as their identifier. Data gathered were stored and kept in a locked cabinet at the St. Luke's Medical Center 2nd Floor Medicine Conference room until study completion. An informed consent was not obtained since data collection relied solely on chart review. There was neither a direct or indirect risk posed on the patients. A notification letter was given to the attending physician within the 1st 48 hours of ICU admission regarding the inclusion of their patient in the study.

The calculated sample size was 114 subjects, based on a prospective cohort study which indicated a 48.6% mortality rate and an alpha of 5%.[7,8]

Descriptive statistics was used to summarize the general and clinical characteristics of the participants. Independent sample T-test, Mann-Whitney U test and Fisher's Exact/Chi-square test were used to determine the difference of mean, median and frequency between groups, respectively. Spearman's rank correlation was used to determine the association of modified NUTRIC versus modified SGA in terms of length of mechanical ventilator days and length of ICU stay. Sensitivity, specificity, NPV, PPV, likelihood and hazard ratios were used to determine the predictive value of the modified NUTRIC compared to modified SGA for 28-day ICU mortality. A receiver operating characteristic curve of modified NUTRIC in predicting 28-day mortality was also formulated. Null hypothesis was rejected at 0.05 α-level of significance. STATA 15.0 was used for data analysis.

RESULTS

There were 116 patients admitted at the ICU who were initially included in the study from July to November 2017. There were 2 patient drop-outs: 1 patient was discharged from ICU against medical advice and the other patient was transferred to hospital of choice.

A total of 114 patients was analyzed. The mean age of the patients was 68.82 14.33 years, of which 50% were males, with a mean BMI of 23.6 kg/m^2. Baseline qSOFA and APACHE II were at 1.72 0.89 points, and 15.23 6.98 points, respectively. The most common indication for ICU admission was a respiratory disease (54%). Majority (66%) of ICU-admitted patients required invasive means of artificial respiration. Most patients (81.58%) were fed enterally (Table 1).

The modified SGA classified all patients as having a high SGA score with a high risk of malnutrition. However, the modified NUTRIC scoring system classified only 65% (74/114) of patients as having a high score with a high risk of malnutrition. Table 2 shows a comparison in the baseline characteristics and outcomes of patients with low and high NUTRIC score. Those with high NUTRIC score were older, had significantly higher qSOFA and APACHE II scores, had a higher proportion of patients admitted to ICU due to a respiratory disease, and higher number of patients who were hooked to invasive mechanical ventilator. Majority of high-risk patients were started with enteral feeding. Majority of postsurgical conditions admitted to ICU were scored low risk.

The high NUTRIC score group had a significantly longer length of ICU stay (7 days versus 3 days) and a higher overall mortality rate (31% versus 5%, p=0.001). Both groups had a median duration of 1 hospital day at floors prior to being admitted to the ICU. Of the 82 patients who were on mechanical ventilation, the high NUTRIC group had a median duration of 7 ventilator days vs 4 days with the low NUTRIC group.

There was a direct yet weak and non-significant relationship between modified SGA scores and ventilator days (ρ=0.128; p=0.253) and ICU days (ρ=0.161; p=0.0.088). In contrast, there was a direct and moderate correlation between NUTRIC score and length of ICU stay (ρ=0.3600; p=0.0001) and a direct yet weak and non-significant relationship between NUTRIC score and duration of mechanical ventilation days.

Table 1. Characteristics of included patients (n=114)

Characteristic	Value
Age (Years)	68.82 ± 14.33
19 – 39 years old	1 (0.88%)
40 – 59 years old	30 (26.32%)
60 – 79 years old	55 (48.25%)
≥ 80 years old	28 (48.56%)
Height (cm)	161.18 ± 10.2
Weight (kg)	60 (37–141)
BMI	23.6 (14.5–55.1)
Baseline qSOFA	1.72 ± 0.89
Baseline APACHE II	15.23 ± 6.98
Sex	
Male	58 (50.88%)
Female	56 (49.12%)
Primary admitting diagnosis at the ICU	
Cardiovascular disease	2 (1.75)
Gastrointestinal disease	17 (14.91)
Neurologic disease	7 (6.14)
Renal	8 (7.02)
Respiratory disease	62 (54.39)
Postsurgical condition	15 (13.16)
Others	3 (2.63)
Allergy	1 (33.33)
Bacteremia	1 (33.33)
DKA	1 (33.33)
Mechanical ventilator	
Invasive	76 (66.67%)
Non-invasive	6 (5.26%)
None	32 (28.07%)
Route/mode of nutrition	
Enteral	93 (81.58%)
Parenteral	21 (18.42%)

Table 2. Characteristics of patients by NUTRIC score status (n=114)

Characteristics	Modified NUTRIC Score		P-value
	Low (n=40)	High (n=74)	
	Frequency (%); Mean ± SD; Median (Range)		
Age (Years)	60.4 ± 12	73.36 ± 13.46	<0.001*
19 – 39 years old	1 (2.5)	0	
40 – 59 years old	20 (50)	10 (13.51)	<0.001ǂ
60 – 79 years old	17 (42.50)	38(51.35)	
≥ 80 years old	2 (5)	26 (35.14)	
Height (cm)	163.2 ± 8.1	160.09 ± 11.1	0.120*
Weight (kg)	63.5 (37 – 90)	60 (37 – 141)	0.517‡
BMI	23.91 (14.5 – 31.28)	23.5 (15.6 – 55.1)	0.943‡
Baseline qSOFA	1.02 ± 0.86	2.09 ± 0.64	<0.001*
Baseline APACHE II	10.18 ± 4.28	17.96 ± 6.64	<0.001*
Sex			
Male	23 (57.60)	35 (47.30)	0.298§
Female	17 (42.50)	39 (52.70)	
Primary admitting diagnosis at the ICU			
	0	2 (2.7)	
Cardiovascular disease	7 (17.5)	10 (13.51)	
Gastrointestinal disease	3 (7.5)	4 (5.41)	
Neurologic disease	4 (10)	4 (5.41)	
Renal	12 (30)	50 (67.57)	<0.001ǂ
Respiratory disease	12 (30)	3 (4.05)	
Postsurgical condition	2 (5)	1 (1.35)	
Others	1 (50)	0	
Allergy	1 (50)	0	
Bacteremia	0	1 (100)	
DKA			
Mechanical ventilator			
Invasive	15 (37.5)	61 (82.43)	<0.001ǂ
Non-invasive	2 (5)	4 (5.41)	
None	23 (57.5)	9 (12.16)	
Route/mode of nutrition			
Enteral	26 (65)	67 (90.54)	0.001§
Parenteral	14 (35)	7 (9.46)	

(ρ=0.2148; p=0.053).

Computing the diagnostic accuracy, sensitivity, specificity and predictive value of SGA was not feasible since all patients were classified as high risk using the tool (Table 4).

Modified NUTRIC scoring had good sensitivity and poor specificity to predict mortality in adults who were admitted to the ICU. Among high-risk NUTRIC patients, there was a 31% probability that the patient would expire (PPV).

Table 3. Clinical outcomes of patients admitted to ICU

Outcome	Total (n=114)	Modified NUTRIC Score		p-value
		Low (n=40)	High (n =74)	
	Frequency (%) or Median (range)			
Length of ICU stay (days)	5 (1 – 40)	3 (1 – 25)	7 (1 – 40)	0.0003‡
Length of hospital stay prior to ICU admission	1 (0 – 63)	1 (0 – 53)	1 (0 – 63)	0.345‡
Length of mechanical ventilation in days (n=82)	6.5 (1 – 54)	4 (1 – 25)	7 (1 – 54)	0.079‡
ICU Mortality	25 (21.93)	2 (5)	23 (31.08)	0.001§

** - Independent sample t-test; ‡- Mann-Whitney U test; § - Chi-square test; ₴ - Fisher's exact test*

Table 4. Predictive value of SGA in predicting 28-day ICU mortality (n=114)

Modified SGA scoring	28-day ICU mortality		Total
	Expired	Alive	
	Frequency (%)		
≥ 5 (high risk)	25 (21.9)	89 (78.1)	114 (64.91)
< 5 (low risk)	0	0	0
Total	25 (21.9)	89 (78.1)	114 (100)
Sensitivity	-	Positive LR	-
Specificity	-	Negative LR	-
PPV	-	Accuracy	-
NPV	-		

Table 5. Predictive value of NUTRIC in predicting 28-day ICU mortality (n=114)

Modified NUTRIC scoring	28-day ICU mortality		Total
	Expired	Alive	
	Frequency (%)		
≥ 5 (high risk)	23 (20.18)	51 (44.74)	74 (64.91)
< 5 (low risk)	2 (1.75)	38 (33.33)	40 (35.09)
Total	25 (21.93)	89 (78.07)	114 (100)
Sensitivity	92% (74% - 99%)	Positive LR	1.61 (1.3 – 1.99)
Specificity	42.7% (32.3 - 53.6%)	Negative LR	0.19 (0.05 – 0.72)
PPV	31.08% (26.7 - 35.8%)	Accuracy	53.51% (43.9 - 62.9%)
NPV	95% (83.1% - 98.7%)		

Overall, the accuracy of NUTRIC scoring to predict ICU 28-day mortality was low at 53.51%. (Table 5).

Kaplan-Meier survival curve by NUTRIC score showed that those with low NUTRIC scores had better survival compared with those with high scores (Figure 1).

Based on Cox's proportional hazards ratio, patients who had a modified NUTRIC score of ≥ 5 were 5.15 times more likely to die during the ICU admission within 28 days (95% CI 1.14 to 23.18, p=0.033). Age and sex were not found to be statistically significant predictors of ICU mortality in this study (p=0.245 and 0.965, respectively).

ROC analysis showed that at a cutoff point of 5, the sensitivity and specificity of the modified NUTRIC score were 92% and 42.7%, respectively (Table 11). The area under the ROC curve of NUTRIC was 0.7004 (95% CI 0.60-0.801) and 0.552 (95% CI 0.42 – 0.68) for SGA (Figure 2).

The ROC area of the both modified SGA and modified NUTRIC were not statistically significantly different with a p-value of 0.0882.

DISCUSSION

The modified SGA was validated for use at the SLMC-QC in a study done in 2013 and is currently being used hospital-wide for nutritional care of its patients even those admitted at the critical care units.[6] The modified SGA has been shown to be highly sensitive and specific in identifying severely malnourished patients, who in turn are associated with having a higher risk of morbidity and mortality.[6]

Our data on the other hand only showed a direct yet very weak relationship between modified SGA score and ventilator days and ICU days but were not statistically significant. However, it is important to note that computation of the sensitivity, specificity and predictive value

Figure 1. Probability of survival by modified NUTRIC score

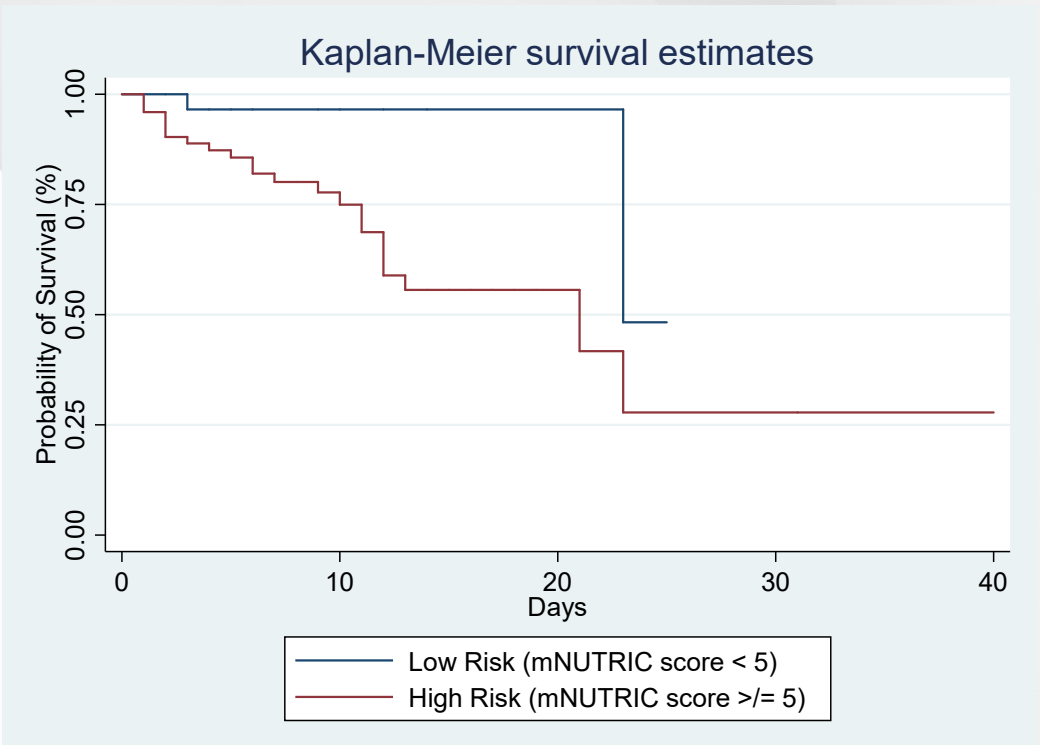
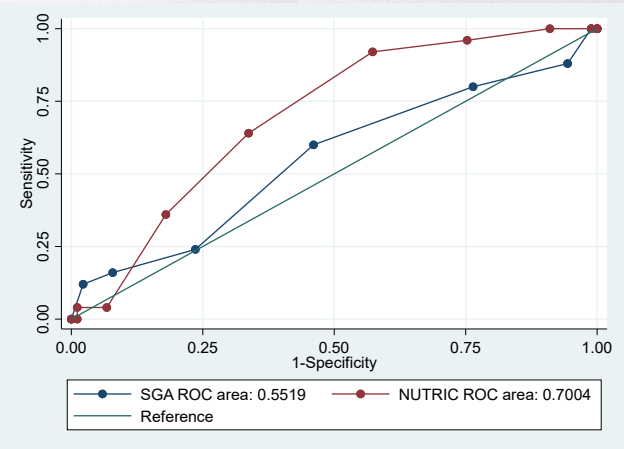


Figure 2. ROC curves of modified NUTRIC score and modified SGA score in predicting mortality



of SGA was not feasible as all patients in the study were automatically classified as high risk using the tool. Hence, we were not able to compare the diagnostic accuracy of SGA in predicting 28-day ICU mortality in this study.

Several studies suggest that not all critically ill patients are the same in terms of their nutrition risk.[5] Of 114 patients included in the study, all (100%) were classified as high risk using the SGA as compared to NUTRIC wherein 40 (35%) were classified as low risk while the other 74 (65%) was high risk. It may be necessary to further revisit how patients are classified using the SGA at the ICU setting since classifying patients at high risk may be inappropriate for some ICU admissions where patients apparently can be classified as low risk based on certain parameters unlike when using NUTRIC.

At present, there are no efforts yet to use the newer NUTRIC tool in the ICU of our institution, despite suggestions by several studies that the tool is more appropriate in the ICU setting. NUTRIC uses objective parameters unlike SGA which is highly subjective of which data may not be obtained for ICU patients who are comatose or intubated. This study is the first to evaluate the predictive value of NUTRIC on certain clinical outcomes such as 28-day ICU mortality, length of mechanical ventilator days and length of ICU stay for patients admitted at the ICU of the SLMC QC.

Based on our computed Cox's proportional hazard ratios, patients who had a modified NUTRIC score ≥ 5 were 5.15 times more likely to die during the ICU admission, within 28 days. Kalaiselvan et al reported similar results, stating that a high NUTRIC score is associated with increased length of stay at the ICU and higher mortality. This is likely because the NUTRIC score includes severity of illness, since these patients also had higher APACHE II and qSOFA scores.[10] Other studies report similarly better outcomes in those with lower NUTRIC scores.[5,7]

The stark difference in our study in comparison to the cited studies is that the computed accuracy of NUTRIC scoring to predict mortality was low at 53.51% which correlates with the computed area under the ROC curve of 0.0074. This may have been because of confounding factors such as varying nutrition therapy for each patient which are not taken into consideration on this study. Outcomes such as mortality would be affected depending on the nutrition intervention given which is one of the limitations of this study.

Our study has a number of limitations. The study used a modified NUTRIC scoring system due to indeterminate qSOFA and APACHE II scores. Furthermore There was no information on the nutritional intervention provided for each patient and there might be heterogeneities on the nutrition strategies employed by itself. Another limitation is the subjectivity in answering the modified SGA form. For instance, some patients admitted at the ICU just for monitoring and with apparent lower degrees of stress may be indiscriminately classified as high risk due to severe stress. Lastly, this is only a single center study and the results can be validated by other institutions.

For patients with a high NUTRIC score, increased provision of calories was associated

with improved 6-month survival whereas no such relationship was observed in patients with low NUTRIC scores. In an observational study done in 2009, there was an observed inverse linear relationship between the odds of mortality and total daily calories received.[11] An increase of 1,000 calories per day or an increased protein intake was associated with an overall reduction in mortality, and may therefore be recommended.

CONCLUSION

The use of NUTRIC in the ICU setting is beneficial. A higher modified NUTRIC score relates to higher 28 day mortality and hence a more thorough nutritional assessment is required for these patients for more effective nutrition therapy. .

The authors state no conflict of interest. The manuscript has not been supported by any source of support, including sponsorship or any financial sources.

REFERENCES

1. Fessler T. Malnutrition: A Serious Concern for hospitalized Patients. Today's Dietitian, Issue. Vol. 10 No. 7, page 44, July 2008.
2. Rasmussen HH, Holst M, Kodrup, J. Measuring Nutritional Risk in Hospitals. Clinical Epidemiology, 2:209-216, 2010.
3. Coltman A. Use of 3 Tools to Assess Nutrition Risk in the Intensive Care Unit. Journal of Parenteral and Enteral Nutrition, 39(1): 28-33, January 2015.
4. Rahman A, Hasan RM, Agarwala R, Martin C, Day AG, Heyland DK. Identifying Critically-Ill Patients Who Will Benefit Most From Nutritional Therapy: Further Validation of the "Modified NUTRIC" Nutritional Risk Assessment Tool, Clin Nutr., 2015.
5. Heyland DK, Dhaliwal R, Jiang X, Day AG. Identifying Critically Ill Patients Who Benefit the Most from Nutrition Therapy: The Development and Initial Validation of a Novel Risk Assessment Tool. Critical Care, 15(6):R268, 2011.
7. Lacuesta-Corro L, Paguia G, Navarette D, Llido L.. The Results of the Validation Process of a Modified SGA (Subjective Global Assessment) Nutrition Assessment and Risk Level Tool Designed by the Clinical Nutrition Service of St. Luke's Medical Center, a Tertiary Care Hospital in the Philippines. PhilSPEN Online Journal of Parenteral and Enteral Nutrition. Issue Feb 2012 – Dec 2014: 1-7, 2013.
8. Mendes R, Policarpo S, Fortuna P, Alves M, Virella D, Heyland DK. Nutritional Risk Assessment and Cultural Validation of the Modified NUTRIC Score in Critically Ill Patients – a Multicenter Prospective Cohort Study, Journal of Critical Care, doi: 10.1016/j.jcrc.2016.08.001, 2016.
9. Buderer NM. Statistical Methodology: Incorporating the Prevalence of Disease into the Sample Size Calculation for Sensitivity and Specificity. Academic Emergency Medicine; 3(9), 1996.
10. Detsky AS et al. What is Subjective Global Assessment of Nutritional Status? Journal of Parenteral and Enteral Nutrition, 11:8-13, 1987.
11. Kalaiselvan MS, Renuka MK, Arunkumar AS. Use of Nutrition Risk in Critically Ill (NUTRIC) Score to Assess Nutritional Risk in Mechanically Ventilated Patients: A Prospective Observational Study. Indian J Crit Care Med, 21:253-6, 2017.
12. Albedra C, Gramlich L, Jones N. The Relationship Between Nutritional Intake and Clinical Outcomes in Critically Ill Patients: Results of an International Multicenter Observational Study. Intensive Care Med, 35:1728-1737, 2009.
13. Mukhopadhyay A, Henry J, Ong V, Leong CS, The AL, van Dam RM, Kowitlawakul Y. Association of Modified NUTRIC Score With 28-Day Mortality in Critically Ill Patients. Clinical Nutrition, 36(4):1143-1148, August 2017.

PROSPECTIVE STUDY

Diaphragm muscle thickness and rapid shallow breathing index (RSBI) as predictors for successful extubation among critically ill adult patients

Geraldine Garcia, MD; Jose Gil Archie Causing, MD; Judy Lin-Ong, MD, Mary Joy P. Ordanza, MD; Chito Paulo A. Sistoza, MD

Institute of Pulmonary Medicine, St. Luke's Medical Center, Quezon City

ABSTRACT

Objective: This study aimed to evaluate the use of ultrasonographic measures of structure and function of the diaphragm muscle and their clinical value in predicting success in assisted mechanical ventilator weaning and subsequent extubation.

Methods: This was a prospective observational study of adult intubated patients admitted at the critical care units of St. Luke's Medical Center – Quezon City. Patient has been intubated for more than 48 hours and has met the criteria for weaning readiness assessment. Patients underwent ultrasound of the diaphragm muscle to measure its thickness and spontaneous breathing parameters (SBP) to measure RSBI. The outcome measured was extubation success or failure.

Results: A total of 20 patients were included in the study. There were 12 male subjects (60%) and eight female subjects with an average age of 68.1 + 13.0 years. Fifteen subjects (75%) were intubated due to pneumonia and majority of the subjects included have hypertension. Successful extubation was achieved in 15 patients (75%). The mean duration of mechanical ventilator days in the successful group was seven days, whereas it was 13 days in the failed group. The ROC curve determines ≤102.73 as the best cut-off score for RSBI. This cut-off score of RSBI gives 93.3% sensitivity but 40% specificity in predicting successful extubation. However, resulting AUC of 0.587 suggest that RSBI is not a significant predictor for successful extubation (p=0.6262).

INTRODUCTION

Prolonged mechanical ventilation is associated with significant morbidity and mortality. Therefore, weaning should be considered as early as possible in the course of the mechanical ventilation. However, a prevalent clinical problem in critically ill adult patients is failure to wean from mechanical ventilation. Studies found that difficulties in weaning from mechanical ventilation are encountered in approximately 20% of patients, and more than 40% of the time passed in the intensive care unit (ICU) is spent to try to wean off from mechanical ventilation.[1] Tools available for determining the optimal timing and success of weaning and extubation are limited. Thus, prolonged assisted mechanical ventilation ensues which poses another burden as studies have shown that this is associated with decreased muscle weight and alterations in contractile properties of the diaphragm within 48 hours of intubation.[2,3] This has led to suspicion that diaphragm dysfunction may contribute to weaning failure, even in patients with no obvious reason to suspect phrenic nerve or diaphragm pathology.

Stroetz and Hubmayr found that clinical prediction of extubation success or failure was

often incorrect with the decision to extubate biased toward ventilator dependency.[4] Subjective clinician's decisions are often wrong. Furthermore, several indexes that have been used in clinical practice and employed to assess the patient's ability to recover spontaneous breathing have shown limitations and disadvantages. These include problems with accessibility, invasiveness of the procedure and the need for skilled or specifically trained operators. The rapid shallow breathing index (RSBI) was found to be one of the most accurate predictors of failure.[5] However, values of sensitivity and specificity and negative predictive values for the suggested threshold of RSBI <105 were highly variable in different studies.[6-8]

Recently, ultrasound has been used to evaluate diaphragmatic function but direct measures of the diaphragm function as a predictor of weaning and subsequent extubation success or failure have not been extensively evaluated.[9] Bedside ultrasonography, which is already crucial in several aspects of critically illness, has been recently proposed as a simple, inexpensive, non-invasive and readily available and reproducible method of quantification of diaphragmatic contractile activity. Ultrasound can be used to determine diaphragm excursion, which may help to identify patients with diaphragm dysfunction, and can also allow for the direct visualization of the diaphragm thickness in its zone of apposition.

This paper aimed to evaluate the use of ultrasonographic measures of structure and function of the diaphragm muscle and their clinical value in predicting success in assisted mechanical ventilator weaning and subsequent extubation.

METHODOLOGY

This was a prospective observational study of adult intubated patients admitted at the critical care units of St. Luke's Medical Center – Quezon City.

Intubated adult patients age 19 years old and above, that have been admitted at the critical care units of St. Luke's Medical Center – Quezon City were included in the study. Patient has been intubated for more than 48 hours and has met the criteria for weaning readiness assessment (Table 1). Patients with neurologic disease/s, patients with tracheostomy tube, patients intubated due to trauma, due to upper airway obstruction or post-operatively on temporary mechanical ventilation, pregnant and pediatric patients aged <19 years were excluded. Patients who have history of empyema or pleurodesis have also been excluded.

All intubated patients admitted at the critical care units of St. Luke's Medical Center were assessed every day for readiness to be weaned from the assisted mechanical ventilator. Clinical assessment and objectives measures were obtained daily and patients who met the criteria were considered as being ready to wean from assisted mechanical ventilation. All patients who met the criteria for readiness to wean were included in the study and were subjected to full history taking and clinical examination after informed consent was obtained from the patient or their relative and from their attending pulmonologist. Patients underwent ultrasound of the diaphragm muscle to measure its thickness and SBP to measure RSBI. Patients were followed through weaning until successfully extubated from assisted mechanical ventilation, regardless of the ultrasound and RSBI result.

There was no variation in the standard of care for weaning of intubated patients. However, in our institution, there was a non-standard use of ultrasound and RSBI measurement during the clinical course of intubated patients.

SBP to measure RSBI was performed by the respiratory therapist. Patient was disconnected from the ventilator and patient's tidal volume was obtained at the end of one minute from a hand-held spirometer and the patient's respiratory rate was observed and was counted in one full minute. The consultant radiologist performed the ultrasound at patient's bedside and measured the diaphragm muscle thickness. The right hemidiaphragm was chosen for sonographic examination due to better sonographic window provided by the liver. The patient was instructed to perform inspiratory breathing to total lung capacity (TLC) and then exhale to residual volume (RV). It was noted in some studies that diaphragm thickness differed

significantly between TLC and RV in patients with spontaneous breathing. The said examinations were carried out by persons who had no role in the management of the patient. To prevent inter-reader variability, two ultrasound consultants read the results.

Statistical Analysis

Descriptive statistics was used to summarize the clinical characteristics of the patients included in the study. Frequency and proportion were used for nominal variables and mean with standard deviation for interval/ratio variables. Sample size was calculated based on the comparison of success rate in extubation of patients with thick versus thin diaphragms. Assuming that, success rate among those with thick diaphragm is 63% (n=46)[1] and those with thin diaphragm was hypothesized to be 50% less successful, with an alpha error of 5%, power of 80% and a 1-tailed alternative hypothesis, sample size calculated is 60 subjects.

The outcome measured was extubation success or failure. Patients were divided into two groups: the successful group, which includes patients who were able to sustain spontaneous breathing for more than 48 hours following extubation, and failure group, which includes patients who will require re-intubation or non-invasive ventilations within 48 hours after extubation.

The area under the curve (AUC) was determined using receiver operating characteristic (ROC) curve to compute for and establish the cut-off value of diaphragm muscle thickness and RSBI (Figures 1 and 2). The number of successfully extubated patients with the computed cut-off value for RSBI was compared with the number of successfully extubated patients with the computed cut-off value for diaphragm muscle thickness. The sensitivity, specificity, positive predictive value and negative predictive value of the diaphragm muscle thickness measurement in predicting success of weaning were compared with RSBI as a reference standard using contingency 2 x 2 tables and exact binomial confidence intervals.

Ethical considerations

The Clinical Protocol and all relevant documents have been reviewed and approved by the St. Luke's Medical Center – Institutional Ethics Review Committee.

Informed consent was obtained by the investigator from the patient or their relative and from their attending pulmonologist when the patient met the criteria for readiness to wean. Patients had undergone ultrasound of the diaphragm muscle to measure its thickness and spontaneous breathing parameters (SBP) to measure RSBI. There was no significant clinical risk other than mild discomfort and anxiety during ultrasonography and obtaining SBP.

Patient's confidentiality was respected by ensuring anonymity of patient's records by using their initials in collection of data. Only the researcher knew the patient's initials and it was not shared with or given to anyone except their clinician. All study data have been recorded and the investigators were responsible for the integrity of the data in terms of accuracy, completeness and legibility. The manner of disseminating and communicating the study results guaranteed the protection of the confidentiality of patient's data. After the research, the collected data has been submitted to Research Committee of the Institute of Pulmonary Medicine and was kept as reference for checking of the completed research work.

RESULTS

A total of 20 patients were included in the study, with their demographic data shown in Table 2. The study was pre-terminated before reaching the required number of subjects due to lack of time. There were 12 male subjects (60%) and eight female subjects with an average age of 68.1 $\pm$ 13.0 in years. Fifteen subjects (75%) were intubated due to pneumonia and majority of the subjects included have hypertension. The number of days prior to SBP and Diaphragm Muscle Thickness measurement had no significant difference at 6.2 $\pm$ 3.6 and 6.6 $\pm$ 3.7 days respectively. The number of days prior to extubation was 8.7 $\pm$ 4.3 days.

Table 1. Considerations for assessing readiness to wean

Clinical assessment	Objective measurements		
• Adequate cough • Absence of excessive tracheobronchial secretion • Resolution of disease acute phase for which the patient was intubated	**Clinical stability** • Stable cardiovascular status (i.e. HR: <140 beats/min, systolic BP 90–160 mmHg, no or minimal vasopressors)	**Stable metabolic status** • Adequate oxygenation • SaO_2 >90% on FIO_2 of $\leq$0.4 (or PaO_2/FIO_2 of $\geq$150 mmHg) • PEEP of $\geq$ 8 cmH_2O • Adequate pulmonary function • RR $\leq$ 24 breaths/min • MIP $\leq$ 20–25 cmH_2O • VT $\geq$ 5 mL/kg • No significant respiratory acidosis	**Adequate mentation** • No sedation or adequate mentation on sedation (or stable neurologic patient)

HR, heart rate; BP, blood pressure; SaO_2, oxygen saturation; FIO_2, fraction of inspired oxygen; PaO_2, partial pressure of oxygen; PEEP, positive end expiratory pressure; RR, respiratory rate; MIP, maximal inspiratory pressure; VT, tidal volume.

Table 2. Characteristics of intubated patients admitted at the critical care units

Profile of patients	n (%)
Age (years), mean ± SD	**68.1 ± 13.0**
Gender (Male)	**12 (60.0)**
Reason for Intubation	
Bronchial Asthma	1 (5.0)
Hypoventilation (Cardio-pulmonary Arrest)	2 (10.0)
Peri-Operative Complications	1 (5.0)
Pneumonia (Community Acquired Pneumonia)	5 (25.0)
Pneumonia (Hospital Acquired Pneumonia)	7 (35.0)
Pneumonia (Healthcare-associated Pneumonia)	3 (15.0)
Pulmonary Congestion	1 (5.0)
Co-Morbidities	
Chronic Obstructive Pulmonary Disease	3 (15.0)
Hypertension	17 (85.0)
Diabetes Mellitus	8 (40.0)
Coronary Artery Disease	8 (40.0)
Number of Days Prior SBP, mean ± SD	6.2 ± 3.6
Number of Days Prior USG, mean ± SD	6.6 ± 3.7
Number of Days Intubated Prior Extubation, mean ± SD	8.7 ± 4.3

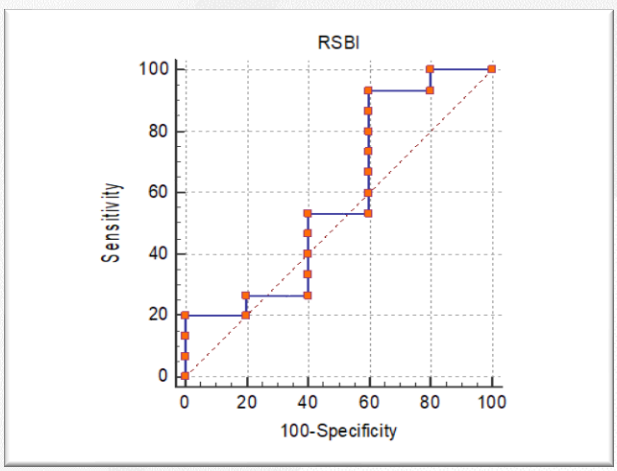
Successful extubation was achieved in 15 patients (75%). The mean duration of mechanical ventilator days in the successful group was seven days, whereas it was 13 days in the failed group. An ROC was constructed for RSBI and diaphragm muscle thickness at the end of inspiration to determine the best cut-off value that will in turn determine the success in extubation (Figures 1 and 2, respectively).

The ROC curve determines ≤102.73 as the best cut-off score for RSBI. This cut-off score of RSBI gives 93.3% sensitivity but 40% specificity in predicting successful extubation. However, resulting AUC of 0.587 suggest that RSBI is not a significant predictor for successful extubation (p=0.6262).

The ROC curve determines >3.2mm as the best cut-off score for diaphragm muscle thickness on inspiratory phase [DTM (insp)]. Moreover, resulting area under the curve of 0.707 indicates that DTM (insp) can significantly predict successful extubation (p=.0786) with a sensitivity of 73.3% and 80% specificity.

Using the cut-off computed for RSBI, there were 13 out of 15 (87%) successfully extubated patients using the cut-off of ≤ 102.72. For the DTM (Insp), there were 11 out of 15 (73%) successfully extubated patients using the cut-off value of > 3.2cm (Table 3).

Figure 1. Receiver operating characteristic curve of rapid shallow breathing index



On the two by two contingency table (Table 4), there were nine (60%) patients that were successfully extubated who had both the cut-off RSBI of ≤102.73 and DTM (insp) of ≥3.2mm. Moreover, there was no patient with RSBI and DTM (insp) beyond or outside the acceptable cut-off value that was successfully extubated.

Although the computed cut-off of DTM (insp) has higher AUC of 0.707 compared to only 0.587 of the computed cut-off value of RSBI, its difference is not significant (p=.5732) (Table 5).

DISCUSSION

It has been said that RSBI can help predict weaning outcome, and is now widely used in clinical practice. However, this index reflects the contribution of all respiratory muscles, rather than the function of the diaphragm muscle alone. Therefore, diaphragm muscle fatigue can be masked by compensatory action of the other muscles of respiration during spontaneous breathing and contributes substantially to proportion of patients who pass RSBI test but fails in weaning process. Moreover, weaning outcome can be affected by a variety of factors, hence, a single parameter is

Figure 2. Receiver operating characteristic curve of diaphragm muscle thickness on inspiratory phase

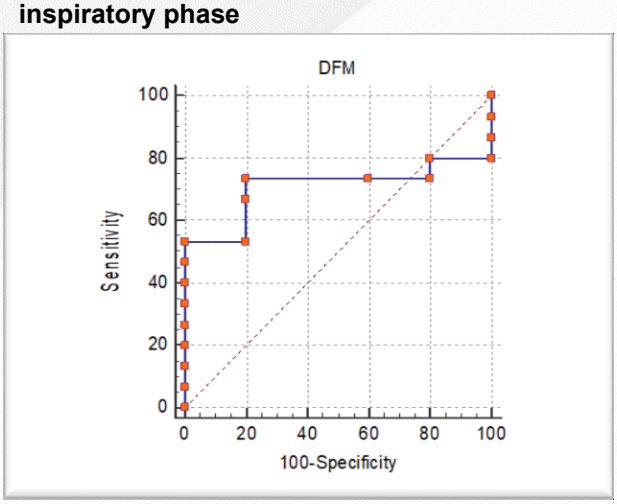


Table 3. Outcome measure comparison

Measurement	Extubation		Total
	Successful	Failed	
Rapid shallow breathing index			
> 102.73	2	2	4
≤ 102.73	13	3	16
		TOTAL :	20 ----------
Diaphragm thickness measurement (insp)			
> 3.2 mm	11	3	14
≤ 3.2 mm	4	2	6
		TOTAL :	20 ----------

Table 4. True positive, false positive, true negative and false negative comparing number of patients successfully extubated (n=15) with the rapid shallow breathing index as reference standard

	No. of successfully extubated pts within the RSBI cut-off	No. of successfully extubated pts outside RSBI cut-off	Total
No. of pts within the diaphragm thickness cut-off	9 (TRUE POSITIVE)	2	11
No. of pts outside the diaphragm thickness cut-off	4	0 (TRUE NEGATIVE)	4
Total	13	2	15

Table 5. Rapid shallow breathing index and diaphragm muscle thickness on inspiratory phase

	Sensitivity	Specificity	AUC	p-value
RSBI ≤102.73	93.3	40.0	0.587	0.5732
DTM (insp) >3.2	73.3	80.0	0.707	

inadequate to make an accurate prediction. With the attempts to devise tools that can accurately predict the outcome of weaning and with the widespread use of ultrasound machines in the clinical settings such as ICUs, studies have been made on the utilization of the ultrasound in assessing diaphragm function and its use in the weaning process. Diaphragmatic displacement and more recently, the diaphragmatic thickening as measured using ultrasound are now being proposed as a surrogate for assessment of diaphragmatic function.[10] In our institution, the RSBI is a major determinant in the process of the weaning among pulmonologists. The current study was designed to assess whether the diaphragm muscle thickness can be used like RSBI in terms of ability to predict

success in weaning and extubation.

The RSBI have historically been recommended by the *American Thoracic Society and European Respiratory Society* and is one of the most widely used predictors of weaning outcome in clinical practice. First described by Yang & Tobin in 1991, the RSBI allows assessment of respiratory mechanics by f/V_T and a RSBI of less than 105 breaths/L is said to predict successful weaning from mechanical ventilation.[11]

Since its first description, several modifications have been suggested, such as the serial measurements, the rate of change of RSBI, and lower cut-off value to further improve its predictive value. In the study done by Baess et al, a cut-off value of 73.5 had 87% sensitivity and 100% specificity for predicting extubation success which was lower compared to our study result of 102.73 as the best cut-off score for RSBI in our study population.[10] However, the cut-off score in our study has higher sensitivity at 93.3% but with lower specificity of 40%. This is probably due to the longer mechanical ventilator days of 8.7 days in our study population compared to 4 days in Baess et al's study.

According to Tokioka et al, the RSBI can only provide useful information regarding weaning success during spontaneous breathing trials or in those receiving mechanical ventilation for durations <1 week, but its value is limited to predict successful extubation in those being weaned using pressure support or requiring mechanical ventilation >7 days.[12] The said conclusion has been proven in the recent study done by Goncalves et al on how mechanical ventilation duration affects RSBI.[13] Their subjects were grouped according to at most 72 hours of mechanical ventilation or over 72 hours. RSBI values in the group over 72 hours were higher (78 ± 29 vs. 55 ± 22) (p-value = 0.039). Grouping the subjects with up to 72 hours and over 72 hours of mechanical ventilation according to the extubation outcome, the group of up to 72 hours had 82% of subjects successfully weaned from mechanical ventilator. On the group of mechanical ventilator day over 72 hours, only 52% of the study group population were successfully extubated.

Optimal function of the diaphragm, the primary muscle of inspiration, is key to resuming successful spontaneous ventilation regardless of the cause of respiratory failure. Contrary to prior beliefs, controlled mechanical ventilation for as little as 24 hours has been associated with development of human diaphragm muscle atrophy.[14] Moreover, factors such as breath size, impedance of neighboring structures and abdominal compliance can affect the extent to which the diaphragm muscle will move during respiration. These confounders can be circumvented by direct visualization of the diaphragm muscle itself. Diaphragm muscle fibers shorten with contraction and cause muscle thickening. These diaphragmatic muscle movement is said to be the product of diaphragmatic strength and poor endurance of the diaphragm muscle is an important cause of failed weaning. Ultrasonography arises as an important tool in the visualization and evaluation of diaphragm muscle structure and movement and direct measurement of diaphragm thickness during spontaneous respiration as a predictor of extubation success or failure may be important in assessing weaning outcome.

Kim et al used ultrasonography to measure vertical excursions or paradoxical movement of the diaphragm in 88 medical ICU patients who received mechanical ventilation >48 hours and met criteria for spontaneous breathing trials.[15] Patients with limited or paradoxical diaphragmatic dome excursions had longer weaning times and total ventilation times than patients without diaphragm dome dysfunction and also had higher rates of primary and secondary weaning failures. However, diaphragm dome imaging fails to directly visualize diaphragm muscle function. Direct imaging of changes in diaphragm thickness during spontaneous breathing may provide a more accurate assessment of the diaphragm as a contractile muscle and the propensity of the patient to have the necessary respiratory pump function necessary for success in resumption of spontan-

eous respiration. Hence, the study of Cohn and co-workers using diaphragm muscle ultrasound to assess the thickness of the muscle over a wide range of lung volumes from RV to TLC.[16] They have found that during inspiration, the diaphragm thickens as it shortens and the increase in diaphragm thickness as lung volume increased was alinear, with the slope of diaphragm muscle thickness increasing more rapidly as lung volume increased. This is the reason the diaphragm muscle thickness on end-inspiration is the parameter used for this study.

Many studies conducted has used ultrasonography to determine normal values for diaphragm excursion and focuses on diaphragm displacement instead of end-inspiratory diaphragm muscle thickness. Two studies have recently evaluated the concept of using diaphragm displacement, said to be a surrogate for diaphragmatic strength, as a predictor index for weaning outcome. Di Nino et al examined 63 intubated patients with ultrasonography before their first weaning trial and determined the percentage change in diaphragm thickness between end-expiration and end-inspiration.[17] They found that a cut-off percentage of 30% or more was a good predictor for weaning success. Ferrari et al included 46 tracheostomized patients who failed weaning at least once and underwent sonographic evaluation of the diaphragm thickness during maximal inspiration during a weaning trial in their study.[1] They found that a cut-off percentage change in diaphragm thickness between end-expiration and end-inspiration of 36% was associated with successful weaning. Despite the different cut-off values, the two groups agreed that percentage change in diaphragm thickness is more accurate compared with the RSBI in predicting successful extubation. The researchers held a similar argument that the RSBI is a product of the work of diaphragm and accessory muscles, which are fatigable, whereas diaphragm thickness expresses the degree of the more sustainable power. However, the percentage change in diaphragm thickness between end-expiration and end-inspiration or diaphragm displacement was not the outcome measured in this study.

To the best of our knowledge, there is no research that aims to establish a certain cut-off level for diaphragm thickness that will likely correlate with success in weaning and extubation which was done in this study. Some studies only established the evolution of diaphragm thickness during mechanical ventilation. Golinger et al found that over the first week of mechanical ventilation, diaphragm thickness decreased by more than 10% in 44 % (47 out of 107 subjects) of their study population.[18] They also found that low diaphragm contractile activity was associated with rapid decreases in diaphragm thickness, whereas high contractile activity was associated with increases in diaphragm thickness ($p=0.002$).

Umbrello et al used diaphragm ultrasound as indicator of respiratory effort in critically ill patients undergoing assisted mechanical ventilation and have found that with increasing levels of pressure support, parallel reductions were found between diaphragm thickening during tidal breathing.[9] They concluded that diaphragm thickening is a reliable indicator of respiratory effort, whereas diaphragm displacement should not be used to quantitatively assess diaphragm contractile activity.

Finally, Baess et al found that, based on an ROC curve for the end-inspiratory, end-expiratory, diaphragm displacement and RSBI, they found that sonographically measured diaphragm thickness measurement performed better than diaphragm displacement measurement in predicting success in weaning.[10]

CONCLUSION

In ICU patients who have met the criteria for weaning, an RSBI of $\leq$ 102.73 can be a predictor a successful weaning. Likewise, diaphragm muscle thickness measurement can be done on the ICU patients who have met the criteria for weaning, and a cut-off level of > 3.2 mm can also be a predictor of successful weaning. Based on outcome measure comparison done, diaphragm muscle thickness can successfully predict success in weaning as much as RSBI can.

REFERENCES

1. Ferrari G, De Filippi G, Elia F, et al. Diaphragm ultrasound as a new index of discontinuation from mechanical ventilation. *Crit Ultrasound J* 2014;6(1):8.
2. Le Bourdelles G, Viires N, Boczkowski J, et al. Effects of mechanical ventilation on diaphragmatic contractile properties in rats. *Am J Respir Crit Care Med* 1994; 149(6):1539–44.
3. Capdevila X, Lopez S, Bernard N et al. Effects of controlled mechanical ventilation on respiratory muscle contractile properties in rabbits. *Intensive Care Med* 2003; 29(1):103–10.
4. Stroetz RW, Hubmayr RD. Tidal volume maintenance during weaning with pressure support. *Am J Respir Crit Care Med* 1995;152:1034–40.
5. Yang KL, Tobin MJ. A prospective study of indexes predicting the outcome of trials of weaning from mechanical ventilation. *N Engl J Med* 1991;324:1445–50.
6. Epstein SK. Etiology of extubation failure and the predictive value of the rapid shallow breathing index. *Am J Respir Crit Care Med* 1995;152:545–9.
7.
8. Lee KH, Hui KP, Chan TB, et al. Rapid shallow breathing (frequency-tidal volume ratio) did not predict extubation outcome. *Chest* 1994;105:540–43.
9. Krieger BP, Isber J, Breitenbucher A, et al. Serial measurements of the rapid-shallow-breathing index as a predictor of weaning outcome in elderly medical patients. *Chest* 1997;112:1029–34.
10. Umbrello M, Formenti P, Longhi D, et al. Diaphragm ultrasound as indicator of respiratory effort in critically ill patients undergoing assisted mechanical ventilation: a pilot clinical study. *Critical Care* 2015;19:161.
11. Baess, A, Abdallah, T, Emara, D, et al. Diaphragmatic ultrasound as a predictor of successful extubation from mechanical ventilation: thickness, displacement, or both? *Egypt J Bronchol* 2016;10:162–6.
12. Yang KL, Tobin MJ. A prospective study of indexes predicting the outcome of trials of weaning from mechanical ventilation. *N Engl J Med* 1991;324(21):1445-50.
13. Tokioka H, Saito S, Niguma T, et al. The effect of pressure support ventilation on breathing patterns and the work of breathing. *Kokyu To Junkan* 1990; 38:269–72.
14. Goncalves EC, Lago AF, Silva EC, et al. How mechanical ventilation measurement, cutoff and duration affect rapid shallow breathing index accuracy: a randomized trial. *J Clin Med Res* 2017;9(4):289-96.
15. Levine S, Nguyen T, Taylor N, et al. Rapid disuse atrophy of diaphragm fibers in mechanically ventilated humans. *N Engl J Med* 2008;358:1327–35.
16. Kim WY, Suh HJ, Hong SB, et al. Diaphragm dysfunction assessed by ultrasonography: influence on weaning from mechanical ventilation. *Crit Care Med* 2011; 39(12):2627–30.
17. Cohn D, Benditt J, Eveloff S, et al. Diaphragm thickening during inspiration. *Journal of Applied Physiology* 1997; 83(1):291-6.
18. DiNino E, Gartman EJ, Sethi JM, et al. Diaphragm ultrasound as a predictor of successful extubation from mechanical ventilation. *Thorax* 2014;69:423–7.
19. Goligher E, Fan E, Herridge M, et al. Evolution of diaphragm thickness during mechanical ventilation: impact of inspiratory effort. *Am J Respir Crit Care Med* 2015; 192(9):1080–8.

CROSS-SECTIONAL STUDY

Lung cancer detection rates of conventional bronchoscopic techniques: bronchial brushing, endobronchial biopsy, bronchial lavage and bronchial washing

Marlo P. Bagano, MD, FPCP; John Clifford E. Aranas, MD, FPCP, FPCCP; Martiniano C. Zanoria, MD, FPCP, FPCCP

Perpetual Succour Hospital, Cebu City, Philippines

ABSTRACT

Reported diagnostic yield from bronchoscopies in patients with lung cancer varies greatly and optimal combination of sampling techniques has not been finally established. We reviewed all bronchoscopy reports and the official biopsy results of all conventional bronchoscopic techniques and were subsequently recorded. A total of 200 patients have undergone flexible bronchoscopy from June 2011 to December 2016. Only 154 underwent conventional bronchoscopic techniques. Majority were males (65%), average age was 59 years old, with the main indication as diagnosis (95.5%) and was done via conscious sedation (85.5%). Endobronchial biopsy (EBB) obtained the highest rate of positive yield for malignant lung disease with 34% while any combination of two tests would increase the yield to 35%. The most common histopathological result was squamous cell carcinoma (CA) for EBB and bronchial brushing while adenocarcinoma and small cell CA for bronchial lavage and washing. The presence of endobronchial lesion was associated with malignant lung disease.

INTRODUCTION

The first inspection and therapeutic intervention in the tracheo-bronchial tree was performed by Gustav Killian in 1887.[1] In the early part of the 20th century, bronchoscopic techniques were further advanced with the development of improved lighting, unique foreign body removal instruments and rigid bronchoscopy training programs. Since then, flexible bronchoscopy has become the mainstay investigation in the evaluation of patients suspected of lung cancer. It is employed mainly as a diagnostic tool providing tissue to determine the histological type of the tumor.[2] Fiberoptic bronchoscopy is usually performed via the oral or the nasal route, and either route provides excellent access to the lower airways.[3]

There are four main diagnostic tools for use during bronchoscopy to obtain diagnostic material: bronchoalveolar lavage (BAL), brushings, forceps biopsies and needle aspiration. The British Thoracic Society (BTS) guidelines recommended biopsies, brushings and washings for sampling from visible lesions. However, reported diagnostic yield from bronchoscopies in patients with lung cancer varies greatly and optimal combination of sampling techniques has not been finally established.[4-6]

Flexible bronchoscopy has become one of the most frequently performed minimally invasive procedures in pulmonary medicine. In order to sample the specimen, the accurate location of the pulmonary nodule or mass must be known.[7]

Because of the lack of data regarding the lung cancer detection rate of conventional bronchoscopic techniques available in our institution, our study reviewed all bronchoscopy reports and the official biopsy results of all the conventional bronchoscopic techniques and were subsequently recorded. The primary aim was to record the experience gathered in 200 cases in the

use of flexible bronchoscopy in Perpetual Succour Hospital. The study also aimed to determine the lung cancer detection rate of conventional bronchoscopic techniques [bronchial brushing (BB), endobronchial biopsy (EBB), bronchial lavage (BL) and bronchial washing (BW)].

METHODOLOGY

After institutional approvals, we reviewed all data including bronchoscopy reports and biopsy results of patients who underwent conventional bronchoscopic technique with BB, EBB, BL and BW at Perpetual Succour Hospital, Cebu City, Philippines between June 2011 and December 2016. Criteria for inclusion in the study were: (i) all bronchoscopies performed with conventional bronchoscopic techniques such as BB, EBB, BL and BW; (ii) a final histopathologic diagnosis of malignant lung disease obtained during bronchoscopy. All information written in the worksheet was recorded. Details regarding the study population are presented in Figure 1. Data collected were the age, sex, type of sedation, indications of bronchoscopy, route of access to the lower airways, bronchoscopic findings and histopathological results.

Endobronchial visibility was categorized into: 1) visible endobronchial lesion, 2) compression or narrowing, or 3) no visible lesion. Malignant lung disease was defined as positive histological or cytological results. Cells suspicious of malignancy usually lead to further investigations and were not included in the definition of malignant lung disease.

Patients' categorical profiles were expressed in frequency and percentage while those continuous variables were described in mean and standard deviation. In testing association between bronchoscopic findings and conventional technique, Chi square test of independence was used. Any associated p-values lesser than 0.05 alpha were considered significant. IBMSPSS ver 21 was used as software. All patients were labelled according to their hospital numbers instead of their names. Patient's data and clinical conditions were collated with utmost confidentiality.

RESULTS

The study involved 200 patients who underwent flexible bronchoscopy, in which majority were males (65%) (Table 1). Average age of patients was 59 years old, the youngest being 14 years of age and the oldest at 85 years of age. Meanwhile, 85.5% were under conscious sedation and in 95.5% of the cases the main indication was for diagnosis. As far as the route of access most bronchoscopists prefer the nasal route in about 24.5%; however, in 65.5% of cases it was not documented.

Of the 200 patients who underwent flexible bronchoscopy, only 154 patients had conventional bronchoscopic techniques (BB, EBB, BL and BW). A total of 46 patients were excluded from the study because no conventional diagnostic tech-

Table 1. Clinical characteristics of bronchoscopy patients

Characteristic	Value
Age, years	
Average	59
Range	14 – 85
Sex	
Male	130 (65.0%)
Female	70 (35.0%)
Sedation Type	
Conscious Sedation	171 (85.5%)
Deep Sedation	28 (14.0%)
N/A	1 (0.5%)
Indication	
Diagnostic	191 (95.5%)
Therapeutic	9 (4.5%)
Route of Access	
Nostril	49 (24.5%)
Oral	4 (2.0%)
Endotracheal Tube	14 (7.0%)
Tracheostomy	2 (1.0%)
N/A	131 (65.5%)

niques were performed during bronchoscopy and/or the indication was for treatment. Thus, 154 patients were included in the study sample. Of these, 102 underwent endobronchial biopsy, 57 underwent bronchial lavage, 116 underwent bronchial washing and 76 underwent bronchial brushing.

EBB had the highest rate of positive yield with 34% in 102 total cases (Table 2). BW was second with 18% in 116 cases, while both BB and BL had only 14% rate of positive yield for malignant histopathological lung disease. Any two combinations among the different techniques increased the rate of positive yield to 35%.

The most common histopathological result in EBB was squamous cell CA with 11 cases (10.8%), followed by adenocarcinoma with nine cases (8.8%), large cell CA with six cases (5.9%) and small cell CA with four cases (3.9%) (Table 3). In BW, both adenocarcinoma and small cell CA had two cases (1.7%) of malignant lung disease followed by large cell CA with one case (0.9%). In BB, five cases were classified under non-small cell lung CA unspecified, two cases were squamous cell CA (2.6%) and adenocarcinoma and small cell CA with one case each (1.3%). For BL both adenocarcinoma and small cell CA had one case each (1.8%).

On one hand, carinal involvement results were not statistically associated with malignant lung disease as detected by flexible bronchoscopy ($p=0.116$). On the other hand, the presence of endobronchial lesion was associated with malignant lung disease as noted in the distribution of cases, where 29/57 endobronchial lesion cases were found to be malignant ($p<0.001$).

DISCUSSION

Although new bronchoscopic techniques have been developed to facilitate accuracy in locating a lesion, they are not used in routine practice, especially in developing countries such as in our setting. Nevertheless, our institution has already had 200 cases of flexible bronchoscopy both diagnostic and therapeutic for the past five years. Of the 200 cases, only 154 underwent

Table 2. Histopathological results and rate of positive yield of conventional bronchoscopic techniques by single technique or in combination

Technique	Total	Malignant (-)		Malignant (+)		Positive Yield	
		N	%	N	%	Rate	95% CI
Single Technique							
EBB	102	67	66%	35	34%	34%	26-44%
BL	57	49	86%	8	14%	14%	7-25%
BW	116	95	82%	21	18%	18%	12-26%
BB	76	65	86%	11	14%	14%	8-24%
Combination							
Combined all four	22	15	68%	7	32%	32%	16-53%
Any three	40	29	73%	11	28%	28%	16-43%
Any two	48	31	65%	17	35%	35%	23-50%

EBB, endobronchial biopsy; BL, bronchial lavage; BW, bronchial washing; BB, bronchial brushing.

Table 3. Histopathological results from conventional bronchoscopic techniques

Results	Bronchial lavage	Bronchial washing	Bronchial brushing	Endobronchial biopsy
Malignant Lung Disease	8 (14%)	21 (18.1%)	11 (14.5%)	35 (34.3%)
Non-Small Cell Lung CA	1 (1.8%)	3 (2.6%)	8 (10.5%)	26 (25.5%)
Adenocarcinoma	1 (1.8%)	2 (1.7%)	1 (1.3%)	9 (8.8%)
Squamous Cell	0 (0%)	0 (0%)	2 (2.6%)	11 (10.8%)
Large Cell	0 (0%)	1 (0.9%)	0 (0%)	6 (5.9%)
Unspecified	0 (0%)	0 (0%)	5 (6.6%)	0 (0%)
Small Cell Carcinoma	1 (1.8%)	2 (1.7%)	1 (1.3%)	4 (3.9%)
Carcinoma	2 (3.5%)	6 (5.2%)	2 (2.6%)	3 (2.9%)
(+) Malignancy	4 (7%)	10 (8.6%)	0 (0%)	2 (2%)
Negative Results	49 (86%)	95 (81.9%)	65 (85.5%)	67 (65.7%)
Total	57 (100%)	116 (100%)	76 (100%)	102 (100%)

conventional bronchoscopic techniques. The average age of patients who underwent bronchoscopy was 59 years old, which approximates the average age of patients suspected with lung malignancy. Most of the cases were under conscious sedation which holds true since the requirement of minimal sedation makes it acceptable as an outpatient procedure and it has almost completely replaced rigid bronchoscopy in the initial assessment. The preferred route of access to the lower airways was thru the nasal route with 24.5%. A study by Gonzales-Aguirre et al found out that the route of access/insertion did not affect patient comfort. However, the oral route was associated with faster vocal cord visualization, less use of lidocaine and no insertion failure.[9] Our bronchoscopy finding does not report the time to visualization of the vocal cord as well as patient comfort during bronchoscope insertion.

The rate of a positive yield for malignant lung disease in our institution was highest for EBB (34%), followed by BW (18%) and lastly by both BB and BL (14%). The reported diagnostic yield for endobronchial biopsy is 80% with a range of 51% to 97% depending upon the patient population.[9] BL had an overall diagnostic yield range of 33% to 69%, being exclusively diagnostic in 9% to 11% of cases. BW is the easiest to perform but has the lowest yield 27% to 90%, with a higher yield for central lesions while bronchial brushings provide diagnostic yield in 72% of patients with central lung lesions and 45% of patients with peripheral lesions, when obtained under fluoroscopic guidance. A local study by A.T. Dilao, et al found out that the best result to obtain a higher positive rate for malignant lung disease was via EBB (57%), followed by BW (24%) and bronchial brushings (8.3%).[10] Although the lung cancer detection rate in our institution is lower as compared to literature, a lot of factors could have contributed to our results and these includes the number of biopsy specimens obtained which was not written in our bronchoscopy report, presence of surface necrosis which may be falsely negative, location of the lesion and the operator

experience. Any two conventional bronchoscopic techniques would increase the rate of positive result to 35% while all four would increase it to 32%, as compared to any single technique with the exception of EBB. Just like in the literature a combination of brushing, biopsy and washing can expect to establish a diagnosis in >60% of cases.[2] The most common histopathologic diagnosis in our institution was squamous cell CA for both EBB (10.8%) and BB (2.6%), while adenocarcinoma and small cell CA were common in both BL and BW. Endobronchial visibility of the lesion is one of the predictors of a higher diagnostic yield for a positive result for malignant lung disease. In our study, the presence of endobronchial lesion was associated with malignant lung disease in 29 out of 57 cases which was statistically significant with a p value of <0.001. However, carinal involvement was not associated with malignant lung disease. A study by Boonsarngsuk V et al, found out that endobronchial visibility is one of the predictors of a higher diagnostic yield for malignancy.[7]

An important limitation of our study is that we were not able to correlate the clinical and radiologic profiles of these patients who underwent flexible bronchoscopy, since no data regarding the clinical and radiologic characteristics is available in our bronchoscopy reports. In addition, the retrospective nature of our analysis is associated with its inherent limitations.

For the future researchers, the authors recommend a prospective multi-center study correlating the clinical profiles (ie, risk factors for lung cancer, co-morbidities, clinical presentation, etc) and radiologic profiles (ie, chest x-ray and/or chest CT-Scan findings) to all bronchoscopies performed and its histopathological results.

For the Adult Pulmonary Medicine Training Programs and the different Bronchoscopy Units, the author recommends an updated Bronchoscopy Report which should include clinical and radiologic profiles of each patient, a detailed bronchoscopy report (i.e., specific indications for

Table 4. Association of carinal involvement and endobronchial visibility of the lesion with the histopathological results

Bronchoscopic findings	Total bronchoscopy (Diagnostic only)	Conventional Bronchoscopic Techniques		Total	Test of Association
		Malignancy (-)	Malignancy (+)		p-value
Carinal involvement					
Sharp carina	120	73	26	99	0.116
Blunted carina	50	26	18	44	
N/A	21	11	0	11	Excluded in analysis
Endobronchial visibility					
Endobronchial lesion	62	28	29	57	<0.001
Compression/narrowing	35	23	10	33	
No visible lesion	94	59	5	64	

the procedure, safety checklist and precautions done prior to the procedure, number and exact location of biopsy specimens taken, proper description and documentation of the normal and abnormal trachea-bronchial tree findings, bronchoscopy-related complications during and after bronchoscopy and its management, medications given prior and during bronchoscopy in order to achieve optimal sedation, etc.)

CONCLUSION

It can be concluded from this study that majority of patients who underwent flexible bronchoscopy were males with 65% while females accounted for only 35%. The average age was 59 years old and mostly under conscious sedation with 85.5%. The main indication of doing the procedure was for diagnosis with 95.5% while only 4.5% were therapeutic. The preferred route of access to the lower airways was mostly intranasally with 24.5%, although 65.5% of the cases the route of access was not specified in our bronchoscopy report. In terms of rate of positive yield for malignant lung disease EBB had the highest rate with 34%, followed by BW with 18% and lastly, both BL and BB with 14% each. Any two combination of the conventional bronchoscopic technique would increase the rate of positive yield for malignant lung disease to 35%, while the combination of four techniques would increase the yield to 32% as compared to using the techniques alone.

The most common histopathological result in EBB and BB was squamous cell CA while both adenocarcinoma and small cell CA were common for BL and BW techniques. The presence of endobronchial lesion was associated with malignant lung disease, while carinal involvement was not.

REFERENCES

1. Haas AR, Vachani A, Sterman DH. Concise clinical review: advances in diagnostic bronchoscopy. Am J Respir Crit Care Med 2010;182:589-97.
2. Herth FJF. Bronchcoscopic techniques in diagnosis and staging of lung cancer. Breathe 2011;7:324-37.
3. Mehta AC, Dweik RA. Nasal versus oral insertion of the flexible bronchoscope: pronasal insertion. J Bronchology 1996;3(3): 224-8.
4. Du Ran AI, Blaikley J, Booton R, et al. British Thoracic Society guide line for diagnostic flexible bronchoscopy in adults: accredited by NICE. Thorax 2013;68(1):i1-i44.
5. Ohata M. History and Progress of Bronchology in Japan. JJSB 1998;20:539-46.
6. Barlesi F, Doddoli C, Greillier L, et al. Bronschopy in the diagnosis of lung cancer: an evaluation of current practice. Rev Mal Respir 2006; 23:17-26.
7. Boonsarngsuk V, Raweelert P, Sukprapruet A, et al. Factors affecting the diagnostic yield of flexible bronchoscopy without guidance in pulmonary nodules or masses. Singapore Med J 2010;51(8):660-5.
8. Kupeli E, Feller-Kopman D, et al. Diagnostic Bronchoscopy. Murray & Nadel's Textbook of Respiratory Medicine 6th Edition. Philadelphia, PHA: Elsevier Saunders; 2016.
9. Gonzalez-Aguirre, JE, Chavarria Martinez U, Rodriguez Mier D, et al. Bronchoscope insertion route and patient comfort during flexible bronchoscopy. Int J Tuberc Lung Dis 2015;19(3):356-61.
10. Dilao AT, Mendoza J. Fiberoptic bronchoscopy in the evaluation of multiple malignant pulmonary nodules. Scientific Proceedings (LCP) 1995;3(2).

META-ANALYSIS

A Meta-analysis on Indwelling Pleural Catheters versus Pleurodesis in the Management of Malignant Pleural Effusions: A Modern Dilemma

Anjuli May Jaen, MD; Ralph Elvi Villalobos, MD; Irene Rosellen Tan, MD; Ruth Divinagracia, MD

Section of Pulmonary Medicine, University of the Philippines-Philippine General Hospital

ABSTRACT

INTRODUCTION: Pleural effusion is a common sequela of malignant disease and signifies poor prognosis. Patients with pleural effusions often present with dyspnea, which impairs their quality of life. Studies have shown that indwelling pleural catheters (IPC) can be done even to patients who fit the criteria for pleurodesis as the goal of treatment shifts from treating the patient by radiologic evidence of pleural effusion to patient symptoms and quality of life.

METHODS: We conducted an extensive search for published studies that compared pleurodesis with IPC as the management for malignant pleural effusion. Eligibility and bias assessments were done by the authors. A meta-analysis was done using control of effusion as the primary outcomes and length of hospital stay, dyspnea, quality of life, chest pain and complication rates as secondary outcomes.

RESULTS: Twenty-four studies were initially screened. However, only 9 studies with a total of 1,333 patients met the inclusion criteria. Patients who underwent indwelling pleural catheter insertion had significantly decreased length of hospital stay by 3.83 days (95% CI, -5.83, -1.83), decreased effusion-related hospital days by 4.83 days (CI 95% -8.99, -0.66) and less loculations or recurrence of pleural effusion that required re-intervention by 41% (CI 95%, 0.34, 0.77). There is a trend favoring IPC in terms of short-term dyspnea (RR 0.62, [CI 95% 0.31, 1.27]), long-term dyspnea (RR 0.78 [CI 95%, 0.53, 1.14]), complications (RR 0.78, [CI 95% 0.47, 1.31]), which were not statistically significant. Pleurodesis resulted in a non-significant trend towards better quality of life with a mean difference of 2.02 (95% CI -5.41, 9.45) and a non-significant decrease in empyema rates (RR 1.7, [95% CI, 0.77, 3.73]). Lastly, chest pain (RR 1.05 [95% CI, 0.42, 2.59]) and survival with a mean difference of 0.00 (95% CI, -1.34, 1.34) did not differ between groups.

CONCLUSIONS: Patients who underwent IPC insertion significantly had fewer hospital days and more control of effusion. There was also a non-significant trend towards decreased short-term dyspnea, long-term dyspnea, and complication rates in favor of IPC. Pleurodesis showed a non-significant trend towards better quality of life and fewer empyema rates.

INTRODUCTION

Pleural effusion is one of the most common sequelae of malignancy. Patients with malignant pleural effusion (MPE) are often symptomatic and present as dyspnea (57%), cough (43%) and chest pain (26%), which all affect quality of life.[1,2] The median length of survival of patients with MPE is only 6 months; hence, treatment is frequently palliative.[3]

MPE accumulates rapidly if no intervention is given. In 2010, the MPE guidelines of the British Thoracic Society indicated that intercostal drainage must be followed by pleurodesis to prevent recur-

rence (Evidence Level A).[4] It is performed by inserting a thoracostomy or a pleural catheter until the parietal and visceral pleura appose followed by the introduction of a sclerosing agent, such as talc, doxycycline, oxytetracycline, minocycline, bleomycin, povidone iodine, or silver nitrate.

In the past, the decision to perform further interventions or procedures was based on radiographic evidence of recurrent effusions.[5] However, a paradigm shift has revolutionized the goals of health care professionals towards symptom relief and improved quality of life for patients. In recent years, randomized controlled trials were conducted to compare the outcomes of indwelling pleural catheterization (IPC) versus pleurodesis in terms of dyspnea, quality of life, survival, length of hospital stay and complications. This meta-analysis was done to determine which palliative procedure (IPC vs pleurodesis) has more favorable outcomes.

METHODS

Search Methodology

We performed an extensive electronic database search to identify studies that compared IPC versus pleurodesis using PubMed, Cochrane, Embase, Medline, and Google Scholar. The terms used were "malignant pleural effusion", "pleural catheter" and "pleurodesis".

Study Eligibility

The following studies were considered for inclusion: 1) Randomized controlled trials, prospective cohort studies and retrospective cohort studies with 2) available full-text articles. Articles were excluded if: 1) they were not written in English; 2) they were review articles, abstracts, editorials, case reports or case series; or 3) the studies compared pleurodesis and IPC with regards to cost only.

Data Collection and Analysis

Three authors independently assessed the studies for inclusion into the analysis. Discrepancies were settled by consensus. The primary outcome was the relief of dyspnea from baseline after the intervention and was categorized as short-term if the assessment was done from the 1st day until the 30th day; or long-term if the assessment was at 6 to 9 months after the intervention. The secondary outcomes were chest pain, quality of life, control of effusions, length of stay, complications, and mortality between each group.

The improvement in chest pain was scored by the studies using the Modified Borg Scale (MBS) and the Visual Analogue Scale (VAS). The improvement in the quality of life (QoL) was measured either using the QLQ-30 or the EQ5D questionnaires. Control of effusion was measured by the number of patients or events with failed pleurodesis or recurrence of pleural effusions needing additional intervention. The length of stay in the hospital was measured by days. All complications of both palliative arms like cellulitis, empyema, loculations, hemothorax, bleeding, tumor seeding and pneumothorax were tallied and a subgroup for empyema was analyzed. Lastly, studies that indicated the mean survival in months were also measured.

Review Manager version 5.3 was used to analyze the data. All data were analyzed either as relative risks, mean differences, or as continuous variables, as appropriate, with a confidence interval of 95%. Calculations based on a study by Hozo et al[6] were done when the median and interquartile range is being stipulated in the studies so an estimate of the mean and standard deviation can be derived.

RESULTS

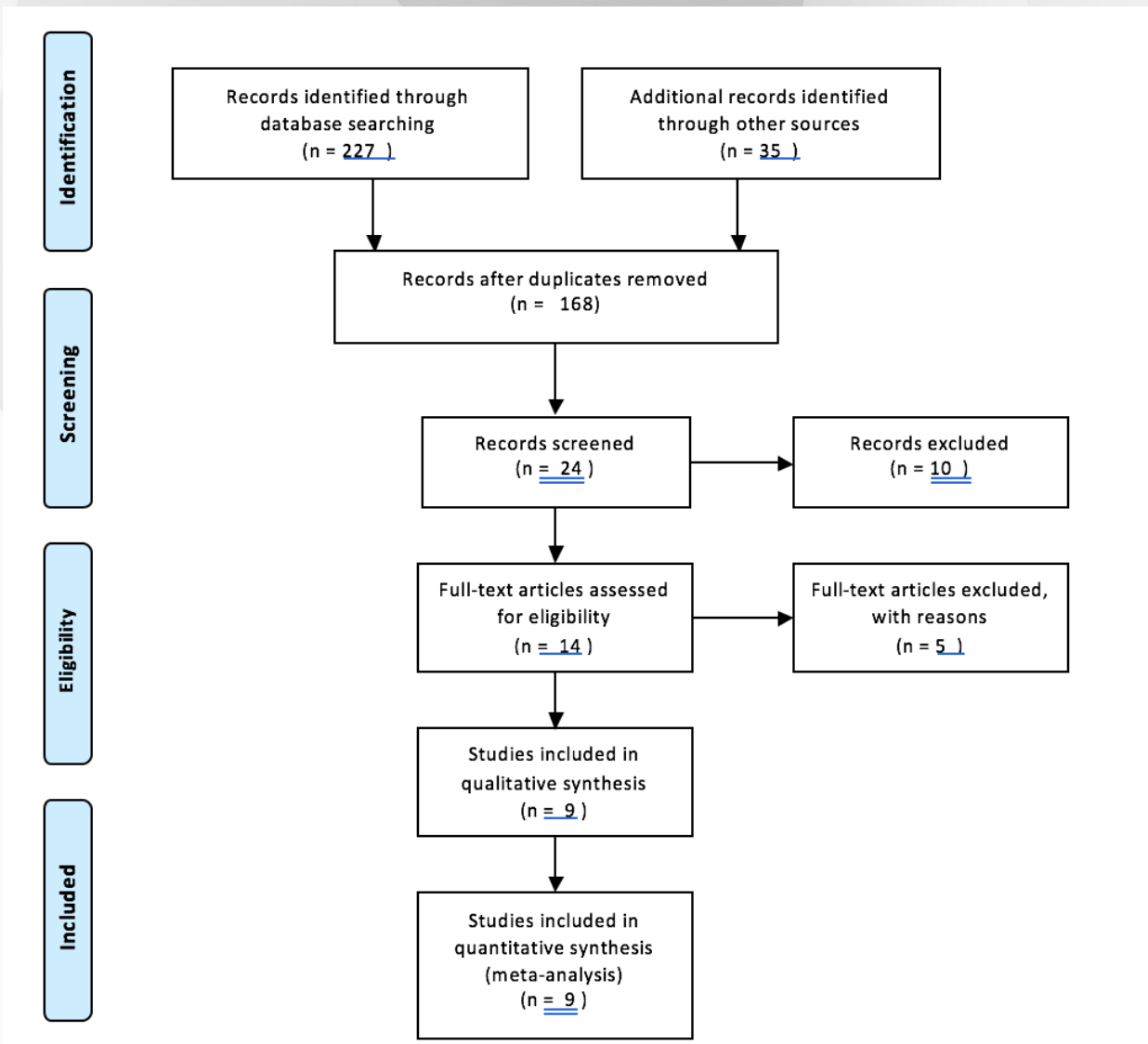
Based on the search criteria, 24 studies were reviewed for inclusion. However, 15 studies were not included due to one or more of the following reasons: 2 studies were not written in English, 3 studies analyzed only the cost of treatment, 7 studies were reviews and editorials, and the remaining studies were abstracts. Nine studies were included, with a total population of

1,333 patients. A total of 691 patients underwent IPC insertion and 652 patients underwent pleurodesis using talc or doxycycline (Figure 1).

Of the nine studies included, four studies were randomized controlled trials, two of which were done in multiple centers. There are two prospective cohort studies, with one study done in multiple centers. Four studies had a retrospective cohort design (Table 1).

Three studies measured the dyspnea or breathlessness of patients after palliative procedures were done.[8-10] Patients who underwent pleurodesis had a tendency towards worsening of dyspnea compared with baseline. Figure 2 below showed that IPC insertion was 38% less likely to lead to dyspneic events after the procedure, but this was not statistically significant (RR 0.62; 95% CI 0.31, 1.27). There

Figure 1. PRISMA 2009[7] Flow Diagram



was no heterogeneity across studies (I^2=0%, p=0.46).

Two studies followed the patients beyond 6 months post-procedure.[9,10] Analysis showed that patients who underwent pleural catheterization are less likely to have dyspneic events by 22% (RR 0.78; 95% CI 0.53, 1.14) than those who underwent pleurodesis, although the difference was not statistically significant. There was no heterogeneity across studies (I^2=0%, p=0.26).

Six studies compared the length of hospital stay associated with each treatment.[9-14] Patients who had IPC insertion stayed 3.83 fewer days (95% CI -5.83, -1.83) in the hospital than those who had pleurodesis (Figure 4). However, study heterogeneity was significant, with an I^2 of 90% (p<0.0001).

Two studies compared effusion-related hospital days between treatments.[10,14] Patients who had IPC insertion had 4.83 fewer effusion-related hospital days (95% CI -8.99, -0.66) than those who had pleurodesis (Figure 4). However, study heterogeneity was significant (I^2=90%; p<0.0001).

All nine studies monitored for recurrence of pleural effusion and loculations after the interventions.[8-17] Those needing re-interventions or procedures was counted as an event. Figure 6 shows a significant 49% reduction in the risk of recurrent effusion or loculations requiring compared with those who had pleurodesis (RR 0.51; CI 95%, 0.34, 0.77). Furthermore, there was no heterogeneity between studies (I^2=27%, p=0.21).

Three studies evaluated quality of life.[9,13,14] Those who had pleurodesis had a non-significant improvement in quality of life with a mean difference of 2.02 points (CI 95% -5.41, 9.45). There was significant heterogeneity (I^2=92%; p<0.001) (Figure 7)

All studies evaluated the total rate of complication events associated with each intervention.[8-17] There was a non-significant decrease in the rate of complications IPC compared with pleurodesis (RR 0.78; CI 95%

Figure 2. Effect of indwelling pleural catheterization vs pleurodesis on short-term dyspnea

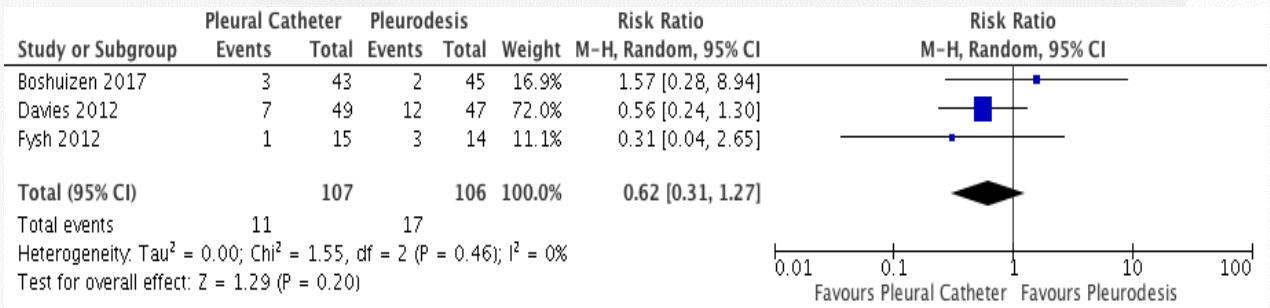


Figure 3. Effect of indwelling pleural catheterization vs pleurodesis on long-term dyspnea

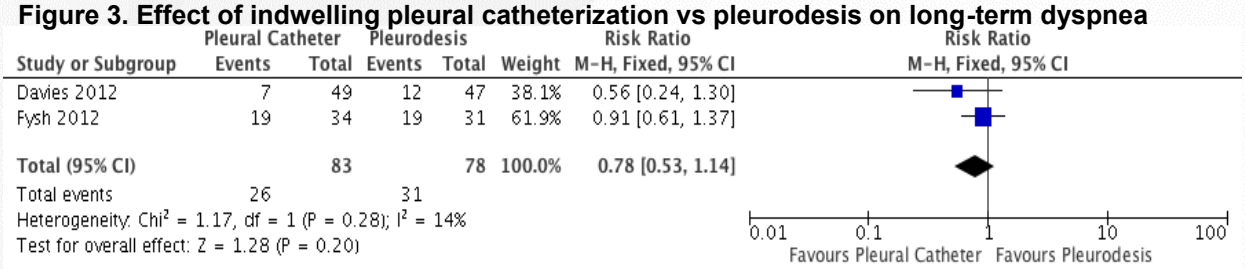


Figure 4. Effect of indwelling pleural catheterization vs pleurodesis on length of stay

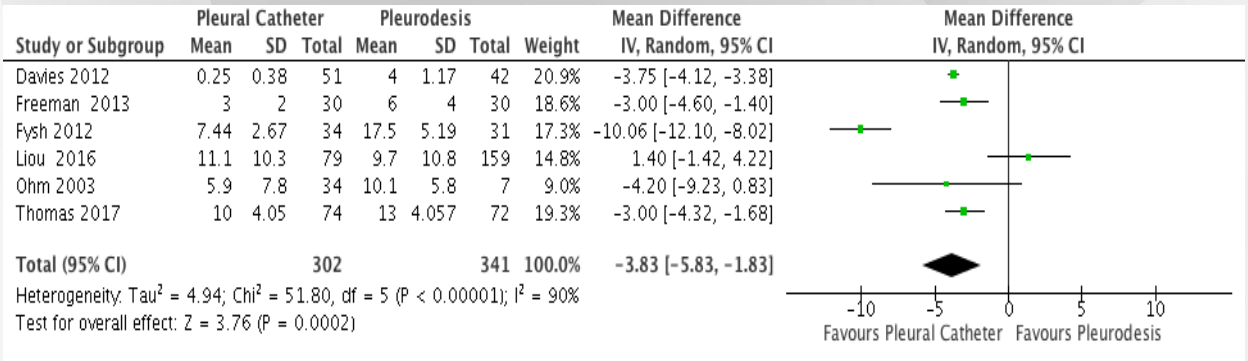


Figure 5. Effect of indwelling pleural catheterization vs pleurodesis on effusion-related hospital days

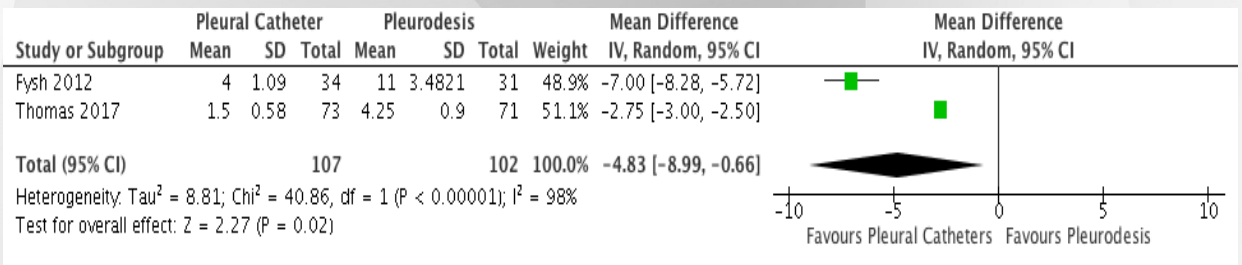
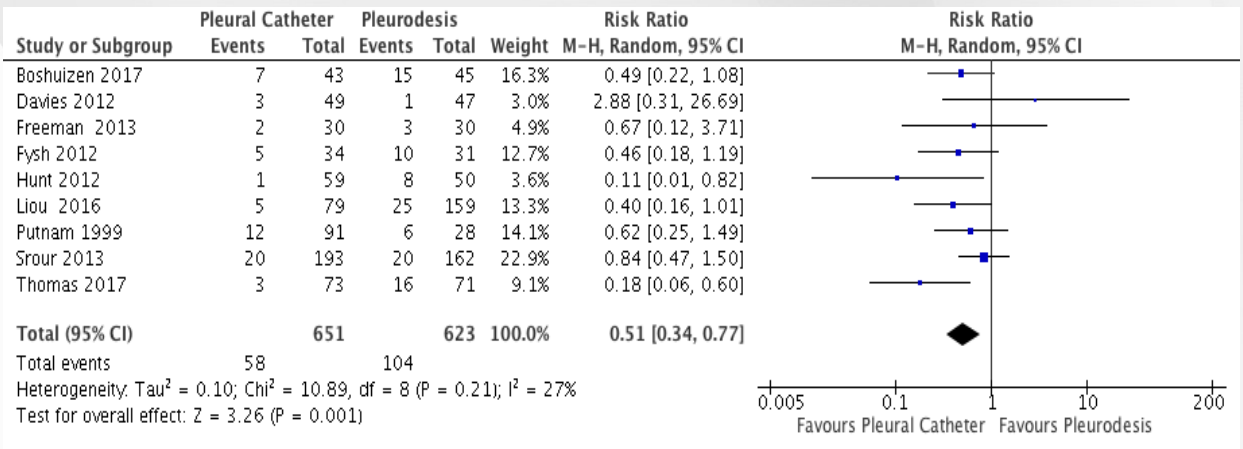


Figure 6. Effect of indwelling pleural catheterization vs pleurodesis on control of effusion



0.35, 1.46) (Figure 8). There was significant study heterogeneity (I^2=72%; p<0.001).

Six studies specifically reported the rates of empyema.[8-10,14,16,17] Pleurodesis was associated with a non-significant decrease in the rate of empyema compared with (Figure 9). There was no study heterogeneity.

Three studies reported the rate of chest pain after intervention.[8,10,14\] There was minimal difference in the occurrence of chest pain after the procedure (RR 1.05; 95% CI 0.42, 2.59) and no heterogeneity (Figure 10).

Three studies reported overall survival.[8,9,11] There was no significant difference in terms of

Figure 7. Effect of indwelling pleural catheterization vs pleurodesis on quality of life

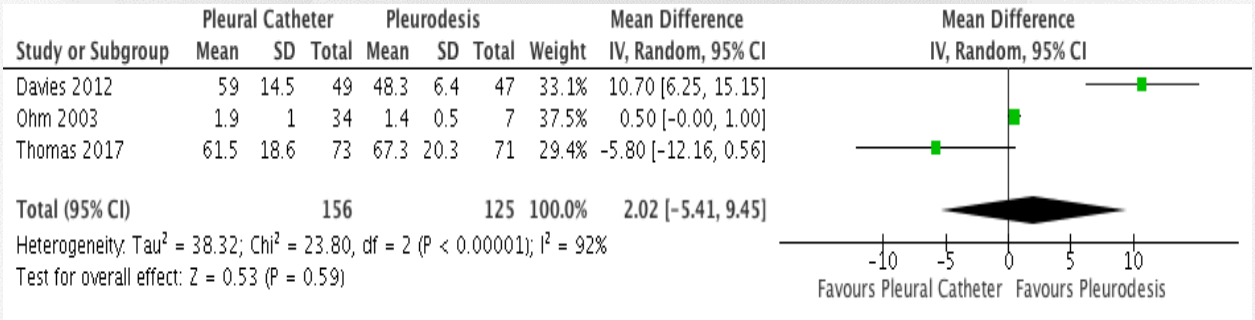


Figure 8. Effect of indwelling pleural catheterization vs pleurodesis on total complications events

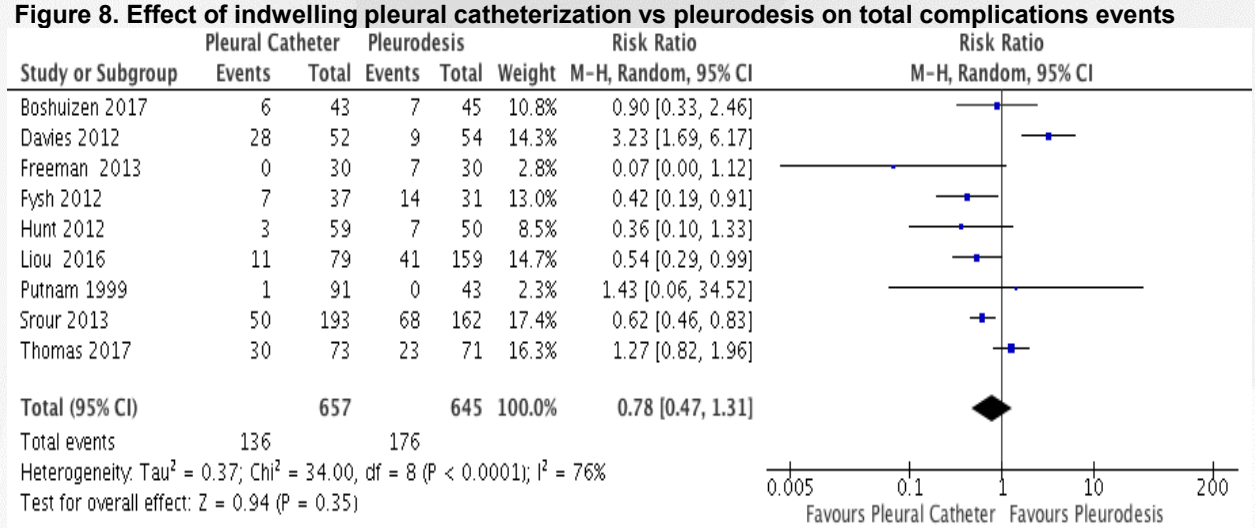
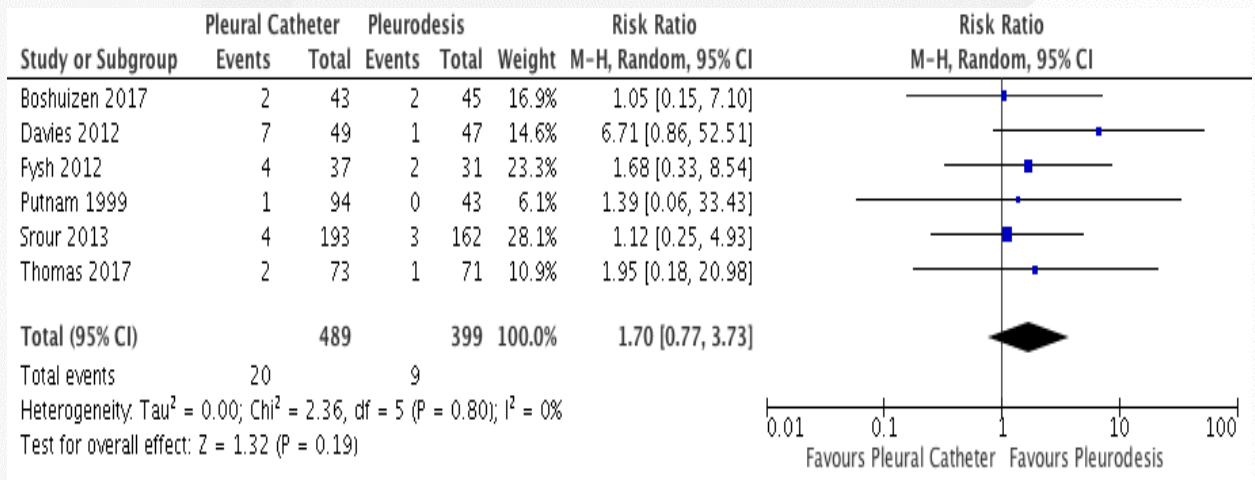


Figure 9. Effect of indwelling pleural catheterization vs pleurodesis on the occurrence of empyema



survival between the patients who underwent IPC insertion and pleurodesis (Figure 11). There was significant heterogeneity.

DISCUSSION

MPE brings unpleasant symptoms for the patient, such as dyspnea and chest pain. These symptoms affect the patient's quality of life and activities of daily living. MPE tends to recur over time. Therapeutic interventions must be done, such as IPC insertion or administration of a sclerosing agent to prevent recurrence. Each procedure has their inherent advantages and disadvantages.

This review showed that the length of hospital stay was significantly shortened in patients who underwent IPC insertion compared with those who underwent pleurodesis. Further analysis showed that IPC was associated with fewer effusion-related hospital days compared with pleurodesis. This finding suggests that with IPC, hospital costs can be minimized, and immunocompromised patients can have a reduced risk of nosocomial infections.

Control of effusion significantly favored IPC as fewer loculations and recurrent pleural effusions that required re-intervention occurred. IPC also tended to have lower rates of dyspnea, both short-term and long-term, and complication events compared with pleurodesis—although the differences were not statistically significant. Pleurodesis, on the other hand, had a non-significant improvement in quality of life and non-significant reductions in the rates of empyema compared with pleurodesis. The level of chest pain and the survival of patients on both groups were similar.

While this meta-analysis showed varying results in terms of benefit in outcomes, such results could still be used to help physicians and patients choose the most appropriate therapeutic intervention for MPE.

Figure 10. Effect of indwelling pleural catheterization vs pleurodesis on chest pain post-procedure

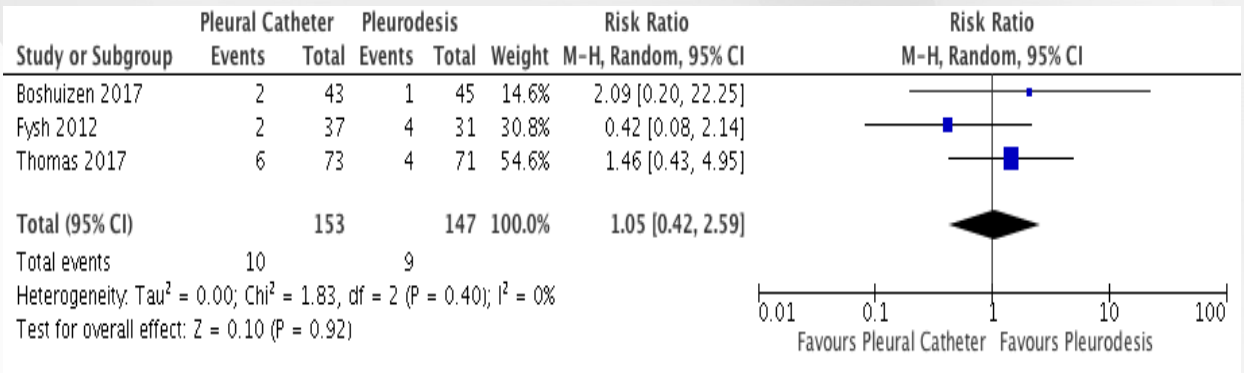
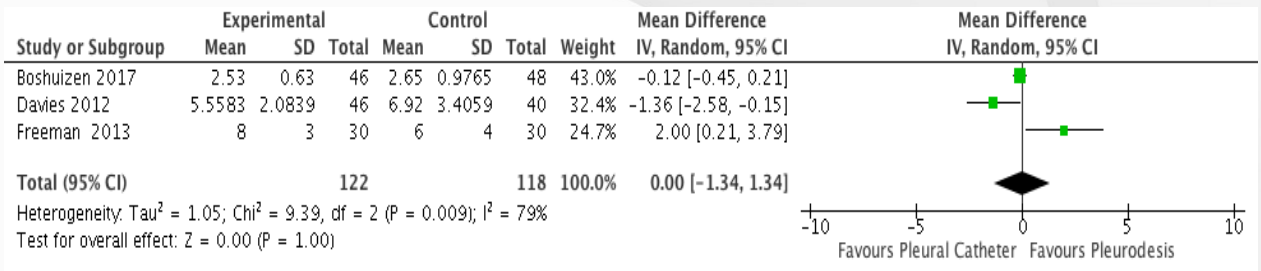


Figure 11. Effect of indwelling pleural catheterization vs pleurodesis on survival (months)



The studies that were reviewed were good-quality randomized controlled trials, prospective cohort, and retrospective cohort studies. However, some studies did not report all relevant outcomes. The researchers recommend that more randomized controlled trials be done to provide a more comprehensive picture of the true benefit-risk ratios of these interventions.

CONCLUSION

Patients who underwent IPC insertion had significantly fewer hospital days and fewer loculations or recurrence of pleural effusion that required re-intervention. There is also a trend towards decreased short-term dyspnea, long-term dyspnea, and complication rates in favor of IPC. However, pleurodesis showed a trend towards a better quality of life and lower rates of empyema.

REFERENCES

1. Chernow B, Sahn SA. Carcinomatous involvement of the pleura: an analysis of 96 patients. Am J Med 1977;63:695-702.
2. Lee YC, Light RW. Pleural effusion: overview. In: Laurent GJ, Shapiro S. editors. Encyclopedia of respiratory diseases. Oxford: Elsevier, 2006:353-8.
3. Ruckdeschel JC. Management of malignant pleural effusions. Semin Oncol 1994;22:58–63
4. Roberts ME, Neville E, Berrisford RG*, et al* Management of a malignant pleural effusion: British Thoracic Society pleural disease guideline 2010 *Thorax* 2010;**65:**ii32-ii
5. Fortin M, Tremblay A. Pleural controversies: indwelling pleural catheter . pleurodesis for malignant pleural effusions. J Thorac Dis 2015;7(6):1052-1057.doi: 10.3978/j.issn.2072-1439.2015.01.51
6. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol 2005; 5: 13.
7. Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009) Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097.
8. Boshuizen RC, Noort V, Burgers JA, et al. A randomized controlled trial comparing indwelling pleural catheters with talc pleurodesis (NVALT-14). Lung Cancer 2017 Jun;108:9-14.
9. Davies HE, Mishra EK, Kahan BC, et al. Effect of an indwelling pleural catheter vs chest tube and talc pleurodesis for relieving dyspnea in patients with malignant pleural effusion: the TIME2 randomized controlled trial. JAMA. 2012;307(22):2383-2389.
10. Fysh ETH, Waterer GW, Kendall PA, et al. Indwelling pleural catheters reduce inpatient days over pleurodesis for malignant pleural effusion. Chest. 2012;142(2):394-400.
11. Freeman RK, Ascioti AJ, Mahidhara RS. A propensitymatched comparison of pleurodesis or tunneled pleural catheter in patients undergoing diagnostic thoracoscopy for malignancy. Ann Thorac Surg 2013;96(1):259–63: discussion 263–4.
12. Liou DZ, Serna-Gallegos D, Chan JL. Survival Difference in Patients with Malignant Pleural Effusions Treated with Pleural Catheter or Talc Pleurodesis. Am Surg, 2016 Oct;82(10):995-999.
13. Ohm C, Park D, et al. Use of an indwelling pleural catheter compared with thorascopic talc pleurodesis in the management of malignant pleural effusions. The American surgeon 2003. 69. 198-202; discussion 202.
14. Thomas R, Fysh ETH, Smith NA, Lee P, Kwan BCH, Yap E, Horwood FC, Piccolo F, Lam DCL, Garske LA, Shrestha R, Kosky C, Read CA, Murray K, Lee YCG. Effect of an Indwelling Pleural Catheter vs Talc Pleurodesis on Hospitalization Days in Patients With Malignant Pleural Effusion. The AMPLE Randomized Clinical Trial. *JAMA.* 2017;318(19):1903–1912.

15. Hunt BM, Farivar AS, Valli`eres E, et al. Thoracoscopic talc versus tunneled pleural catheters for palliation of malignant pleural effusions. Ann Thorac Surg 2012;94:1053–7.
16. Putnam JB Jr, Light RW, Rodriguez RM, et al. A randomized comparison of indwelling pleural catheter and doxycycline pleurodesis in the management of malignant pleural effusions. Cancer. 1999;86(10):1992-1999.
17. N Srour, K Amjadi, AJ Forster, SD Aaron. Management of malignant pleural effusions with indwelling pleural catheters or talc pleurodesis. Can Respir J 2013;20(2):106-110.

PROSPECTIVE STUDY

Screening for Osteoporosis in Male COPD Patients treated with or without Long-term Inhaled Corticosteroid at the Lung Center of the Philippines

Mari Chris H. Mercado, MD, FPCP; Glynna Ong-Cabrera, MD, FPCP, FPCCP
Department of Pulmonary Critical Care and Sleep Medicine, Lung Center of the Philippines

ABSTRACT

Background: Osteoporosis is a significant co-morbidity affecting patients with advanced COPD, wherein inhaled corticosteroid use is a cornerstone of therapy. Its long-term use has been linked to the development of osteoporosis.

Methods: A prospective cross-sectional research design was used to analyze the data. A total of 135 Filipino male COPD patients of the Lung Center of the Philippines Out Patient Department was included in the study. A peripheral bone densitometer utilizing quantitative ultrasound technique was used to obtain the bone density scores of the patients. Based on T-scores obtained using the World Health Organization definition, patients' bone densities were classified as normal (T-score -1.0 and above), osteopenic (T-score between -1.0 and -2.5) and osteoporotic (T-score <-2.5).

Results: Thirty-eight (38) out of the 135 patients were noted to have osteoporosis based on a T-score obtained through the use of a peripheral bone densitometer. Thirty-one of these patients noted to have osteoporosis were on ICS. The prevalence of osteoporosis of COPD patients on inhaled corticosteroids was 29%, which is lower than most countries. The mean age of those with osteoporosis was 69 and 64 for those without osteoporosis. The clinical profile of COPD patients on ICS and not on ICS was similar.

Conclusion: Age was the only factor observed to be associated with osteoporosis (p=0.0076). The use of ICS was not associated with osteoporosis among Filipino male COPD patients. (Please confirm if study included only Filipino patients)

Keywords: Chronic Obstructive Pulmonary Disease, Inhaled corticosteroids, Osteoporosis, T-score

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) remains one of the leading causes of disability and death worldwide. It is a lifestyle-related chronic inflammatory disease and projected to become the third-leading cause of death globally by the year 2020.[1] The Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2017 defines COPD as a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases.[2]

COPD is considered to be a pulmonary disease with many systemic manifestation. One explanation for these systemic effects is the increase in systemic inflammation in COPD, which is suggested by high levels of CRP, oxidative stress and other pro-inflammatory mediators, with effects on bone and other organs.

The 2017 GOLD guideline has also given emphasis on the importance of a comprehensive management of COPD that includes assessment of co-morbidities in these patients. Various co-morbidities reported in COPD patients include cardiovascular diseases, lung cancer, osteoporosis, diabetes, anxiety/depression, and obstructive sleep apnea.[3]

Low mineral bone density (BMD) is frequently seen in COPD patients. Advanced COPD, low body mass index (BMI) and muscle depletion are risk factors for developing a low BMD. Another explanation for the low BMD in these patients, is the low level of physical activity, as they experience dyspnea during exertion.[7] Consequently, these patients have a high risk of developing osteoporosis.[4]

Glucocorticoid use is the most common cause of iatrogenic and secondary osteoporosis. In a meta-analysis, current and prior use of oral corticosteroids was found to be a predictor of the increased risk of fractures.[5,6] The greatest risk of fractures is noted during the first three to six months after beginning steroid therapy, and the risk persists for one year the cessation of corticosteroid use.

For men with chronic lung disease (CLD), osteoporosis is a serious health problem associated with the use of inhaled or oral glucocorticoids, decreased exercise, impaired gonadal hormone production, compromised pulmonary function, and others.[8] Osteoporosis, however, is often under-iagnosed in these patients. The study aimed to screen the prevalence of osteoporosis in Filipino male COPD patients on long-term corticosteroids.

METHOD

The clinical profile and baseline characteristics of the Filipino male COPD patients at the Lung Center of the Philippines seen at the Out-Patient Department were analyzed in this study. A cross-sectional prospective study design was utilized. Filipino male patients aged 40 years and above, diagnosed to have COPD were included in the study. All patients have a pulmonary function test result, confirming the diagnosis of COPD. All patients both on ICS and not on ICS treatment were included in the study. The patients who had a history of recent oral corticosteroid use, who have a history of hypocalcemia from any cause (renal, parathyroid or thyroid disease) were excluded from the study. An identification code was assigned to each patient to maintain confidentiality.

Procedure

We recruited Filipino male COPD patients from OPD of the Lung Center of the Philippines from December 2016 to September 2017. Demographic information from each patient was gathered using a data collection tool. The patient's data included patient's age, co-morbidities such as hypertension, diabetes mellitus, coronary artery disease, hypocalcemia, kidney and parathyroid diseases, smoking history, COPD GOLD Classification, use of oral corticosteroids within the last two weeks, medications used, type of inhaler used, length of ICS use and frequency of exacerbation. Nutritional status with regard to intake of food rich in calcium, intake of calcium supplements and BMI were also noted.

Bone mineral density measurement

We conducted a free bone mineral density measurement on the patients at the COPD clinic of the Lung Center of the Philippines from December 2016 to September 2017. The bone mineral density measurements were performed by a trained technician. Bone mineral density was measured using Omni Sense peripheral bone densitometer. The probe was applied to the distal 1/3 of the forearm and bone mineral density was then measured. The machine utilized a patented axial transmission form of quantitative ultrasound. It measured the velocity of ultrasonic wave (speed of sound) that propagate axially along the distal 1/3 of the radius. The system

utilized the World Health Organization criteria in determining the bone mineral density (ie, T score –1.0 or above for normal, –1.0 and –2.5 for osteopenia and –2.5 or below for osteoporosis.

Statistical analysis

Analysis of data utilized both descriptive and inferential (univariate and multivariate). The clinical profile of the patients was described using measures for central tendency for continuous variables. Normality of the data were assessed using the Shapiro Wilk Test. Pearson Chi-Square Test and Cramer's V test for associated were used to determine which factors of the subjects was significantly associated with osteoporosis.

All factors deemed significant were included in the logistic regression model Adjusted odds ratio was calculated and level of significance was set at 5% and Statistical Package for the Social Science (SPSS) version 20.0 was used to calculate statistics.

Ethical considerations

The Institutional Ethics Review Board (IERB) of the Lung Center reviewed and approved the study protocol in compliance with the ethical principles set in the Declaration of Helsinki. A written letter of confidentiality was obtained by the investigators before data was collected.

RESULTS

A total of 135 patients were included in this study, 107 of the patients were on inhaled corticosteroids. The mean age of the patients was 65.8 years old and the mean smoking history (in pack-years) was 40. 41.6% of these patients had hypertension, 25.5% had DM and 2.9% had coronary artery disease. Additionally, 18.2% of these patients take dairy products and 5.1% were on calcium supplements.

Table 1 shows the clinical profile of these patients. Results showed that the demographic data of the two groups did not differ in all variables compared. Specifically, those who are on ICS have an average age of 66 years, which is not significantly different from the mean age of 63.5 years for patients who are not on ICS. The two groups had the same proportion of hypertension, DM, CAD and renal diseases. Results also showed that the two groups have the same mean bone density and mean BMI. The two groups have the similar GOLD Classification, average smoking history in pack years, annual rate of exacerbation, dietary intake of products high in calcium (milk, dairy products) and intake of calcium supplements. The majority of the patients belonged to GOLD Class B, comprising a total of 89 patients, 67 of which were on ICS while 22 were not on ICS therapy.

Figure 1 shows that 46% of patients use Fluticasone than any other type of inhaler (n=61), 34% use Budesonide (n=45), 8% on SAMA and 6% on LAMA. For those on ICS, most patients reported usual dosage of 320 mcg daily for Budesonide and 500 mcg daily for Fluticasone.

Figure 2 shows that among patient on ICS therapy those on Fluticasone (n=61) treatment had more patients noted to be osteoporotic (n=23) compared to the Budesonide group. Patient receiving LAMA (n=8) had equal percentage of osteopenic and osteoporotic patients (both at 50%). Patients on SAMA (n=12) had the highest percentage of normal T-score at 42%. Patients on combination medications showed that those receiving LAMA + LABA 14% were osteoporotic and 43% were osteopenic. Of the patients on LAMA + LABA + ICS, 33% cases of osteoporosis and 67% were osteopenic.

The prevalence of osteoporosis among male COPD patients on long-term inhaled corticosteroid is 29.0% while for those on not on ICS is 25% (Table 2). It can be inferred that the true prevalence of osteoporosis at 95% confidence interval will range from 21.2% to 38.2% for those on ICS and 12.7% to 43.44% for those not on ICS treatment.

Table 1. Clinical profile of Filipino male COPD Patients seen at the Lung Center of the Philippines Out-patient Department

Characteristic	With ICS (n=107)	Without ICS (n=28)	P-value
Age (years), mean ± SD	66.1 ± 9.1	63.5 ± 12.6	0.2291
Spirometry, mean ± SD	63.5 ± 9.4	63.8 ± 11.5	0.8725
Co-morbidities			
Hypertension	48 (44.9)	8 (28.6)	0.1205
Diabetes	29 (27.1)	6 (21.4)	0.5414
Coronary artery disease	4 (3.7)	0 (0.0)	0.3034
Renal disease	1 (0.9)	0 (0.0)	0.6157
Bone Density, mean ± SD	-1.8 ± 1.3	-1.6 ± 1.8	0.4065
BMI, mean ± SD	20.8 ± 3.8	20.9 ± 3.0	0.9414
GOLD Classification, n, %			
B	67 (62.6)	22 (78.6)	0.2759
C	11 (10.3)	2 (7.1)	
D	29 (27.1)	4 (14.3)	
Smoking Years, mean ± SD	40.2 ± 28.2	36.4 ± 24.9	0.5211
Annual rate of exacerbation, n,%	35 (32.7)	6 (21.4)	0.2496
Nutritional Status (e.g. intake of milk, dairy products and calcium supplements)	23 (21.4)	4 (14.3)	0.3976

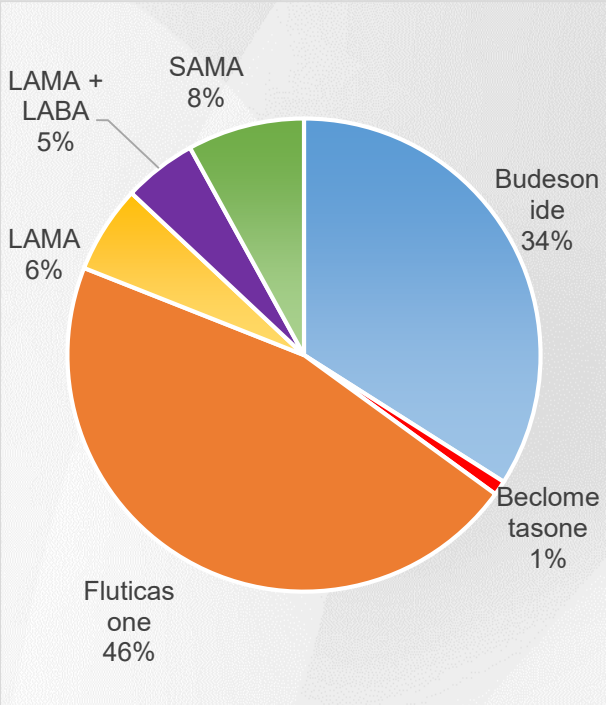
Age was the only significant factor that is associated with osteoporosis among these patients (Table 3). Those with osteoporosis were significantly older at 69 years compared to those who do not have osteoporosis at 64 years.

DISCUSSION

Our results showed that the prevalence of osteoporosis in COPD patients on long-term inhaled corticosteroid was 29.0% and that increasing age was a significant factor observed to have an association with osteoporosis. In comparison with the prevalence of osteoporosis with other countries, prevalence in the Philippines was lower. In a study by Rittayamai the prevalence of osteoporosis in Thai COPD patients was noted at 31.4%. [9] In Brazil, a similar study by Silva et al reported the prevalence of osteoporosis was at 42% [10]. The lower prevalence in the Philippines could probably be accounted for by the fewer studies done in the Philippines regarding osteoporosis among Filipino subjects. In a study done by Mendoza et al., of the 184 patients, 40.2% and 29.9% have osteopenia and osteoporosis. Sixteen (21.6%) and 18 (32.1%) osteopenic and osteoporotic men have fragility hip, spine, or forearm fractures. Men aged 50 to 69 years have the same risk of osteoporosis and fractures as those ≥70 years.[11]

In our study, it was demonstrated that age

Figure 1. Distribution of patients according to type of inhaler used



as a significant factor associated with osteoporosis. Nuttapol et al reported that the mean age for Thai COPD patients were 74.7 and 71 years, for those with osteoporosis and those without osteoporosis, respectively, which are slightly higher than those reported in our study (69.3 and 64 years, respectively). Several other risk factors have been studied in the past which had been shown to have an association with osteoporosis. These include more severe COPD (GOLD C and D), low BMI, level of physical activity, and treatment with corticosteroids. This was noted in the study Graat-Verboom et. al in a systematic review of 13 studies involving 775 COPD patients.[12]

Smoking history, mean BMI and years of ICS use were almost comparable for those with osteoporosis and without osteoporosis. These is in contrast to previous studies with noted association of low BMI and ICS use. The use of ICS observed more non-osteoporotic patients It is believed that circulating levels of osteocalcin indirectly reflect new bone formation. Results of

Figure 2. Comparison of bone mineral density of patients with corresponding type of inhaler used

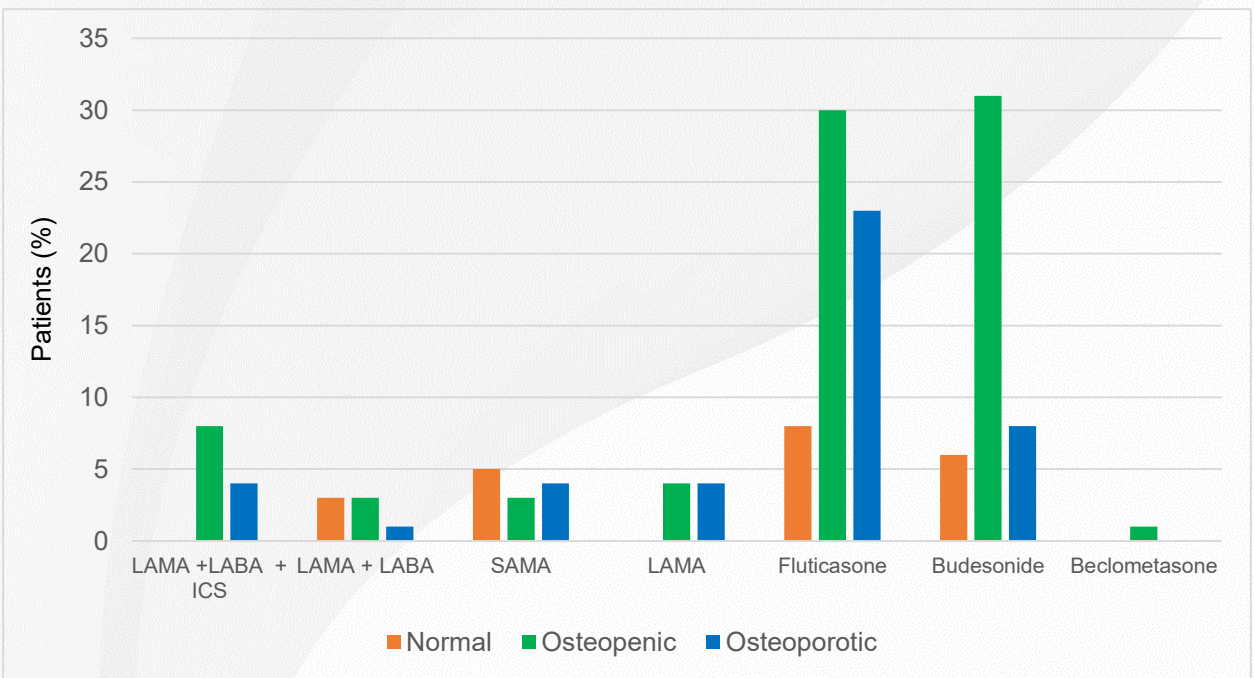


Table 2. Prevalence of Osteoporosis among Filipino male COPD Patients at the Lung Center of the Philippines Out-patient Department

Patients	N	Osteoporotics	Prevalence	95% CI
ICS Users	107	31	29%	21.2% to 38.2%
Non-ICS Users	28	7	25%	12.7% to 43.44%

a study done by Meeran et al showed that both oral prednisone (15 mg OD x 1 week) and inhaled beclomethasone (500 mcg BID x 1 week) caused a significant reduction in serum osteocalcin levels. (11.8±-1.1 ng/mL to 6.9± ng/mL and 11.6± 0.6 ng/mL to 9.6± 0.6 ng/mL, respectively). Though the study is not a direct comparison, osteocalcin levels were substantially lower in asthma/COPD patients who had taken corticosteroids as compared to the baseline values of normal volunteers who participated in the study.[13]

Several studies indicate a dose-dependent association between ICS use and osteoporosis in COPD patients.[14,15] However, a randomized controlled trial showed that long-term use of low-dose ICS protects the COPD patients from developing osteoporosis.[16] This is secondary to the decrease in the inflammation in the lungs, which decreases the systemic spillover of ICS. However, at higher doses, ICS may gain access to the systemic circulation and can produce systemic side effects.[17]

Osteoporosis is a silent disease unless it is complicated by fractures. Patients with osteoporosis are at an increased risk of fractures, particularly fragility fractures. Fragility fractures are caused by injury that would be insufficient to break a normal bone. The impact of osteoporosis-induced fractures in COPD is enormous. [8] The most common type of osteoporosis-inducted fracture is the vertebral compression fractures (VCFs). VCFs are associated with back pain and kyphosis. Kyphosis can cause loss of height, resulting in impaired lung function. Every single VCF decreased the vital capacity by % and the lung function impairment is most notable when kyphotic angle is more than 55°.[19] Given this burden, we recommend routine or annual screening for osteoporosis in those with advanced age, regardless of ICS use, using the DEXA, the gold standard for diagnosing osteoporosis for future studies on osteoporosis. We also recommend using an Osteoporosis Risk Assessment questionnaire to determine presence of factors that may potentially confound the results of bone mineral density.

The following are the limitations of our study: First the sample size was not met due to the limited availability of the machine used. Second, other potential factors in the screening of patients with osteoporosis such as vitamin D deficiency, hypogonadism, patient's level of physical activity were not taken into consideration in this study.

CONCLUSION

The prevalence of osteoporosis in patients on ICS was 29%, which is lower in comparison with previous studies done in other countries, particularly Thailand and Brazil. The mean age for patients with osteoporosis was 69.3 and 64.1 for those without osteoporosis. Among the variables, only age was noted to have an association with osteoporosis. Other factors like smoking history, Diabetes Mellitus, more severe GOLD classification, low BMI and ICS use, which have been noted in previous studies to have an association with osteoporosis were not observed in this study.

Disclosure of Conflict of Interest: The investigators have no conflict of interest.

Table 3. Factors Related to Occurrence of Osteoporosis among Filipino male COPD patients at the Lung Center of the Philippines Out-patient Department

Variables	Osteoporosis		OR	95% OR	p value
	Yes (n=38)	No (n=97)			
Age, mean ± SD	69.3 ± 10.5	64.1 ± 9.3	1.06	1.02 to 1.11	0.0076*
Smoking History, mean ± SD	45.2± 34.1	37.1 ± 24.3	1.01	0.997 to 1.02	0.1292
Hypertension, n,%	15 (39.5)	41 (42.3)	0.89	0.41 to 1.91	0.7670
Diabetes Mellitus, n, %	6 (15.8)	29 (29.9)	0.44	0.17 to 1.16	0.0983
Kidney Disease, n,%	0 (0.0)	1 (1.0)	0	-	0.9981
Coronary Artery Disease, n,%	2 (5.3)	2 (2.1)	2.64	0.36 to 19.44	0.3409
Intake of Dairy products, n,%	7 (18.4)	18 (18.6)	0.99	0.38 to 2.61	0.9854
Intake of Calcium suppl, n,%	2 (5.3)	4 (4.1)	1.29	0.23 to 7.36	0.7732
FEV1/FVC, mean ± SD	63.0± 8.4	63.8 ± 10.3	0.99	0.96 to 1.03	0.6934
Gold Classification, n, % B C D	 22 (57.9) 5 (13.2) 11 (28.9)	 67 (69.1) 8 (8.2) 22 (22.7)	 - 1.9 1.52	 - 0.56 to 6.43 0.64 to 3.63	 - 0.2998 0.3431
ICS use overall, n, % Budesonide Fluticasone Beclomethasone	31 (81.6) 8 (21.1) 23 (60.5) 0	76 (78.4) 37 (38.1) 38 (39.2) 1 (1.0)	1.22 0.45 2.0096 -	0.47 to 3.17 0.18 to 1.03 0.94 to 4.31 -	0.6777 0.0573 0.0726 0.9981
LAMA	8 (21.1)	14 (14.4)	1.58	0.60 to 4.14	0.3516
SAMA	4 (10.5)	8 (11.3)	0.92	0.27 to 3.09	0.8924
LABA + LAMA	1 (2.6)	6 (6.2)	0.41	0.05 to 3.52	0.4165
Years of ICS use, mean ± SD	4.7± 2.5	5.0 ± 2.6	0.95	0.82 to 1.10	0.4898
Height (cm), mean ± SD	163.2 ± 6.5	164.4 ± 6.1	0.97	0.91 to 1.03	0.3145
Weight (kg), mean ± SD	54.9 ± 9.2	56.6 ± 10.9	0.98	0.95 to 1.02	0.4168
BMI, mean ± SD	20.6 ± 3.3	20.9 ± 3.8	0.98	0.88 to 1.09	0.6724
Underweight, n, %	11 (28.9)	26 (26.8)	1.11	0.48 to 2.56	0.8018
Annual rate of exacerbation, n, %	14 (36.8)	27 (27.8)	1.51	0.68 to 3.35	0.3076

REFERENCES

1. Sarkar, M. and Bhardwaj, R. et al., Osteoporosis in Chronic Obstructive Pulmonary Disease. Clinical Medicine Insights: Circulatory, Respiratory and Pulmonary Medicine. 2015:9 5-21.
2. Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease. 2017.
3. Choudhury, G. et al., Comorbidities and Systemic Effects of Chronic Obstructive Pulmonary Disease. Clinical Chest Medicine. 2014;35 (1); 101-30
4. Jorgensen, N.R. and P. Schwaz, et al., The Prevalence of Osteoporosis in Patients with Chronic Obstructive Pulmonary Disease – A cross-sectional Study. Respiratory Medicine. 2006.
5. Kanis, JA, Johansson, H. and Oden A. et al. A meta-analysis of prior corticosteroid use and fracture risk. Journal of Bone Mineral Respirology. 2004;19(6);893-9.
6. Van Staa TP, Leukfens HG and Cooper. The epidemiology of corticosteroid-induced osteoporosis: a meta-analysis. Osteoporosis International. 2002;13(10):777-87.
7. Vrieze, A., de Greef, M.H.G. and P.J.Wyskstra. Low mineral bone density in COPD patients related to worse lung function, low weight and decresed fat free mass. Osteoporosis International. 2007.18:1197-1202.
8. Graat-Verboom, M.D. et al. Current Status of Research on Osteoporosis in COPD: a systematic review. European Respiratory Journal. 2009.
9. Rittayamai, Nuttapol, M.D, et al., Prevalence of Osteoporosis and Osteopenia in Thai COPD patients. J Med Assoc Thai 2012; 95(8):1021-7.
10. Silva, D.R. et al. Osteoporosis Prevalence and Associated Factors in Patients with COPD: A Cross-Sectional Study. Respiratory Care. 2011.
11. Mendoza E et. al., Osteoporosis and Prevalent Fractures among Adult Filipino Men Screened for Bone Mineral Density at a Tertiary Hospital.
12. Graat-Verboom L, et al., Current Status of Research on Osteoporosis in COPD: a systematic review. European Respiratory Journal. 2009. 34(1):209-18.
13. Meeran et al, Oral and inhaled corticosteroids reduce bone formation as shown by plasma osteocalcin levels. Am J Respir Critical Care Med 1995; 151:333-36.
14. Loke, Y.K. et al, Risk of fractures with inhaled corticosteroid use in chronic obstructive pulmonary disease: a systematic review and meta-analysis of randomized controlled trials and observational studies. Thorax. 2011;66(8):699-708.
15. Lee, T.A. Fracture risk associated with inhaled corticosteroid use in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2004;169(7):855-9.
16. Mathioudakis AG, Amanetopoulou SG, Gialmanidis IP, et al. Impact of long- term treatment with low-dose inhaled corticosteroids on the bone mineral density of chronic obstructive pulmonary disease patients: aggravating or beneficial? *Respirology*. 2013;18(1):147–53.
17. Man SF, Sin DD. inning bone and inhaled corticosteroid in COPD: what to do until there is definitive proof? *Chest*. 2009;136(6):1448–9.
18. Goch, M., et. al., Surgeons save bones: an algorithm for orthopedic surgeons managing secondary fracture prevention. Arch Orthop Trauma Surgery. 2013:133:1101-8.
19. Harrison, R.A. et. al., Osteoporosis-related kyphosis and impairments in pulmonary function: a systematic review. J Bone Miner Res. 2007;22:447-57.
20. Buist, AS Vollmer WM, Sullivan SD, Weiss KB, Lee TA et. al., The Burden of Obstructive Lung Disease Initiative (BOLD); rationale and design. COPD: Journal of Chronic Obstructive Pulmonary Disease. 2005.

NOTES

The Philippine Journal of Chest Diseases
An official publication of:
Philippine College of Chest Physicians
84-A Malakas St., Pinyahan, Quezon City, Philippines
Email: secretariat@philchest.org
Phone: (+632) 924 9204