PHILIPPINE JOURNAL OF CHEST DISEASES

Volume 21 Number 2
May-August 2023

IN THIS ISSUE

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: Editor-in-Chief, Philippine Journal of Chest Diseases, 84-A Malakas St., Pinyahan, Quezon City. Email: secretariat@philchest.org. Phone: (+632) 8924 9204.

INSTRUCTIONS TO AUTHORS

The Philippine Journal of Chest Diseases, the official publication of the Philippine College of Chest Physicians (PCCP), 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, systematic reviews and meta-analyses), original investigations, case reports, clinical practice guidelines, editorials, or letters to the editor.

Manuscripts of prospective and retrospective studies must include appropriate institutional review board and ethical approval or exemption statements.

Manuscripts will be subjected to editorial review and modification. 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the property of the Philippine College of Chest Physicians and are published with the understanding that they are not for publication elsewhere without approval.

Author Responsibility

1. Submission of a manuscript implies that: (a) the research work or article has not been published nor under review for publication in any other scientific journals (local or international); (b) its publication has been approved by all co-authors (if any); and (c) if and when it is accepted for publication, all authors grant copyright ownership to PCCP. Publication as an abstract during scientific meeting proceedings is not considered prior publication and can be submitted for publication.
2. The author who submits the manuscript shall be the Corresponding Author and will be responsible for corresponding with the Editorial Staff in all matters related to the manuscript. The Corresponding Author has the responsibility in the content of the final manuscript for publication, including changes suggested by the Editorial Staff or reviewers of the manuscript.
3. If copyrighted/published material (e.g. tables and figures) are reproduced in the manuscript, the author(s) must obtain written permission from the copyright holder (usually the publisher) for republication in the PJCD. Evidence that permission has been granted should be included when submitting the manuscript. The PCCP shall not be legally responsible should there be any claims for compensation.

Manuscript Preparation

1. General instructions - Write using the first person, active voice for example, “We analyzed data,” not “Data were analyzed” except for the abstract and acknowledgments or disclaimers which should be written in the third person, active voice – “The authors analyzed,” “The authors wish to thank.” 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 (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.
2. Margins and paper size - 1 inch margins on all sides and format for 8 ½ x 11 paper.
3. Mode of submission - All manuscripts must be submitted electronically to secretariat@philchest.org.
4. Font - The font must be in Times New

Roman. All main headings must be bold-faced, size 12. Subheadings and content must be in font size 11.

5. Format
   A. Title page - must contain the title of the manuscript, authors' names and contact details, and the abstract.
      - The manuscript's full title which should provide sufficient information regarding the contents of the manuscript. The title of the manuscript must be in bold, size 18, Times New Roman.
      - The title must be followed by the full names of the authors, institutional affiliation, and the contact details (preferably email) of the corresponding author.
      - After the names, state if the paper has been presented in any convention and whether any awards have been conferred.
      - Abstract - should not be longer than 250 words. It should contain the **background, objective/s, methods, results, conclusion, and three keywords under which the article can be indexed.** Only findings restricted to the study should be mentioned in the abstract and must include the year of the study.

   B. Headings
      - The order of the main headings is: Introduction, Objective/s, Methods, Results, Discussion, Limitations, Conclusions, Recommendations, References. Font must be bold-faced, size 12.
      - Subheadings and content must be in font size 11.

6. Tables
   A. 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 * † ‡ § ¶.
   B. Table titles must be placed on top of the table, using font size 11. Headings within the table must be bold-faced. Columns should be clearly labeled, including unit of measure.
   C. Explanatory notes or legends should be written at bottom of the table or figure. All abbreviations should also be explained.
   D. Footnotes may be placed at the bottom of the table if there is a need to make the table understandable that will not easily fit into the table title or data cells. Table footnotes must be in font size 8 and single-spaced.

7. Figures
   A. 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.
   B. Figures are acceptable as Word, PowerPoint or Excel 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.
   C. Figures must have appropriate labels. Figure labels must be placed at the bottom of the table, using font size 11.
   D. 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.

8. Supplementary Material
   A. Supporting material that cannot be included in the publication of the manuscript for reasons of space but is complementary and directly relevant to the manuscript content, can be made available online as supplementary material. These may include additional figures or tables, data sets or detailed methods.
   B. The supplementary material should be referred to in the main manuscript for example as "See Supplementary Table 1" or "See Supplementary Figure 1". It cannot be modified or replaced after the manuscript has been published.

9. References
   A. 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 as superscript.
   B. For the names of authors, start with author family name followed by abbreviated first/second names (e.g. Rosales RL). No marks should be placed between family name
   C. and abbreviated first name. A comma separates between author names till the last author. Do not place "and" before the last author.
   D. Journal article references must contain, in order, the following:
      - Authors - List all when there are six authors. In the case of more than six authors, list the first three authors followed by "et al."
      - Title of the article - sentence case, no quotation marks
      - Publication source – the journal name should be italicized and abbreviated according to Index Medicus.
      - Year of publication
      - Volume number
      - Issue number
      - Page number (inclusive)

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

TABLE OF CONTENTS

— Volume 21 No. 2 May to August 2023 —

—ORIGINAL RESEARCH—

—META-ANALYSIS—

—CASE REPORT—

EDITORIAL

Miriam Y. Lalas, MD, FPCCP
Editor-in-Chief

"Moving to new frontiers"

This issue marks the close of a chapter in the history of the Journal. After this issue, our readers will cease seeing the Journal in printed format as we shift to purely digital publication.

Buoyed by factors such as the desire to bring our studies, especially pandemic researches, to the international community; the advocacy of the College to help mitigate climate change by reducing our carbon footprint; and the high cost of print publication, we made the decision to finally go digital.

Going digital shall also allow us to maximize the impact of open access. Open access publication is defined by the absence of any financial, legal, or technical barriers to access research, thereby allowing anyone to "read, download, copy, distribute, print, search for and within the information, or use it in education or in any other way within the legal agreements."[1] While open access may also be available in print format, the medium is expectedly restricted in its capacity for visibility, discoverability, and wide dissemination.

As the last part of our digitalization efforts, starting with our next issue, readers may now access PJCD via our online publishing platform. This transition ensures that our Journal becomes not only a repository of knowledge but a searchable, interactive hub for the scientific community, offering a myriad of benefits.

Coming off the heels of the pandemic, we are ever-cognizant of the importance of knowledge in our work as healthcare professionals. The research process should not end with knowing the answer to a question; we pass on those answers, those benefits, so that other people may partake of that knowledge and information may progress, ultimately benefiting the society – that is the value of publication. This digital leap exemplifies our dedication to advancing the body of knowledge, no matter how modest our contribution may be.

We would like to thank the previous editors of the Journal for their work in sustaining its oper-

ations for the past years that finally enabled this transformation. The work of digitalization has not been easy and there was the attendant task of revisiting our editorial policies and processes to ensure that we are moving forward efficiently, responsibly, and in abidance with the standards for scholarly publication.

We have tremendous work ahead of us. But with the full support of the PCCP Board and the dedication of our peer reviewers, we know that that the task is not insurmountable. We are excited for you to finally see the new and improved PJCD, now fully online.

References:

[1]Open Access.nl. https://www.openaccess.nl/en/what-is-open-access. Accessed December 11, 2023.

Philippine Journal of Chest Diseases

Original Research

Effect of Virtual Pulmonary Rehabilitation Among Patients with Chronic Obstructive Pulmonary Disease

Aldrin John S. Almario, MD, and Glynna Ong-Cabrera, MD, FPCCP*

Lung Center of the Philippines, Quezon City

Corresponding Author: *Dr. Aldrin Almario (asalmario@gmail.com)*

PAPER PRESENTED IN THE FOLLOWING FORUM: Philippine College of Chest Physicians (PCCP) Research 41st Annual Chest Convention's E-Poster Presentation and Philippine College of Physicians 52nd Annual Congress' virtual abstract presentation under the Post Residency Category (Top 10 Finalist)

ABSTRACT

BACKGROUND: Pulmonary rehabilitation (PR) is a recognized management among COPD patients with persistent symptoms despite optimal use of pharmacologic therapy. Virtual PR is an innovative adjunct in the remote delivery of the intervention especially during a pandemic.

OBJECTIVES: To determine the effect of virtual PR among patients with chronic obstructive pulmonary disease (COPD) enrolled in the Lung Center of the Philippines (LCP) COPD Support Group.

METHODS: We conducted an ambispective cohort study employing chart review of COPD patients who participated in the virtual PR from November 2020 to October 2021. Outcome measures specifically exercise capacity, functional performance, perceived breathlessness, and quality of life were evaluated pre- and post-virtual PR. These parameters were assessed using the 6 Minute Walk Test (6MWT), Modified Medical Research Council (mMRC) dyspnea scale, Modified Borg's Scale (MBS), and COPD Assessment Test (CAT).

RESULTS: A total of 24 patient charts were included and reviewed. The average age of patients was 65.4+8.6 years. Majority of the patients were male and former smokers with ->10 pack years' smoking history. For the exercise capacity, there was a significant increase between the average pre- and post-virtual PR distance during the 6MWT; with an average increase of 139.6+220.1m (p-value 0.069). There was also significant improvement between the average pre- and post-virtual PR mMRC score: 2.2 +1.1 to 1.5+1.0 (p-value <0.001); MBS score: 1.7+1.1 to 0.8+0.8 (p-value <0.001); and, CAT score: 13.3+7.6 to 9.8+6.6 (p-value <0.001).

CONCLUSION: Virtual PR improved exercise capacity, functional performance, perceived breathlessness, and quality of life of COPD patients enrolled in the LCP COPD Support Group.

KEYWORDS: *Telerehabilitation, Virtual Pulmonary Rehabilitation, COPD*

**This is the corrected online version of the article entitled "The Predictive Value of SpO_2/FiO_2 (SF) Ratio on the Chest CT Severity Score (CTSS) of Adult COVID-19 Patients Admitted in Chinese General Hospital and Medical Center" published in print in the Philippine Journal of Chest Diseases Vol. 21 No. 2 in January 2024. The Table of Contents reflects the corrections made to the author name as well.*

INTRODUCTION

Pulmonary rehabilitation (PR) is a key management strategy among persons with chronic respiratory diseases such as chronic obstructive pulmonary disease (COPD). It is a comprehensive therapeutic management, usually composed of exercise training, education, and self-management intervention, which aims to improve exercise capacity, dyspnea, health status, and psychological well-being. Pulmonary rehabilitation is also designed to promote long-term adherence to health-enhancing behaviors.[1,2]

Technology-assisted rehabilitation or telehealth is recognized as an innovative adjunct to PR that can be done remotely. The access to pulmonary rehabilitation programs, including the program being offered in the Lung Center of the Philippines, has been limited by the COVID-19 pandemic due to safety reasons. With this limitation brought by the pandemic, the British Thoracic Society recommends telerehabilitation using online platforms to facilitate PR among patients with chronic respiratory diseases. The same outcome measures of the conventional PR like the exercise capacity, functional performance, and breathlessness are also evaluated through the same set of outcome assessments.[3]

Telerehabilitation is associated with positive results including improvement in exercise capacity, dyspnea, quality of life, and sense of social support. Telerehabilitation systems such as videoconference programs are safe to use and can improve access to PR especially for those living in remote areas.[(4)] In a systemic review done by Rush et al, the virtual delivery of health services was comparable with the usual care among patients with chronic diseases. In the subset of patients with COPD receiving web-based instructional video, improvements in pulmonary function measures were noted at the end of program. Virtual delivery of health services including rehabilitation also reduced healthcare utilization.[5]

There is a dearth of studies in the local setting regarding the use of telerehabilitation or virtual pulmonary rehabilitation in the management of chronic respiratory diseases especially during a pandemic. This study aims to determine the effect of virtual PR among COPD patients in terms of exercise capacity, functional status, breathlessness, and quality of life.

METHODS

Study Design

This was a preliminary study to determine the effect of virtual pulmonary rehabilitation among COPD patients enrolled in the Lung Center of the Philippines (LCP) COPD Support Group. We used an ambispective cohort study design employing chart review of COPD patients who participated in the virtual PR.

Study Period and Procedure

We reviewed charts of COPD patients who participated in the virtual PR of the LCP COPD Support Group from November 2020 to October 2021. These included patients with clinical diagnosis of COPD by a pulmonologist within and outside LCP who had the following characteristics: >40 years old with history of chronic cough, dyspnea, or sputum production and with >10 pack year smoking history; and patients who had completed a course of pulmonary rehabilitation more than one year previously. There was no available data regarding baseline spirometry among the participants of the program.

Due to the limited number of patients, we reviewed all the available charts. Charts of patients who attended the virtual PR from November 2020 to May 2021 were reviewed retrospectively. On the other hand, the charts for June 2021 to October 2021 were prospectively reviewed. We reviewed a total of 26 charts and recorded the demographics (age, gender, COPD history including date or year of diagnosis and smoking history, co-morbidities, and medications); and pre- and post-virtual PR parameters: 1) distance achieved during the six-minute walk

test (6MWT) and step count using a pedometer; 2) daily pedometer step count and distance achieved in the 1st and 6th week of the rehabilitation; 3) Modified Medical Research Council (mMRC) dyspnea scale score; 4) Modified Borg's Scale (MBS) score; 5) and the COPD Assessment Test (CAT) score. We subsequently excluded two charts due to incomplete data.

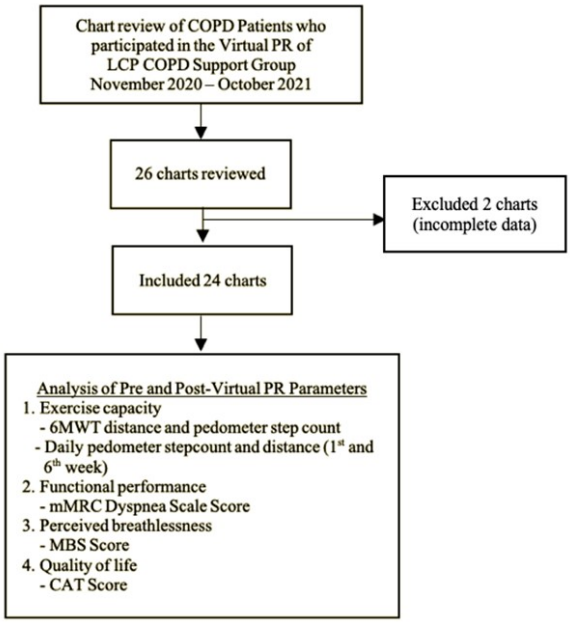


Figure 1. Study period and procedure

Virtual Pulmonary Rehabilitation

The virtual pulmonary rehabilitation was a six-week program composed of exercise trainings and education sessions under the LCP COPD Support Group. It was conducted twice a week by the LCP Pulmonary Rehabilitation Unit using online platform via videoconference. Each participant had pre- and post-rehabilitation examinations to obtain the following parameters: exercise capacity, functional performance, perceived breathlessness, and quality of life. The exercise trainings were composed of marching/step-up exercises and warm-up/cool down exercises. Educational sessions were done using online lectures with the following topics: COPD definition, anatomy and physiology of the lungs, COPD medications, smoking cessation, and inhaler techniques.

Outcome Measures

The primary outcome was exercise capacity which was assessed using the 6MWT. The secondary outcomes were the functional performance, perceived breathlessness, and quality of life which were evaluated using the mMRC dyspnea scale, MBS, and CAT.

Statistical Analysis

We presented the demographic data as average ± standard deviation and frequencies with percentage. We also presented the pre- and post-virtual PR parameters of study outcomes as average ± SD in terms of the number of steps and distance in the 6MWT, mMRC dyspnea scale score, MBS score, and CAT score. As part of the exercise capacity assessment, we also determined the average daily pedometer step count and distance during the 1st and 6th week of the virtual PR. We employed parametric tests such as T-test and student's T-test for correlated samples including the pre- and post- virtual PR parameters. We considered parameters with a p value of <0.05 as statistically significant. Data analysis was done using SPSS Statistics 20.

Ethical Considerations

We conducted this study in accordance with the National Ethical Guidelines for Health and Health Related Research and abided by principles of the Data Privacy Act. The protocol was approved by the Lung Center of the Philippines – Institutional Ethics and Review Board (LCP-IERB).

RESULTS

Study Recruitment and Outcome

Out of the available charts of the COPD patients who participated in the virtual PR, only 24 charts were included for data collection and analysis. Two charts were excluded due to absence of post-virtual PR outcome measurements including the mMRC dyspnea scale score and CAT score.

Baseline Characteristics

Table 1 shows the baseline characteristics of the study population. Majority of the COPD patients

Table 1. Baseline characteristics of the study population

Characteristics	Total n=24
Age, average ± SD	65.4 ±8.6
Age, ≥ 60 years (%)	17 (71)
Gender, Male (%)	19 (79)
Smoking History	
Never Smoker (%)	4 (17)
Second hand smoking (%)	4 (100)
Current Smoker (%)	0 (0)
Former Smoker (%)	20 (83)
Smoking pack years, average ± SD	29.4±31.2
≥10 pack years (%)	20 (83)
Second Hand Smoking (%)	4 (17)
Co-Morbidities	
Hypertension (%)	13 (54)
Diabetes (%)	3 (13)
Pulmonary Tuberculosis (%)	0 (0)
Coronary Artery Disease (%)	3 (13)
COPD Medications	
LABA (%)	0 (0)
LAMA+LABA (%)	8 (33)
LABA+ICS (%)	3 (13)
LAMA+LABA+ICS (%)	6 (25)
Baseline mMRC Dyspnea Scale Score	
<2 (%)	16 (67)
≥2 (%)	8 (33)
Baseline CAT Score	
<10 (%)	9 (38)
10-20 (%)	8 (33)
21-30 (%)	7 (29)
>30 (%)	0 (0)
With previous exacerbation or hospitalization, ≥1 year previously (%)	4 (17)
Completed a course of PR, >1 year previously (%)	4 (17)

CAT: COPD Assessment Test, COPD: Chronic Obstructive Pulmonary Disease, LABA: Long Acting Beta Agonist, LAMA: Long Acting Muscarinic Antagonist, ICS: Inhaled Corticosteroid, MBS: Modified Borg's Scale, mMRC: Modified Medical Research Council, PR: pulmonary rehabilitation

were male. The average age was 65.4±8.6 years. More than half of the subjects were former smokers and with -≥10 pack years' smoking history. A larger percentage of the population was hypertensive and on long acting muscarinic antagonist+long acting beta agonist (LAMA+LABA) inhalers. Most of the patients had a baseline mMRC score of <2 and baseline CAT score <10. Only 4 patients had a history of exacerbation or hospitalization for the past one year and completed a course of PR more than 1 year previously.

Primary Outcome

Table 2 shows the exercise capacity of the COPD patients during the pre- and post-virtual PR in terms of the number of steps and distance covered in the 6MWT. There were increased measurements of the average pre- and post-virtual PR 6MWT step count from 387.0+171.0 to 522.6+205.5 (p-value <0.001); and six-minute walk distance (6MWD) from 330.4+169.1m to 470.0+205.8m (p-value 0.005).

There was no significant difference (p-value 0.069) between the pre- and post-virtual PR 6MWD difference of 139.6 + 220.1m and the improvement standard of 54m as shown in Table 3.

There was increased average number of steps and distance covered in the 6th week of the virtual PR from the 1st week as listed in Table 4.

Secondary Outcome

Table 5 shows the secondary outcome measures of the study in the pre- and post-virtual PR. The post-virtual PR measurements of all the outcomes were significantly lower than the baseline values (p value <0.001).

DISCUSSION

Pulmonary rehabilitation is an established management among patients with chronic respiratory diseases such as COPD with persistent symptoms despite standard medical therapy. Telerehabilitation or virtual PR is considered as an alternative way of delivering the intervention remotely specifically in cases with physical restrictions including a pandemic. The results of the study showed improvement in the exercise capacity, functional performance, perceived

Table 2. Primary outcome measure in the pre- and post-virtual PR

Study Outcome	Pre-Virtual PR Average ± SD	Post-Virtual PR Average ± SD	p-value
Exercise Capacity			
6MWT, pedometer step count	387.0 ± 171.0	522.6 ± 205.5	<0.001
6MWD, m	330.4 ± 169.1	470.0 ± 205.8	0.005

Table 3. Evaluation of the pre- and post-virtual PR 6MWD difference and the improvement standard

	Average ± SD	p-value
6MWD difference, m	139.6 ± 220.1	0.069

**Test value/improvement standard: 54 m*
6MWD: six-minute walk distance

Table 4. Pedometer step count and distance in the 1st and 6th week of virtual PR

Exercise Capacity Parameters	1st week of Virtual PR Average ± SD	6th week of Virtual PR Average ± SD	p-value
Pedometer step count	1754.1 ± 756.9	1902.6 ± 823.0	0.25
Distance, m	1486.0 ± 882.9	1599.8 ± 950.2	0.27

PR: pulmonary rehabilitation

breathlessness, and quality of life among COPD patients who participated in the virtual PR of the LCP COPD Support Group.

Table 5. Secondary outcome measures in the pre- and post-virtual PR

Study Outcomes	Pre-Virtual PR Average ± SD	Post-Virtual PR Average ± SD	p-value
Functional Performance			
mMRC Dyspnea Scale Score	2.2 ± 1.1	1.5 ± 1.0	<0.001
Perceived Breathlessness			
MBS Score	1.7 ± 1.1	0.8 ± 0.8	<0.001
Quality of Life			
CAT Score	13.3 ± 7.6	9.8 ± 6.6	<0.001

CAT: COPD Assessment Test, MBS: Modified Borg's Scale, mMRC: Modified Medical Research Council, PR: pulmonary rehabilitation

Exercise Capacity

Exercise intolerance is one of the main factors that limits COPD patients in their activities of daily living.[1] The results of the study showed an increase in the exercise capacity of COPD patients who participated in the virtual PR, denoting beneficial effects of the program in terms of improvement of exercise intolerance. There was a significant increase in the average 6MWD from the baseline at the end of the virtual PR. This finding is consistent with a study done by Vasilopoulou et al. which showed a clinically significant increase from the pre- and post-rehabilitation of 389.1±91.3m and 422.1±70.5m, respectively. In the same study, there was again a significant difference in the 6MWD measurements when the program was extended up to 14 months.[6]

The study also showed that virtual PR can improve exercise capacity in terms of achieving the minimum test standard of improvement in 6MWT which is 54m.[7] Step counter use such as pedometers also augments exercise capacity of COPD patients undergoing PR as seen in the increased average step counts and 6MWD at the end of the program. These findings were also

end of the program. These findings were also noted in the study by Qiu et al. which showed an improvement of 1000 step counts and 11m 6MWD at the end of PR.[8]

Functional Performance

Enhancement of functional performance or the patient's ability to engage in activities of daily living is another goal of PR.[1] The results of the study showed that the functional performance of COPD patients improved after completing virtual PR. In addition, the minimum clinically significant difference in mMRC score which is a reduction of at least 0.5 units was attained at the end of the program.[9] This indicates that the virtual PR was able to improve the functional performance of COPD patients by meeting the minimum change associated with improvement. This finding is consistent with the study of Knox et al which demonstrated the same reduction in the dyspnea score among COPD patients who attended virtual PR via videoconference with a pre- and post-PR scores of 3.3 and 2.5, respectively.[10] In a randomized controlled trial on face-to-face versus online PR among COPD patients, there was also lower average mMRC score after completing the PR in both forms of PR – scores of 2 to 1.5 in the face-to-face PR and scores of 2 to 1 in the online PR – denoting improvement of functional performance. The same study also showed non-inferiority for the online group in terms of the dyspnea score.[11]

Perceived Breathlessness

Dyspnea and fatigue are the most common symptoms among patients being referred to PR. Symptom evaluation including the extent of perceived breathlessness is used to assess response to exercise rehabilitation.[1,2] The study showed a clinically significant reduction in the perceived breathlessness at the end of the virtual PR which can also contribute to the improvement of exercise intolerance. One study showed that home-based PR improved MBS score of COPD patients after 6 weeks of rehabilitation with a pre-PR score of 6.03$\pm$1.15 and post-PR score of 3.64$\pm$1.18. There was also a clinically significant difference between the MBS scores of patients attending home-based PR and hospital-based PR.[12] However, the minimum improvement standard of a 1 unit reduction in the MBS score was not attained at the end of the program.

Quality of Life

It is well recognized that COPD does not only affect the level dyspnea but also the quality of life. In the study, there was an improvement in the quality of life of patients after completing the rehabilitation program. The virtual PR attained the minimum standard of improvement which is at least a 2-unit difference in the CAT score.[13] The same results were also observed in another study showing lower CAT score and a significant difference between the pre-PR score of 17.6$\pm$8.1 and post-PR score of 12.9$\pm$7.5 after completion of a home-based telerehabilitation. Improvement in the quality of life was also recorded during a maintenance pulmonary rehabilitation among patients with COPD.[6,14]

Moreover, there were no recorded adverse events during the virtual PR including hypotension or hypertension (blood pressure <90/60 or 180/90), tachycardia (heart rate >120), or desaturation (oxygen saturation <85%) despite oxygen supplementation. Home-based telerehabilitation is considered as a safe form of delivering PR associated with improved exercise tolerance and dyspnea among patients with COPD. All patients completed the program which is consistent with existing studies showing high completion rates among patients attending telerehabilitation.[9,12,15] In this COVID-19 pandemic wherein physical restrictions are implemented, virtual PR can be a safer alternative for COPD patients needing rehabilitation program. Recent guidelines suggest a repeat PR among patients who have completed a course more than one year previously and still functionally limited.[2] There are only four patients in the current study who had a repeat PR. One study showed an improved quality of life and exercise capacity with a repeat conventional PR but the response was heterogenous.[16] However, there is a paucity of studies regarding the effect of repeat telerehabilitation among patients with chronic respiratory diseases.

LIMITATIONS

Existing guidelines strongly recommend pulmonary rehabilitation among COPD patients who have more symptoms. It can be noted in the study that a majority of the virtual PR participants were less symptomatic, denoted by the baseline mMRC score <2. In addition, another limitation as a preliminary study was the small sample size. Continuation of the study is highly recommended to strengthen the study's findings by having a larger sample and well-represented COPD population, particularly those who remain symptomatic despite use of conventional treatment. Another limitation of the study was the absence of baseline spirometry brought by the restrictions of the COVID-19 pandemic. This will provide pertinent information regarding the severity of the condition for each participant. Establishing the disease severity can facilitate sub-analysis of the outcome measures per COPD stage which can be included in future studies.

CONCLUSION

This preliminary study on virtual pulmonary rehabilitation showed improvement in the exercise capacity, functional performance, perceived breathlessness, and quality of life among COPD patients after completing the program. The virtual PR met the minimum standard of improvement for COPD which establishes its role in the management of patients with persistent symptoms despite maximal use of pharmacologic treatment. The results of the study can be a basis for including virtual PR as a complementary program to the conventional PR or an alternative form of PR in limited setting including a pandemic.

FUNDING

This study did not receive funding from any institutions.

REFERENCES

1. Nici L, Donner C, Wouters E, et al. ATS/ERS Pulmonary Rehabilitation Writing Committee. American Thoracic Society/ European Respiratory Society statement on pulmonary rehabilitation. Am J Respir Crit Care Med. 2006 Jun 15;173(12):1390-413.
2. Bolton CE, Bevan-Smith E, Blakey J, et al. British Thoracic Society guideline on pulmonary rehabilitation in adults: accredited by NICE. Thorax 2013, 68 (Suppl 2), ii1–ii30.
3. Gardiner L, Graham L, Harvey-Dunstan T, et al. Pulmonary Rehabilitation Remote Assessment. British Thoracic Society. 2020 April 22; https://www.brit-thoracic.org.uk/document-library/quality-improvement/covid-19/bts-pulmonary-rehab-remote-assessment/
4. Almojaibel AA. Delivering pulmonary rehabilitation for patients with chronic obstructive pulmonary disease at home using telehealth: A review of the literature. Saudi J Med Med Sci 2016;4:164-71.
5. Rush K, Hatt L, Janke R, et al. The efficacy of telehealth delivered educational approaches for patients with chronic diseases: A systematic review. Patient Education and Counseling, 101 (2018) 1310–1321
6. Vasilopoulou M, Papaioannou AI, Kaltsakas G, et al. Home-based maintenance telerehabilitation reduces the risk for acute exacerbations of COPD, hospitalisations and emergency department visits. Eur Respir J 2017; 49: 1602129.
7. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: Guidelines for the six-minute walk test. Am J Respir Crit Care Med. 2002;166(1):111-7.
8. Qiu S, Cai X, Wang X, et al. Using step counters to promote physical activity and exercise capacity in patients with chronic obstructive pulmonary disease: a meta-analysis . Ther Adv Respir Dis 2018, Vol. 12: 1–14.
9. Oliveira A, Andrade L, Marques A. Minimal clinically important difference and

predictive validity of the mMRC and mBorg in acute exacerbations of COPD . European Respiratory Journal 2017 50: PA4705.

10. Knox L, Dunning M, Davies C, et al. Safety, feasibility, and effectiveness of virtual pulmonary rehabilitation in the real world. International Journal of COPD 2019:14 775–780.
11. Bourne S, DeVos R, North M, et al. Online versus face-to-face pulmonary rehabilitation for patients with chronic obstructive pulmonary disease: randomised controlled trial. BMJ Open 2017;7:e014580.
12. Priya N, Isaac BT, Thangakunam B, et al. Effect of home-based pulmonary rehabilitation on health□related quality of life, lung function, exercise tolerance, and dyspnea in chronic obstructive pulmonary disorder patients in a tertiary care center in South India. Lung India 2021;38:211-5.
13. Kon S, Canavan J, Jones S, et al. Minimum clinically important difference for the COPD Assessment Test: a prospective analysis. Lancet Respir Med 2014; 2: 195–203.
14. Zanaboni P, Hoaas H, Lien L, et al. Long-term exercise maintenance in COPD via telerehabilitation: a two-year pilot study. Journal of Telemedicine and Telecare (0) 1–9.
15. Holland A, Hill C, Rochford P, et al. Telerehabilitation for people with chronic obstructive pulmonary disease: feasibility of a simple, real time model of supervised exercise training. J Telemed Telecare 2013 19: 222.
16. Ingram K, Canavan J, Kon S, et al. Repeat pulmonary rehabilitation programmes: Are they beneficial in COPD? European Respiratory Journal 2014 44: P610.

The Predictive Value of SpO_2/FiO_2 (SF) Ratio on the Chest CT Severity Score (CTSS) of Adult COVID-19 Patients Admitted in Chinese General Hospital and Medical Center

Paolo C. Hilado, MD, and Jennylyn T. Go, MD, FPCCP*
Chinese General Hospital and Medical Center, Manila, Philippines
Corresponding Author: *Dr. Paolo C. Hilado (drpaolohilado@yahoo.com)*

ABSTRACT

BACKGROUND: In assessing the severity of Coronavirus disease 2019 (COVID-19) pneumonia, chest computed tomography (CT) scan with CT severity score (CTSS) is most sensitive but is sometimes unavailable. The ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO2/FiO2 or PF ratio), determined by arterial blood gas (ABG), correlates with lung parenchymal injury extent assessed using CTSS. However, primary healthcare facilities may not have ABG analyzers. Hence, the ratio of oxygen saturation to FiO2 (SpO2/FiO2 or SF ratio), determined using a pulse oximeter, which is a measure of oxygen in the blood and is an important indicator of a patient's respiratory status, has a potential value.

OBJECTIVES: To correlate SF ratio with CTSS in adult COVID-19 patients.

METHODS: We conducted a retrospective cross-sectional study of 402 COVID-19 patients admitted in Chinese General Hospital and Medical Center (CGHMC) between March 11, 2020 and March 10, 2022. Demographics, SF ratio, and chest CTSS stratified as mild, moderate, or severe were determined and analyzed.

RESULTS: The mean age of participants was 62.78±20.83 years and 50.94% were male. The mean SF ratio and CTSS were 200.17±93.35 and 12.23±6.44, respectively. Most had moderate CTSS (35.82%). Sex was associated with CTSS ($p<0.027$). SF ratio was negatively correlated with CTSS ($p<0.01$). Using mild CTSS as base outcome, the odds of having moderate or severe CTSS decreased when SF ratio increased ($p<0.001$). The probability of mild CTSS increased when SF ratio increased but only for ratios 150 (p=0.000-0.011). For moderate CTSS, the probability increased when SF ratio increased from 0 until 200 (p=0.000-0.028). For severe CTSS, the probability increased when SF ratio decreased but only for ratios £200 (p=0.000-0.002).

CONCLUSION: The SF ratio was negatively correlated with chest CTSS in adults with COVID-19. It can be an independent predictor of CTSS and be useful in assessing COVID-19 severity in resource-limited healthcare facilities.

KEYWORDS: *Coronavirus disease 2019, SpO2/FiO2 ratio, chest CT severity score*

**This is the corrected online version of the article entitled "The Predictive Value of SpO_2/FiO_2 (SF) Ratio on the Chest CT Severity Score (CTSS) of Adult COVID-19 Patients Admitted in Chinese General Hospital and Medical Center" published in print in the Philippine Journal of Chest Diseases Vol. 21 No. 2 in January 2024. The Table of Contents reflects the corrections made to the author name as well.*

INTRODUCTION

Patients with COVID-19 may develop respiratory failure without signs of respiratory distress.[1] Hence, monitoring oxygenation parameters is important, specifically the ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2 or PF ratio) and the ratio of oxygen saturation to FiO_2 (SpO_2/FiO_2 or SF ratio). Both ratios can predict severe outcomes in acute lung injury and acute respiratory distress syndrome (ARDS).[2,3] The PF ratio, determined invasively using an arterial blood gas (ABG), is significantly associated with severe outcomes and prolonged hospitalization in COVID-19 patients.[4,5] The SF ratio on admission, determined non-invasively using a pulse oximeter, is a strong predictor of ARDS occurrence in COVID-19 patients and is successful in predicting clinical outcomes in mechanically-ventilated patients secondary to acute respiratory failure.[6,7] The SF ratio can also be a surrogate for the PF ratio in monitoring acute respiratory failure which is essential for managing COVID-19 effectively and in evaluating outcomes of COVID-19 patients.[8]

Chest computed tomography scan (CT scan) is used in the initial evaluation of COVID-19 patients and is sensitive in the early detection of lung parenchymal involvement, typically described as subpleural changes and ground-glass opacity lesions.[9] The chest CT severity score, or CTSS, is a semi-quantitative scoring system calculated based on the extent of lobar involvement and lung variations.[10] Each of the five lung lobes is visually scored on a scale of 0-5. A score of 0 indicates no involvement, 1 indicates <5% involvement, 2 indicates 5-25% involvement, 3 indicates 26-49% involvement, 4 indicates 50-75% involvement, and 5 indicates >75% involvement. The total CT severity score is the sum of the individual lobar scores and can range from 0 to 25. The CTSS can evaluate pulmonary involvement rapidly and objectively in COVID-19 patients, aiding in predicting disease outcome, progression to ICU admission, and may significantly correlate with the body's inflammatory response intensity, thus, with oxygen requirements and laboratory tests results, including pro-inflammatory markers.[11,12,13]

A study by El Megid et al. in 2022 has already shown a significant positive correlation of the CTSS on admission with the oxygen demand, and a study by Attia and Othman in 2020 has already shown a significant negative correlation of the PF ratio on admission with the CTSS, with both studies done in COVID-19 patients.[14,15] Likewise, the SF ratio of ARDS patients due to COVID-19 was already shown to be associated with mortality.[16] However, the correlation between SF ratio and the severity of pulmonary involvement assessed through the chest CT scan of adult COVID-19 patients has not yet been determined, both locally and internationally. The potential predictive value of SF ratio in terms of CTSS in COVID-19 patients has also not yet been studied.

Therefore, this study aimed to correlate the SF ratio with the chest CTSS of adult COVID-19 patients admitted in Chinese General Hospital and Medical Center (CGHMC), Manila, Philippines. It also aimed to determine if the SF ratio can be an independent predictor of the CTSS in these patients.

METHODS

Study Population and Design

This single-center retrospective cross-sectional chart review was approved by the Institutional Ethics Review Board (IERB) of CGHMC. Informed consent was waived due to the retrospective nature of the study design. We included patients more than 18 years of age who (a) tested positive for COVID-19 as confirmed by RT-PCR, (b) had their oxygen saturation and ABG taken upon emergency room (ER) arrival, and (c) had their chest CT scan within 24 hours upon ER arrival between March 11, 2020 and March 10, 2022. We excluded patients who were (a) admitted due to COVID-19 reinfection, (b) had

their chest CT scan, ABG, and/or RT-PCR test performed outside CGHMC, (c) initially were COVID-19 negative during ER arrival and became positive upon repeat RT-PCR testing, (d) had their oxygen saturation and ABG taken more than 1 hour apart, and (e) missing data or incomplete records. There were 3,809 admitted COVID-19 patients during the study duration and the calculated sample size was 364.

Clinical Data

We collected the demographic and clinical data of all admitted COVID-19 patients from the electronic medical records system (MERX) of CGHMC, including the oxygen saturation, ABG results, and chest CT scan results, with the latter showing the CTSS.

Chest CT Severity Score

The axial chest CT images, either plain or contrast-enhanced, were taken using a GE Revolution CT-512 Slice Computed Tomography. Three (3) Philippine board-certified radiologists evaluated the images and visually quantified the severity of the pulmonary involvement using chest CTSS. We stratified the patients based on their total chest CTSS similar to the study of Saeed et al. in 2021, which was as follows: £7 was mild, 8-17 was moderate, and ³18 was severe.[13]

PF and SF Ratios

The arterial blood gas was determined using a Radiometer ABL800 Flex Blood Gas Analyzer. We calculated the PF ratio as: (PaO_2/FiO_2) X 100, with both values taken from the ABG result. The oxygen saturation was determined using a pulse oximeter and we calculated the SF ratio as: (SpO_2/FiO_2) X 100.

Statistical Analysis

We used Stata Version 12.0 for our statistical analysis. We performed exploratory data analysis using summary measures (mean, standard deviation, and percentage). We used Pearson's chi-square test to determine the association between sex and CTSS, and Pearson's correlation to analyze the correlation between the CTSS and the age and the PF and SF ratios of the patients with a *p*-value of <0.05 considered as statistically significant. If a significant correlation existed, we used multinominal logistic regression analysis to determine the average predicted probability of the chest CTSS based on the different SF ratio levels.

RESULTS

A total of 402 patients met the criteria and were included in the study. There were 203 (50.49%) male and 199 (49.51%) female patients. Table 1 shows the summary measures for age, CTSS, and PF and SF ratios of the study population.

Out of 402 patients, 144 (35.82%) were stratified as moderate CTSS, 134 (33.33%) as severe CTSS, and 124 (30.85%) as mild CTSS. In terms of sex, most male patients were stratified as mild CTSS (36.95%) while most females were stratified as moderate CTSS (39.70%). There was a significant association between the sex and CTSS, whether it be mild, moderate, or severe, as presented in Table 2 (p=0.027).

Table 1. Baseline Summary measures for age, PF and SF ratios, and CTSS of the study population (N=402)

			----------	Quantiles	----------
Variable	Mean	SD	Min .25	Median	.75 Max
Age	62.78	20.83	19.00 - 47.00	64.00	79.00 - 108.00
Oxygen saturation	88.76	8.83	58.00 - 83.00	91.00	95.00 - 99.00
FiO_2 (for SF ratio)	55.79	26.37	21.00 - 36.00	44.00	80.00 - 100.00
SF Ratio	200.17	98.35	50.00 - 105.00	198.00	264.00 - 467.00
PaO_2	115.58	36.73	66.00 - 95.00	103.00	126.00 - 378.00
FiO_2 (for PF ratio)	64.00	29.52	21.00 - 40.00	60.00	100.00 - 100.00
PF ratio	224.55	118.48	66.00 - 127.00	207.50	288.00 - 600.00
CTSS	12.23	6.44	2.00 - 6.00	11.00	19.00 - 24.00

PaO2, arterial partial pressure of oxygen; FiO2, fraction of inspired oxygen; SpO2, oxygen saturation; PF ratio, PaO2/FiO2 ratio; SF ratio, SpO2/FiO2 ratio; CTSS, chest computed tomography severity score

Table 2. Association of sex and chest CTSS in adult COVID-19 patients

Chest CT Severity Score	Sex (N=402)			
	Female n=199	Male n=203	Pearson Chi-Square	*p*-value
Mild	49 (24.62%)	75 (36.95%)	7.2513	0.027
Moderate	79 (39.70%)	65 (32.02%)		
Severe	71 (35.68%)	63 (31.03%)		

Table 3 shows the correlation of the chest CTSS with the age and the PF and SF ratios in adult COVID-19 patients. There was a high negative correlation between the CTSS and the PF ratio, r (400) = -0.828, p<0.01, as well as CTSS and SF ratio, r (400) = -0.819, p<0.01, even if the level of significance or p-value was changed to 0.001. With regard to the correlation between the CTSS and age, it was negligible. The PF ratio and SF ratio showed a highly positive correlation with each other, r (400) = 0.884, p<0.01.

The SF ratio was a significant variable in patients who had severe CTSS (p<0.001). The odds of having severe over mild CTSS decreased by 0.926 times for every 1 unit increase in the SF ratio, given again that both age and sex were held constant. This means that it was more likely to have a mild compared to a severe CTSS with an increasing SF ratio.

Table 3. Correlation of the chest CTSS with the age and the PF and SF Ratios in adult COVID-19 patients

Variables	PF Ratio	CTSS	SF Ratio	Age
PF ratio	1.000	-	-	-
CTSS	-0.828**	1.000		-
SF ratio	0.884**	-0.819**	1.000	-
Age	-0.010	0.041	-0.004	1.000

*Note: N=402; **Correlation was significant at the 0.01 level (2-tailed).*
PF ratio, PaO2/FiO2 ratio; SF ratio, SpO2/FiO2 ratio; CTSS, chest computed tomography severity score

Mild CTSS was used as the base outcome to evaluate the odds of having either moderate or severe CTSS based on the SF ratio as shown in Table 4. The SF ratio was a significant variable in patients who had moderate CTSS (p<0.001). The odds of having moderate over mild CTSS decreased by 0.968 times for every 1 unit increase in the SF ratio, given that age and sex were held constant. This means that it was more likely to have a mild compared to a moderate CTSS with an increasing SF ratio.

Table 5 presents the average predicted probabilities for each CTSS stratification at different SF ratio levels. Only SF ratio values ³150 showed significant associated predictions for mild CTSS (p<0.05). There were no SF ratio values £50 for mild CTSS. The probability of having mild CTSS increased as the SF ratio increased. For moderate CTSS, only SF ratio values £350 had significant associated predictions (p<0.05). There were no SF ratio values <50 for moderate CTSS.

Table 4. Odds of having moderate or severe CTSS over mild CTSS with sex, age, and SF ratios as predictors in adult COVID-19 patients (N=402)

CT Severity Score	Odds Ratio	P>z	95% Confidence Interval	
Mild (CTSS £7) (base outcome)				
Moderate (CTSS 8 to 17)				
SF ratio	0.968	0.000*	0.961	0.976
Severe (CTSS ³18)				
SF ratio	0.926	0.000*	0.915	0.938

**p<0.001*
SF ratio, SpO2/FiO2 ratio; CTSS, chest computed tomography severity score

There was an increasing trend in the predicted probability of having moderate CTSS as the SF ratio increased from 0 until 200. This was followed by a decreasing trend in the predicted probability as the SF ratio continued to increase beyond 200 until 350. For severe CTSS, only SF ratio values £200 had significant associated predictions ($p<0.05$). There were no SF ratio values >200 for severe CTSS. The probability of having severe CTSS decreased when the SF ratio increased.

Table 5. Average predicted probabilities of mild, moderate, and severe CTSS at different SF ratio levels in adult COVID-19 patients

SF Ratio	Mild CTSS				Moderate CTSS				Severe CTSS			
	Margin	P>z	95% CI		Margin	P>z	95% CI		Margin	P>z	95% CI	
0	a	a	a	a	a	a	a	a	0.998	0.000*	0.995	1.000
50	a	a	a	a	0.016	0.036	0.001	0.031	0.984	0.000*	0.969	0.998
100	0.001	0.114	0.000	0.002	0.128	0.000*	0.069	0.188	0.870	0.000*	0.810	0.930
150	0.023	0.011	0.005	0.041	0.560	0.000*	0.471	0.648	0.417	0.000*	0.327	0.507
200	0.160	0.000	0.097	0.223	0.776	0.000*	0.706	0.846	0.063	0.002	0.023	0.103
250	0.508	0.000	0.420	0.595	0.488	0.000*	0.401	0.575	a	a	a	a
300	0.839	0.000	0.761	0.918	0.160	0.000*	0.082	0.238	a	a	a	a
350	0.963	0.000	0.931	0.996	0.037	0.028	0.004	0.069	a	a	a	a
400	0.993	0.000	0.983	1.002	0.007	0.129	0.002	0.017	a	a	a	a
450	0.999	0.000	0.996	1.001	0.001	0.244	0.001	0.004	a	a	a	a
500	1.000	0.000	0.999	1.000	0.000	0.344	0.000	0.001	a	a	a	a

Constant variables (mean): Sex (female) = 0.495 (mean); Sex (male) = 0.505 (mean); Age = 62.78
**p<0.001*
aNo observations
SF ratio, SpO2/FiO2 ratio; CTSS, chest computed tomography severity score

DISCUSSION

It is important to have readily available, rapid, and accurate diagnostic tools in primary healthcare facilities for assessing COVID-19 severity. Chest CT scan is still the most sensitive imaging modality for COVID-19 pneumonia evaluation.[17] The unavailability of CT scan in some locations remains a challenge in the assessment of disease severity. Oxygenation seen in the ABG correlated with the extent of pulmonary involvement seen in the chest CT scan.[18,19] However, not all healthcare facilities have blood gas analyzers. Less invasive and more cost-efficient methods in assessing COVID-19 severity are still more desirable especially in resource-limited settings.

Our study showed a strong association between the sex and CTSS (p=0.027). This was in contrast with the studies by Attia and Othman (2020) and Farghaly and Makboul (2021) in Egypt which showed no significant association.[15,20] Our study also showed that the correlation between age and CTSS was negligible. This was again incongruent with the results of both Egyptian studies which observed a positive correlation.

The PF ratio and the SF ratio had a positive correlation with each other, r (400) = 0.884, p<0.01. This was the same with the study by Babu et al. (2021) which showed a positive correlation of these ratios in acute respiratory failure patients.[21] Moreover, a study by Kumar et al. (2022) already showed that the SF ratio can be used as an effective surrogate of the PF ratio in COVID-19 pneumonia patients.[8]

A highly negative correlation was observed between the PF ratio and the CTSS which was similar to the results of two previous studies, r (400) = -0.828, p<0.01.[15,19] The pulmonary function decreased, as reflected in the PF ratio, when the CTSS increased, indicating that there was a high percentage of the lungs involved in the disease process, resulting in a more difficult oxygenation of the blood.

Our study showed that the SF ratio had a highly negative correlation with the CTSS, r (400) = -0.819, p<0.01, similar to the PF ratio. To the best of our knowledge, we cannot find a similar study evaluating the correlation of SF ratio with the CTSS, both in non-COVID-19 and in COVID-19 patients.

In our study, the odds of adult COVID-19 patients of having either a moderate or severe CTSS over mild CTSS decreased if the SF ratio increased (p<0.001). We also could not find any study which evaluated the odds and the probability of chest CTSS based on the different SF ratio levels in adult COVID-19 patients.

The predicted probability of having mild CTSS increased when the SF ratio increased (p=0.000-0.011). There were no significant associations for SF ratios £150, probably secondary to a low number of mild CTSS patients having these values. Since a mild CTSS indicates a lower percentage of the lungs involved, oxygenation is less impaired, as reflected by higher oxygen saturation levels and lower oxygen requirements.[10,14,15,19]

The predicted probability of having moderate CTSS increased when the SF ratio increased from 0 until 200 and decreased for values >200 until 350 (p=0.000-0.028). This means that, in moderate CTSS, the predicted probability of the SF ratio was variable with 200 as the transition value.

The predicted probability of having severe CTSS increased when the SF ratio decreased (p=0.000 -0.002). There were no significant associations for SF ratio >200 probably secondary to a low number of severe CTSS patients having these values. Since a severe CTSS indicates a higher percentage of the lungs involved in the disease process, oxygenation is more impaired, as reflected by lower oxygen saturation levels and higher oxygen requirements.[10,14,15,19]

LIMITATIONS AND RECOMMENDATIONS

This study had a retrospective design and was only single-center. Therefore, the effect of hospital protocols to the study population cannot be ruled out. The diversity of the study population was also limited. A larger cohort and prospective study will be more ideal to have more definitive results. With this, we recommend replicating the study in several facilities. In addition, we recommend using the SF ratio in stratifying the risk for mortality and morbidity of mechanically-ventilated COVID-19 patients in future studies. Evaluation of follow-up imaging done, and the actual disease outcome were not done which could be important in assessing other prognostic factors which may correlate with the ratios. The presenting symptoms, co-morbidities including the presence of congenital cardiac anomalies and other concurrent viral and/or bacterial infections which may contribute to the pulse oximeter reading, model of the pulse oximeter used, and the biochemical parameters were also not taken into consideration and are recommended to be included in future investigations. During the conduct of the study, documenting comorbidites was not done due to technical difficulties. Lastly, the methods of

measuring the pulmonary involvement and severity in the CT scan may have subjectivity and inter-observer variability.

CONCLUSION

Our study showed that the SF ratio had a significant negative correlation with the chest CTSS in adult COVID-19 patients. The probability of having a mild CTSS was proportional to the increase in the SF ratio while the probability of having a severe CTSS was inversely proportional. Therefore, the SF ratio can be an independent predictor for the chest CTSS and can be useful in the preliminary assessment adult COVID-19 severity in remote and resource-limited primary healthcare facilities.

REFERENCES

1. Dhont S, Derom E, Van Braeckel E, Depuydy P, Lambrecht BN. The pathophysiology of "happy" hypoxemia in COVID-19. Respir Res 2020. 12:198.
2. Bilan N, Dastranji A, Behbahani AG. Comparison of the SpO2/FiO2 ratio and the PaO2/FiO2 ratio in patients with acute lung injury or acute respiratory distress syndrome. J Cardiovasc Thora Res 2015. 7 (1): 28-31.
3. Rice TW, Wheeler AP, Bernard GR, Hayden DL, et. al. Comparison of the SpO2/FiO2 ratio and the PaO2/FiO2 ratio in patients with acute lung injury or ARDS. Chest 2007. 132 (2): 410-417.
4. Santus P, Radovanovic D, Saderi L, Marino P, Cogliati C, De Filippis G, et al. Severity of respiratory failure at admission and in-hospital mortality in patients with COVID-19: a prospective observational multicenter study. BMJ Open 2020;10:e043651. doi: 10.1136/bmjopen-2020-043651.
5. Zienellu A, De Vito A, Scano V, Paliogiannis P, Fiore V, et al. The PaO_2/FiO_2 ratio on admission is independently associated with prolonged hospitalization in COVID-19 patients. J Infect Dev Ctries 2021; 15 (3): 353-359. doi: 10.3855/jidc.13288.
6. Choi KJ, Hong HL, Kim EJ. The association between mortality and the oxygen saturation and fraction of inhaled oxygen in patients requiring oxygen therapy due to COVID-19-associated pneumonia. Tuberc Respir Dis (Seoul) 2021. 84: 125-133.
7. Fukuda Y, Tanaka A, Homma T, Kaneko K, et. al. Utility of SpO2/FiO2 ratio for acute hypoxemic respiratory failure with bilateral opacities in the ICU. PLOS ONE. 2021; 16: ppe0245927.
8. Kumar A, Aggarwal KR, Khanna P, Kumar R, Singh AK, Soni KD, Trika A. Correlation of the SpO2/FiO2 (S/F) ratio and the PaO2/FiO2 (P/F) ratio in patients with COVID-19 pneumonia. Med Intensiva 2022 Jul. 46 (7): 408-410.
9. Yang R, Li X, Zhen Y, Liu H, Zhang X, Xiong Q, Luo Y, Gao C, Zeng W. Chest CT severity score: an imaging tool for assessing severe COVID-19. Radiol Cardiothorac Imaging 2020 Mar. 2 (2): 200047.doi: 10.1148/ryct.2020200047.
10. Sayeed S, Faiz BW, Aslam S, Masood K, Saeed R. CT chest severity score for COVID-19 pneumonia: a quantitative imaging tool for severity assessment of disease. J Coll Physicians Surg Pak 2021. 30 (4): 388-392.
11. Hajiahmadi S, Shayganfar A, Janghorbani M, Esahani MM, Mahnam M, Bakhtiarvand N, Sami R, Khademi N, Dehgnhani M. Chest computed tomography severity score to predict adverse outcomes of patients with COVID-19. Infect Chemthor 2021. 53 (2): 308-318.
12. Fracone M, Iafrate F, Masci GM, Coco S, Cilia F, Mangaro L, Panebianco V, et al. Chest CT score in COVID-19 patients: correlation with disease severity and short-term prognosis. Eur Radiol 2020. 30 (12): 6808-6817.
13. Saeed AF, Shah WGA, Al Helali AA, Raidulla E, Ali AB, Elghazali M, Ahmed DY, Al Kaabi SG, Almazrouei S. Correlation between chest CT severity scores and the clinical parameters of adult patients

with COVID-19 pneumonia. Radiol Res Pract 2021:6697677. doi: 10.1155/2021/6697677.

14. El Megid AGI, El Shabrawy M, Abdalla AAEHM. Correlation between chest CT severity scoring system with oxygen saturation and laboratory inflammatory markers in adult patients with COVID-19 infection. Egypt J Radiol Nucl Med 2020, 53 (1): 72.
15. Attia NM, Othman MHM. Chest CT Imaging features of COVID-19 and its correlation with the PaO_2/FiO_2 ratio: a multicenter study in Upper Egypt. Egypt J Radiol Nucl Med 2020. 51: 252-259.
16. Roozeman JP, Mazzinari G, Neto AS, Hollmann MW, Paulus F, Schultz MJ, Pisani L. Prognostication using SpO_2/FiO_2 in invasively ventilated ICU patients with ARDS due to COVID-19 - Insights from the PRoVENT-COVID study. J Crit Care 2022. 68: 31-37.
17. Udugama B, Kadhiresan P, Kozlowski HN, Malekjahani A, Obsorne M, Li VYC, Chen H, Mubareka S, Gubbay JB, Chan WCW. Diagnosing COVID-19: the disease and tools for detection. ACS Nano 2020. 14 (4), 3822-3835. DOI: 10.1021/acsnano.0c02624.
18. Zhang N, Xu X, Zhou LY, Chen G, Li Y, Yin H, et. al. Clinical characteristics and chest CT imaging features of critically-ill COVID -19 patients. Eur Radiol 2020. 30 (11): 6151-6160.
19. Turcato G, Panebianco L, Zaboli A, Scheurer C, Ausserhofer D, Wieser A, Pfeife N. Correlation between arterial blood gas and CT volumetry in patients with SARS-CoV-2 in the emergency department. Int J Inf Dis 2020. 97: 233–235.
20. Farghaly S, Makboul M. Correlation between age, sex, and severity of Coronavirus-19 based on chest computed tomography severity scoring system. Egypt J Radiol Nucl Med 2021. 52 (1): 23.
21. Babu S, Abhilash KPP, Kandasamy S, Gowri M. Association between SpO2/FiO2 ratio and PaO2/FiO2 ratio in different modes of oxygen supplementation. Indian J Crit Care Med 2021; 25 (9): 1001–1005.

Philippine Journal of Chest Diseases

Original Research

A Retrospective Cohort Study on the Outcomes of the Participants of the Department of Health-Lung Center of the Philippines (DOH-LCP) Quitline Program From 2017-2020

Marra Monique S. Cantela, MD and Glynna Ong-Cabrera, MD, FPCCP
Lung Center of the Philippines, Quezon City
Corresponding Author: *Dr. Monique Cantela (marramoniquecantela@yahoo.com)*

ABSTRACT

BACKGROUND: Telephone quitlines provide support for individuals who want to quit smoking. In the Philippines, the Department of Health-Lung Center of the Philippines (DOH-LCP) Quitline program was launched last June 2017 to provide counselling to smokers and help them become nicotine-free.

OBJECTIVES: To determine the outcome of participants of DOH-LCP Quitline program from June 2017 to June 2020, including those who successfully quit and those who relapsed. Specifically, to identify the participants' baseline characteristics and determine the quit rate and relapse rate, reasons for staying quit and relapse, and the stage of change among those with relapse.

METHODS: We conducted a retrospective cohort study among participants of DOH-LCP Quitline program from June 2017 to June 2020.

RESULTS: A total of 118 participants were included in this study. Most participants who enrolled in the program belonged to the 25- to 44-year-old age group (50.1%), were males (83.1%), married (51.7%), college graduate (41.5%), employed (65.2%), without comorbidities (75.4%), and at least 10 pack-year smokers (60.2%). There was no observed statistically significant difference between those who stayed quit and those who had relapse. Across the years, the quit rates were 18% (2017), 70.3% (2018), 57.9% (2019) and 58.8% (2020) while relapse rates were 82% (2017), 29.7% (2018), 42.1% (2019), and 58.8% (2020). The main reason for staying quit was health-related (69%) while the main reasons for relapse were cravings and withdrawal symptoms (56.8%). Among those with relapse, majority were in the preparation stage (72.7%).

CONCLUSION: The Quitline program can serve as an intervention for smoking cessation. An understanding of the sociodemographic factors and reasons for quitting and relapse is also essential to offer a more effective approach with this program.

KEYWORDS: *smoking cessation, quitline, outcomes*

INTRODUCTION

Tobacco use is an important risk factor and the leading single, modifiable cause of disease in general and preventable deaths. It causes an annual mortality of approximately 8 million deaths worldwide. In the Philippines, there are approximately 240 deaths each day or 87, 600 individuals per year who die due to tobacco use[1]. Despite the well-publicized dangers of smoking and global efforts in smoking cessation, a significant amount of the population world-wide continues to smoke.

Several strategies are being used for smoking cessation, including behavioral counselling, telephone-based Quitline program, and cessation medications like nicotine replacement therapy (NRT). Studies have shown that telephone quitlines provide convenience, improve outcomes, and increase the rates of success of smoking cessation especially for those with geographic limitations of face-to-face interventions[1]. Nicotine replacement therapy is also equally effective as a pharmacologic intervention in increasing the quit rates as high as 50-70% [2]. Further studies also revealed that the combination of behavioral counselling and NRT is also an effective strategy and showed even higher quit rates than either intervention alone[3]. Both have demonstrated relevant roles in increasing the chance of success in smoking cessation.

The Department of Health, in partnership with the World Health Organization (WHO), has launched a Quitline program in the Philippines last June 2017. Our institution, the Lung Center of the Philippines, has been tasked to implement this project. The Quitline program is hotline 1558, a telephone-based counseling service, which smokers in the country can call. The program aims to provide counseling to smokers and facilitate their potential of becoming free of nicotine in the future. It also aims to make callers across the country become more aware of the bad effects of smoking, thereby promoting prevention of smoking-related respiratory diseases.

According to a study done by Gordon et al in 2010[4], quitline referral methods have been found to increase quit rates when compared with conventional counseling alone. However, although the quitline service was associated with significant smoking-cessation rates, still, many of those who joined and enrolled in this smoking-cessation program relapsed within a few weeks[5]. Relapse is therefore an emerging problem and the factors associated with it must be determined for improvement of these programs. Relapse rates are strongly associated with the lack of motivation and low attendance in behavioral therapy sessions[6]. The perceived role of motivation as an essential factor is being emphasized as part of the behavior which stimulates attempts to smoking cessation. Assessment of one's readiness to quit smoking can be made through stages of change by Prochaska and Di Clementi[7]. An understanding of these stages of change before quitting is thus important because patients at different stages of quitting also need different types of support or approach. Enhancement of an individual's motivation in smoking cessation is not only important during the early stages of quitting but also during the maintenance stage.

Several studies have also been conducted globally on smoking cessation. However, most of them focus mainly on intentions to quit and determinants of smoking abstinence. Only a few concentrated on the risk factors associated with relapse or unsuccessful quit attempts. An understanding also of these factors may help in providing a more effective support. With these, appropriate modifications in the quitline program can be made to achieve more successful cessation outcomes.

OBJECTIVES

This study was conducted to determine the outcomes among participants of the DOH-LCP Quitline program from 2017-2020 . Specifically to (1) describe the clinical profile of participants of the DOH-LCP Quitline program from 2017-2020 who

stayed quit and who had relapse; (2) determine the quit rate and relapse rate among participants of the DOH-LCP Quitline program from 2017- 2020 ; (3) determine the reasons for staying quit and reasons for relapse among participants of the DOH-LCP Quitline program; and, (4) determine the stage of change among participants of the DOH-LCP Quitline program from 2017-2020 with relapse.

METHODS

Study Design

This study is a retrospective cohort study which included all participants of the DOH-LCP Quitline Program from June 2017 to June 2020.

Study Site

We conducted this study in the DOH-LCP Quitline Program Office located at the 4th floor at the Lung Center of the Philippines. The Quitline, with hotline 1558, was launched last June 2017 and it provides telephone-based counseling services to smokers across the Philippines.

Study Period

This study covered the period of September 2020 to December 2021, from protocol development, Technical Review Board (TRB)/ Institutional Ethics Review Board (IERB) review and approval, budget application and launching, data collection and analysis, research paper writing, to submission to Pulmonary Medicine Department, Research and Development (RND), Institutional Ethics Review Board (IERB), and Philippine College of Chest Physicians (PCCP).

Study Population

We included all adult Filipinos, aged 18 years or above, who participated in the DOH-LCP Quitline Program from June 2017 to June 2020. Callers were from various areas around the country, with most calls received from Metro Manila and provinces in Calabarzon and Central Luzon.

Sample Size

From a total of 422 callers from June 2017 to June 2020, we included all 118 participants who enrolled in the DOH-LCP Quitline program. A total of 304 dropped callers, lost to follow up, unable to abstain from smoking for at least one month were excluded. Sample size was not computed since this involves a small study population.

Sampling Design

This research is a retrospective cohort study. We included Quitline callers from June 2017 to June 2020 who quit and who had relapse. We used the data of participants previously gathered and recorded in an excel file. We also reviewed the subjects' information on their personal, health, and smoking profile based on Quitline Participant's Form.

Study Procedure

In the Quitline program, calls are received by counselors through telephone lines. The program is briefly introduced to interested participants who plan to quit smoking. Once enrollled in the program, participants are also asked to set up their quit date. They will have a series of calls and are followed up 24 hours after their first call, then regularly after 48 hours, 72 hours, weekly until the 4th week of the month, then monthly until 12 months. The 5 A's (Ask, Advise, Assess, Assist and Arrange) approach is primarily the behavioral method used to determine the status of smoking cessation of participants. Smokers are asked about their cigarette use status, including the difficulties or challenges of quitting, benefits or positive changes when quitting was started, withdrawal symptoms, and triggers. Counselors will subsequently give advice and other techniques to address the difficulties of quitting and assess the effectiveness of these techniques. Assessment of willlingness to quit or staying quit is also determined. Participants are then assisted regarding their quit plan and are provided with solutions for the triggers and withdrawal symptoms identified. A next follow-up will then be arranged by the counselor for reassessment.

A review of records was primarily done in this study. We determined the outcomes (relapse or stayed quit) of all participants in the Quitline program since it started last June 2017. After reviewing the records of participants from June 2017-June 2020, we determined the number of those who stayed quit and those who had relapse. A participant who was able to abstain from smoking for at least 6 months from the time he/she signed up for the program was tagged as a "quitter". On the other hand, a participant who was able to stop smoking for at least one month but unable to abstain from smoking for at least 6 months from the time he/she signed up for the program was tagged as "relapse". Using all the data gathered, we also identified the quit rate and relapse rate each year. Reasons for staying quit and reasons for relapse were identified and recorded in an excel file. Finally, among those with relapse, the stage of change upon enrollment in the program was determined.

Outcome Measures

In this study, we determined the sociodemographic characteristics of participants who enrolled in the DOH-LCP Quitline program. We also determined the annual quit rate and relapse rate, and identified the reasons for staying quit and reasons for relapse. Lastly, we also determined the stage of change among those with relapse.

Statistical Analysis

We used summary statistics such as percentages for categorical variables. We also determined the significant differences in the sociodemographic profile of participants between groups using Fisher's exact test for categorical variables. P-values < 0.05 were considered statistically significant. All analyses were performed using Stata version 14.

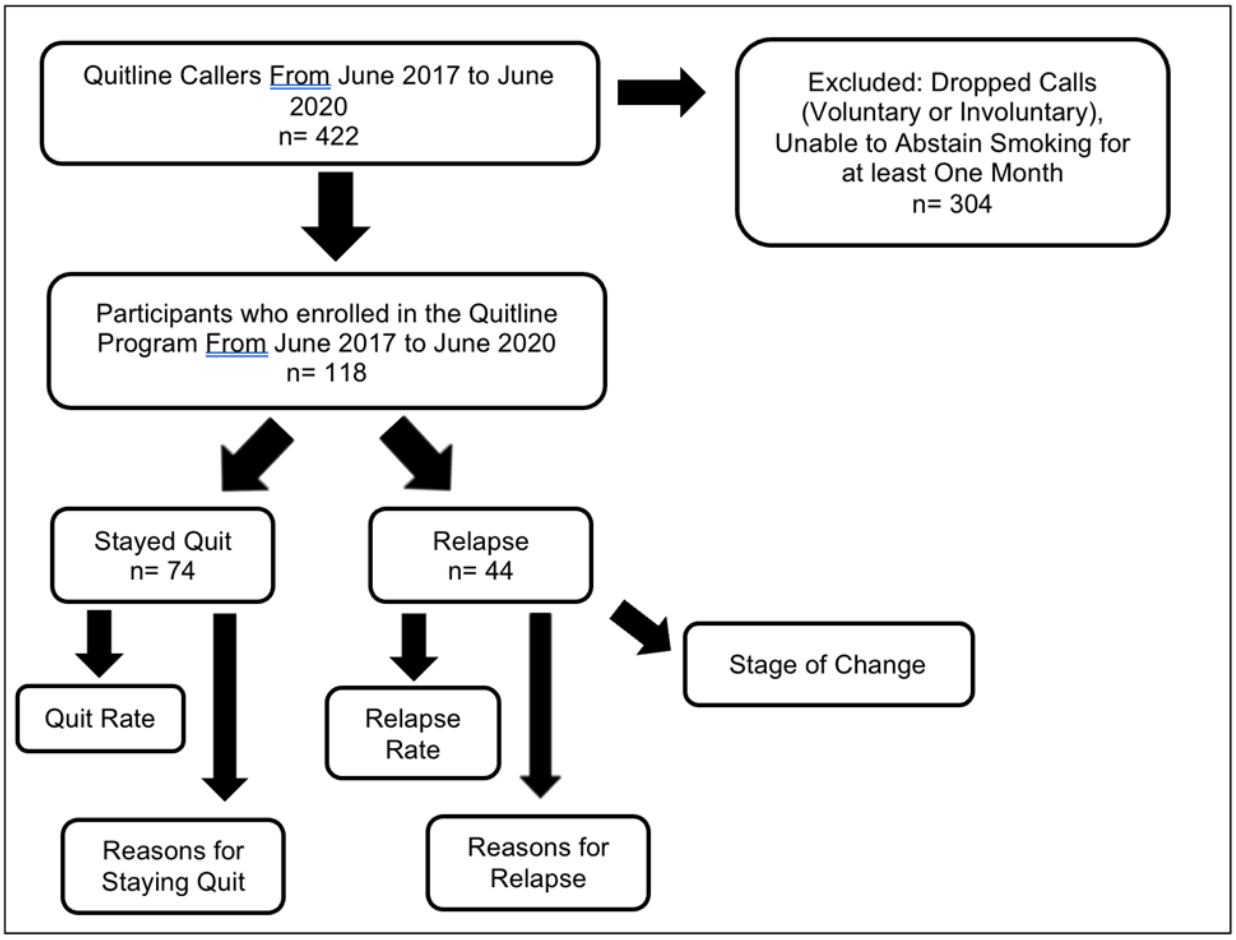


Figure 1. Flow chart of patient recruitment and identification of study population

Operational Definitions

1. Quitter — A participant of the Quitline program who abstained from smoking for at least 6 months from the time he/she signed up for the program
2. Relapse – A participant of the Quitline program who initially stopped smoking for at least 1 month but unable to abstain from smoking for at least 6 months from the time he/she signed up for the program
3. Drop or drop-out — Participants of the Quitline program who never quit or who dropped out of the program either voluntarily (as verbalized through phone calls) or involuntarily (participants who cannot be reached through their contact number; or assessed by the Quitline counselor)
4. Slip — participant of the Quitline program who initially stops smoking for less than 1 month and immediately returned to their regular smoking habit
5. Quit Rate or Abstinence Rate
    - Numerator represents the number of participants who received Quitline services and who quit smoking for at least 6 months
    - Denominator represents the number of participants who enrolled in the Quitline program
6. Relapse Rate
    - Numerator represents the number of participants who initially quit using tobacco for at least 1month but resumed smoking in their usual or regular smoking habit
    - Denominator represents the number of participants who enrolled in the Quitline program

Ethical Considerations

This research protocol study followed the National Ethical Guidelines for Health and Health Related Research and abide by principles of the Data Privacy Act. It was submitted to the Institutional Ethics and Review Board (IERB) for approval. Confidentiality was maintained by the principal investigator. Only the primary investigator, co-author, and research team had access to this data. Participants did not receive any payment or compensation in this research, since this research investigation only involved review of records gathered.

RESULTS

In this study, we identified a total of 422 callers of the DOH-LCP Quitline program from June 2017 to June 2020 (Figure 1). We excluded 304 participants, most of whom were those who voluntary or involuntary dropped and were unable to stop smoking for at least a month. We identified a total of 118 participants to be included in this study. In particular, 74 participants stayed quit for at least 6 months while 44 participants had relapse. From June 2017 to June 2020, the quit rate was 62.7% while the relapse rate was 37.3 %. Among those who stayed quit, we identified the quit rate and reasons for quitting. On the other hand, among those with relapse, we identified the relapse rate, reasons for relapse, and stage of change.

Baseline Characteristics

The baseline characteristics of the study population are further described in Table 1.

Outcome measures

More than half of the participants (50.1%) were between aged 25 and 44. About 47.3% and 56.8% were aged 25-44 among those who stayed quit at least 6 months and had relapse, respectively. The majority of the participants were males. About half were married, followed by participants who were single. About 47.5% have no child or children. A relatively higher proportion of participants who stayed quit for at least 6 months (50%) had child or children compared to those who had relapse (38.6%). Although majority had no information on educational attainment, about 41.5% were college

Table 1. Clinical Profile of Participants of Quitline Program who Stayed Quit and who Relapsed after Smoking Cessation

Clinical Profile	Total Participants (n=118)	Participants who Stayed Quit for at least 6 months (n=74)	Participants who Relapsed (n=44)	*p-value*
Age				0.193
18-24 y/o	10 (8.5%)	6 (8.1%)	4 (9.0%)	
25-44 y/o	60 (50.1%)	35 (47.3%)	25 (56.8%)	
45-64 y/o	41 (34.7%)	26 (35.1%)	15 (34.1%)	
≥ 65 y/o	7 (5.9%)	7 (9.5%)	0	
Sex				0.806
Male	98 (83.1%)	61 (82.4%)	37 (84.1%)	
Female	20 (16.9%)	13 (17.6%)	7 (15.9%)	
Civil Status				0.367
Single	48 (40.6%)	27 (36.5%)	21 (47.7%)	
Married	61 (51.7%)	40 (54.1%)	21 (47.7%)	
Separated	5 (4.3%)	4 (5.4%)	1 (2.3%)	
Widow/er	4 (3.4%)	3 (4.1%)	1 (2.3%)	
Family				0.174
With child/children	54 (45.8%)	37 (50%)	17 (38.6%)	
Without child/children	56 (47.5%)	31 (42%)	25 (56.9%)	
No data	8 (6.7%)	6 (8%)	2 (4.5%)	
Educational Attainment				0.132
High School	3 (2.5%)	3 (4.1%)	0	
College	49 (41.5%)	24 (32.4%)	25 (56.8%)	
No data	66 (55.9%)	47 (63.5%)	19 (43.2%)	
Occupation				0.435
Employed	77 (65.2%)	45 (60.8%)	32 (72.7%)	
Self-employed	4 (3.4%)	4 (5.4%)	0	
Student	5 (4.2%)	4 (5.4%)	1 (2.3%)	
Retired	5 (4.2%)	4 (5.4%)	1 (2.3%)	
Unemployed	13 (11%)	7 (9.5%)	6 (13.6%)	
No data	14 (11.9%)	10 (13.5%)	4 (9.1%)	
Comorbidities/Existing Medical Condition				0.21
No known comorbidities	89 (75.4%)	53 (71.6%)	36 (81.8%)	
Hypertension	19 (16.1%)	14 (18.9%)	5 (11.4%)	
Diabetes	2 (1.7%)	2 (2.7%)	0	
Cardiovascular disease	3 (2.5%)	3 (4.1%)	0	
Asthma	4 (3.4%)	3 (4.1%)	1 (2.3%)	
COPD	1 (0.8%)	1 (1.4%)	0	
Hyperlipidemia	4 (3.4%)	4 (5.4%)	0	
GERD	3 (2.5%)	3 (4.1%)	0	
Depression	4 (3.4%)	2 (2.7%)	2 (4.5%)	
OSA	1 (0.8%)	1 (1.4%)	0	
Smoking history				0.547
Less than 10 pack-years	47 (39.8%)	23 (31.1%)	24 (54.5%)	
At least 10 pack-years	71 (60.2%)	51 (68.9%)	20 (45.5%)	

graduates. There were more college graduates among participants who had relapse (56.8%) compared to those who stayed quit for at least 6 months (32.4%). The majority of the participants were employed (65.2%) including those self-employed (3.4%), and 11% were unemployed. The proportion of those employed was higher among those who had relapse than those who stayed quit for at least 6 months. About 75.4% had no comorbidities. The proportion of those with no comorbidities was significantly higher among those who relapsed (79.6%) compared to those who stayed quit for at least 6 months (71.6%). Most of the participants had a smoking history of at least 10 pack-years (60.2%) wherein the proportion of those who stayed quit was higher (68.9%) compared to those who relapsed (45.5%). There were no significant differences in age (p=0.193), sex (p=0.806), civil status (p=0.367), having family (p=0.174), educational attainment (p=0.132), occupation (p=0.435), comorbidities (p=0.21), and smoking history (p=0.547) between those who stayed quit for at least six months and those who relapsed.

In 2017, the quit rate was 18% while the relapse rate was 82%, as determined by the study done by Batungbacal et al (2018)8 during the program's first year of implementation. In 2018, the proportion of those who stayed quit for at least 6 months was higher (70.3%), compared to those who relapsed (29.7%). In 2019, the quit rate was 57.9% while the relapse rate was 42.1%. In January to June 2020, the quit rate was 58.8% while the relapse rate was 41.2%. Figure 2 shows a graph of the trends of quit rates and relapse rates across the years.

Outcome measures

More than half of the participants (50.1%) were between aged 25 and 44. About 47.3% and 56.8% were aged 25-44 among those who stayed quit at least 6 months and had relapse, respectively. The majority of the participants were males. About half were married, followed by participants who were single. About 47.5% have no child or children. A relatively higher proportion of participants who stayed quit for at least 6 months (50%) had child or children compared to those who had relapse (38.6%). Although majority had no information on educational attainment, about 41.5% were college graduates. There were more college graduates among participants who had relapse (56.8%) compared to those who stayed quit for at least 6 months (32.4%). The majority of the participants were employed (65.2%) including those self-employed (3.4%), and 11% were unemployed. The proportion of those employed was higher among those who had relapse than those who stayed quit for at least 6 months. About 75.4% had no comorbidities. The proportion of those with no comorbidities was significantly higher among those who relapsed (79.6%) compared to those who stayed quit for at least 6 months (71.6%). Most of the participants had a smoking history of at least 10 pack-years (60.2%) wherein the proportion of those who stayed quit was higher (68.9%) compared to those who relapsed (45.5%). There were no significant differences in age (p=0.193), sex (p=0.806), civil status (p=0.367), having family (p=0.174), educational attainment (p=0.132), occupation (p=0.435), comorbidities (p=0.21), and smoking history (p=0.547) between those who stayed quit for at least six months and those who relapsed.

In 2017, the quit rate was 18% while the relapse rate was 82%, as determined by the study done by Batungbacal et al (2018)8 during the program's first year of implementation. In 2018, the proportion of those who stayed quit for at least 6 months was higher (70.3%), compared to those who relapsed (29.7%). In 2019, the quit rate was 57.9% while the relapse rate was 42.1%. In January to June 2020, the quit rate was 58.8% while the relapse rate was 41.2%. Figure 2 shows a graph of the trends of quit rates and relapse rates across the years.

Tables 2 and 3 further shows the reasons for

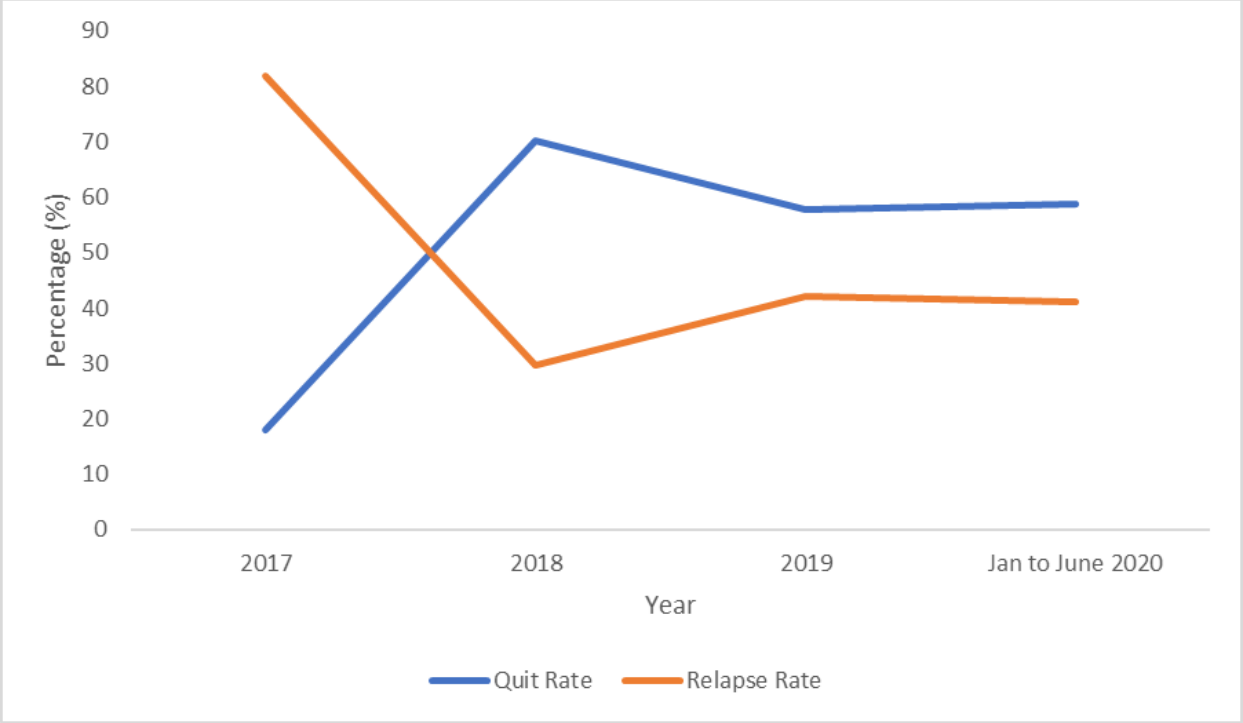


Figure 2. Quit rate and relapse rate among participants of the DOH-LCP Quitline program from June 2017 to June 2020

staying quit and reasons for relapse among the participants, respectively.

Among those who successfully stayed quit, a majority had medical- or health-related reasons (70.2%), such as the participants were able to observe improvement of symptoms, had better appetite and exercise capacity, and had reduced risk of having new illnesses. This was followed by personal reasons (41.9%) - the patient felt better, more productive, with greater sense of accomplishment, and improved stress management. Some have financial reasons (16.2%), that they were able to save more; while some were smoking-related (9.4%), that they were able to manage avoiding cigarette smoke with reduction of cravings. A few had social reasons (4.1%) be-

Table 2. Reasons for Staying Quit Among Participants of Quitline Program from 2017-2020

Reasons for Staying Quit	2017 n=27	2018 n=26	2019 n=11	2020 n=10	n=74
	Frequency (%)				
Personal/Emotional (*Feels better, Sense of accomplishment, productivity, Stress management*)	12 (44.4%)	8 (30.8%)	6 (54.5%)	5 (50%)	31 (41.9%)
Medical/Health-Related (*Reduces risk of having new illness, Improvement of symptoms, better appetite, better exercise capacity)*	15 (55.6%)	17 (65.4%)	9 (81.8%)	10 (100%)	52 (70.2%)
Social (*Sports-related, Peer-related*)	2 (7.4%)	1 (3.9%)	0	0	3 (4.1%)
Financial	5 (18.5%)	3 (11.5%)	1 (9.0%)	3 (30%)	12 (16.2%)
Smoking-related (*Avoidance of smell of cigarette, Reduction of cravings*)	1 (3.7%)	5 (19.2%)	1 (9.0%)	0	7 (9.4%)

cause of peer influences or sports engagement. The majority of participants' relapse was due to withdrawal symptoms and cravings (56.8%). This was followed by emotional stress (13.6%), and peer influence and relationships (4.5%).

Table 4 shows the stage of change among those participants who had relapse which is a measure to quantify motivation to smoking cessation. A majority of them were in the preparation stage (72.7%), followed by contemplation stage (13.6%), and action stage (11.4%).

and 45- to 64-year-old age group, males, married, with child or children, went to college, employed, with no known comorbidities, and with significant smoking history of at least 10 pack-years. There was a general increase in the trend of the quit rate and decrease in the trend of the relapse rate through the years. The main reasons for staying quit were medical- or health-related reasons while those for relapse were withdrawal symptoms and cravings. Among those with relapse, a majority of the participants were in the preparation stage of counseling followed by contemplation stage.

Table 3. Reasons for Relapse Among Participants of Quitline Program from 2017-2020

Reasons for Relapse	2017 n=18	2018 n=11	2019 n=8	2020 n=7	n=44
	Frequency (%)				
Emotional stress	2 (11.1%)	2 (18.1%)	2 (25%)	0	6 (13.6%)
Social *(Peer Influence, Relationships)*	2 (11.1%)	0	0	0	2 (4.5%)
Smoking Related *(Withdrawal symptoms, Cravings)*	11 (61.1%)	5 (45.5%)	5 (62.5%)	4 (57.1%)	25 (56.8%)
*No data	3 (16.7%)	4 (36.4%)	1 (12.5%)	3 (42.3%)	11 (25%)

Table 4. Stage of Change Among Participants of Quitline Program from 2017-2020 with Relapse

Stage of Change	2017 n=18	2018 n=11	2019 n=8	2020 n=7	n=44
	Frequency (%)				
Pre-contemplation	0	0	0	0	0
Contemplation	1 (5.6%)	1 (9.1%)	2 (25%)	2 (28.6%)	6 (13.6%)
Preparation	12 (66.7%)	9 (81.8%)	6 (75%)	5 (71.4%)	32 (72.7%)
Action	5 (27.8%)	0	0	0	5 (11.4%)
No Data	0	1 (9.1%)	0	0	1 (2.3%)

DISCUSSION

In this study, there were a total of 118 participants who enrolled in the DOH-LCP Quitline program from June 2017 to June 2020. A total of 74 participants were successful quitters while 44 participants had relapse. The majority of this study population were 25- to 44-year-old adults, male, married, had a college education, employed, with no known comorbidities, and with significant smoking history of at least 10 pack-years. Specifically, most of the participants who successfully quit were in the 25- to 44-year-old

Sociodemographic Characteristics

In this study, statistically, there was no observed significant difference between the two groups. Based on the sociodemographic profile of the study population, the results were still comparable with other previous studies done which showed that age, sex, marital status, socioeconomic status, education, smoking history and behavior were associated with smoking-cessation outcomes[9]. Majority of quit attempts were seen among males, in younger age group,

and well-educated. In another study made by Hatziandreu et al. (1990)[10], greater educational attainment was positively associated with quit attempts. On further investigations, older adults quit smoking more successfully than younger adult[11], males quit more than females[12], and being married was significantly associated with smoking cessation[9]. Adults with dependent children had greater likelihood of smoking cessation than those without children[13]. Higher successful cessation was also observed among those with college education[14.] In a study done by Youngmee and Won-Kyung (2014)[15], successful quitters also belonged to those who were employed and had higher income. The presence of comorbidities can increase the likelihood of smoking cessation. However, in a study done by Esen and colleagues (2020)[16], there was no significant difference between subjects with comorbidity and those without in terms of smoking cessation. Comorbidities such as chronic cardiovascular or pulmonary conditions have not been shown to have an effect on abstinence to smoking[17,18]. Some studies also showed that in terms of smoking history, the number of cigarettes consumed was not related to more successful smoking cessation as well[19]. Based on the demographic characteristics, it can also be inferred that there was quite a low number of other groups being reached by the Quitline, including the elderly, those without their own family or dependent children yet, those who were unemployed, those with lower educational attainment, and even those with comorbidities. As the Quitline also aims to increase awareness, it may also be necessary to widen its reach with these types of population. Extension of the influence of mass media campaigns and better assistance for callers to make them understand the program more easily can be done. Clinicians also play an important role by discussing the need for smoking cessation among their patients as part of the management of their comorbid conditions.

Quit Rate and Relapse Rate

Quit rate is a measure of success in encouraging smoking cessation among former daily smokers. According to Global Adult Tobacco survey (GATS) last 2015[20], "the percentage of current smokers who are interested in quitting (60.4% in 2009 to 76.7% in 2015) and the percentage of smokers who made quit attempts in the last 12 months (47.9% in 2009 to 52.2% in 2015) both increased significantly". However, the percentage of smokers who successfully quit in the past 12 months had a minimal change from 4.5% in 2009 to 4.0% in 2015. A study done by Batungbacal et al last 2018[8] showed a quit rate of 18% and a relapse rate of 82% during the Quitline's first year of implementation, with higher quit rates compared to the last report of GATS. In this study, we further observed a general increase in the trend of quit rates across the years. On the other hand, there was a decrease in the trend of relapse rate. This quit rate was also comparable with other international studies done with quit rates of 36%[21] and 48%[22]. The results of the study may indicate that in the past few years of the Quitline program, more individuals were becoming more aware of the program. More participants were interested in quitting and less were having relapse. This signifies that the Quitline program is becoming more effective across the years.

Reasons for Staying Quit and Relapse

This study further investigated the reasons for staying quit and reasons for relapse of the study population. The main reasons for staying quit were health-related reasons, personal reasons, and financial reasons. Majority of the participants in this study stayed quit because of the observed improvement of their symptoms (e.g. shortness of breath, easy fatigability, cough), better appetite, better exercise capacity, and avoidance of having new smoking-related diseases. Similar studies also showed that the most common reasons for quitting smoking and staying quit were improvement and protection of one's own health and the health of their family members, and to save money as well[23]. Other former smokers stayed quit because of their present comorbidities, and other future health concerns[24]. Some also accepted the fact that smoking poses health hazards and causes an

eventual decline or worsening of the health status[25]. Some also stayed quit as a practical way to save money for more important needs. A study done by Yang et al last 2006[26] showed that, among smokers, the ratio of the cost of cigarettes was still higher compared to their income, although the price of cigarettes was less compared with other Western countries. This also caused a financial burden to these smokers.

On the other hand, the main reasons for relapse were cravings and withdrawal symptoms, emotional stress, and peer influences. It has been found out that "smokers become dependent on the nicotine, the substance which causes the smoking behavior itself as well as its relapse[27]". Withdrawal symptoms, usually observed at 4-24 hours after cessation of nicotine-containing products, include irritability, anxiety, mood depression, restlessness, poor concentration, anorexia, and insomnia. Nicotine dependence is thus a significant barrier to making quit attempts and smoking cessation. In a study done by Hughes and Carpenter (2005)[28], it was observed that the higher an individual's level of dependence to nicotine, the lower the willingness or attempts to quit. In our study, there was still a number of participants who had relapse. For this group of participants, other strategies for smoking cessation may be done to eventually reduce their consumption and minimize their relapse. A more proactive counselling and more focused approach can be done for those who are still on low dependence, while the use of interventions including NRTs can be given for those with high nicotine dependence. The use of these NRTs may help in addressing the withdrawal symptoms of nicotine-dependent smokers. Another relapse factor is emotional stress, which has been negatively associated with smoking cessation. In this study, participants who had relapse felt that smoking somehow provided them relief during stressful situations. It has been shown in other studies that the feelings of stress encountered by smokers during periods of cessation were also attributed to nicotine dependence. A higher risk of relapse was also observed among those with increased stress levels associated with deprivation of nicotine[29]. Peer influences also contributed to smoking relapse. It has also been shown that peer influences can also contribute to relapse particularly in the younger population since they are more susceptible to peer pressure[30]. Smoking cessation is not only determined by the smoker's intention to quit but also influenced by the smoker's social interaction and environment. The Quitline program may therefore address these factors by improvement of the behavioral aspect of counseling and ways to counter social pressure.

Motivation to Quit

Motivation and readiness to quit were also shown to be one of the predictors of successful quitting. According to the stage of change by Prochaska et al (1992)[7], smokers must progress through several stages of behavior change to quit smoking. It starts with no plan yet to stop smoking (pre-contemplation), followed by the formation of an intention to quit (contemplation), preparation of one's self to quit (preparation), implementation of the new behavior of quitting (action), and finally maintain this new behavior (maintenance). Results from a study done by Iliceto et al (2013)[31] showed that the risk of relapse was the highest in the initial phase of smoking cessation. In this study, we identified that most of the participants with relapse were in the stage of preparation and contemplation at the time of their counseling. Identification of a smoker's stage of change therefore serves as a guide in the assessment of readiness to quit. Since most of the participants were in the stage where they already have intentions to quit and are preparing themselves to quit, it is crucial that the Quitline program provide further education regarding the bad effects of smoking, with emphasis on smoking cessation benefits and continued motivational strategies or techniques.

LIMITATIONS

In this The smoking abstinence of participants enrolled in the program were self-reported. There were no objective methods to ascertain the veracity of these self-reports, hence, may be subject to outcome bias. Among the successful

quitters, follow-ups were only made until one year from the time of smoking cessation. Hence, this study did not further evaluate whether these quitters continued to abstain smoking or had relapse beyond their first year of smoking cessation.

RECOMMENDATIONS

For clinical practice, the Quitline program can serve as an intervention for smoking cessation which can be offered by clinicians.

For the participants, it is recommended to extend follow-up period to more than one year for participants who quit to ensure continuous abstinence from smoking and to make necessary advice if these participants had relapse. Among those who had relapse, a more proactive behavioral counselling, modification of strategies including increasing the frequency of calls and integration of pharmacological interventions like NRTs can be used especially for those who have high nicotine dependence.

For future research, it is also recommended to have a study on the outcomes of participants started on NRTs as the latter has recently been approved to be prescribed for some Quitline participants in our institution. A follow-up of this study on the outcomes of participants enrolled in the Quitline program can still be made since it can also be a way to assess the effectivity of the program and make further improvements as necessary.

CONCLUSION

This study identified 118 participants who enrolled in the DOH-LCP Quitline program From June 2017 to June 2020. Participants were mostly adults (ages 25-44), male, married, had a college education, employed, with no known comorbidities, and with significant smoking history of at least 10 pack years. Statistically, there was no significant difference in the sociodemographic profile of participants who stayed quit and who relapsed. Through the years, there was a general increase in the quit rate and decrease in relapse rate. As of year 2020, the quit rate was 58.8% while the relapse rate was 41.2%. The main reasons for staying quit included medical- or health-related, personal, and financial reasons. On the other hand, reasons for relapse were withdrawal symptoms and cravings, followed by emotional stress, and peer influences. Among those with relapse, majority were in the stage of change of preparation and contemplation.

Since it started last June 2017, the Quitline program has been an effective strategy that helped a lot of smokers who are interested in smoking cessation. It has offered a more personalized approach since counselors are able to reach these individuals through phone calls. As people are becoming more aware of the ill-effects of smoking, some become more conscious of their health and so with the intention to quit this habit. Hence, it is also necessary for more individuals to become more aware of this program by increasing its accessibility, be it through various forms of advertisement.

Quitline and other smoking cessation programs must always consider the personal, emotional, behavioral, and social aspects of smokers for a more successful cessation outcome. An understanding of the various factors of quitting and relapse, as well as the stage of change are also necessary for a more individualized approach. Finally, integration of behavioral counselling, pharmacologic interventions, and other strategies may even provide better outcomes as well.

REFERENCES

1. World Health Organization. WHO report on the global tobacco epidemic, 2008: The MPOWER package (POPLINE Document No. 324513). Author; Geneva, Switzerland.
2. Stead et al. Nicotine replacement therapy for smoking cessation. Cochrane Database Syst Rev. 2008;1: CD000146.
3. Molyneux et al, 2003. Clinical trial comparing nicotine replacement therapy (NRT) plus brief counselling, brief counselling alone, and minimal intervention on smoking cessation in hospital inpatients. Thorax 2003; 58:484-488.

4. Gordon, J. et al. Do faxed quitline referrals add value to dental office-based tobacco use cessation interventions? The Journal of the American Dental Association, 2010, 141(8), 1000–1007.
5. Hughes, J. et al. Shape of the relapse curve and longterm abstinence among untreated smokers. Addiction. 2004;99: 29–38.
6. Reis, R. and Fortes R. Factors associated with non-smoking cessation in participants in the therapy group of a health center in the Federal District. Revisa. 2012;1(1):3-8.
7. Prochaska, J. et al. The process of smoking cessation: an analysis of precontemplation, contemplation, and preparation stages of change. J Consult Clin Psychol 1991;59:295e304.
8. Batungbacal, M. et al. The DOH-LCP Quitline Program: Participant Profiles and Outcomes of an Initial Cohort in the First Year of Implementation. Lung Center of the Philippines 2018.
9. Lee, C. and Kahende J. Factors associated with successful smoking cessation in the United States, 2000. Am J Public Health. 2007; 97: 1503–1509.
10. Hatziandreu E. et al. Quitting smoking in the United States in 1986. J Natl Cancer Inst 1990; 82: 1402e6.
11. Ockene J. et al. Relapse and maintenance issues for smoking cessation. Health Psychol. 2000;19(1 Suppl):17–31.
12. Ward K. et al. Gender differences in the outcome of an unaided smoking cessation attempt. Addict Behav. 1997; 22: 521–533.
13. Jarvis. M. The association between having children, family size and smoking cessation in adults. Addiction. 1996 Mar;91 (3):427-34.
14. Hansol, Y. et al. Factors Affecting Smoking Cessation Success of Heavy Smokers Registered in the Intensive Care Smoking Cessation Camp (Data from the National Tobacco Control Center). Osong Public Health Res Perspect 2018;9(5):240–247.
15. Youngmee, K. and C. Won-Kyung. Factors Associated with Successful Smoking Cessation in Korean Adult Males: Findings from a National Survey. Iranian J Publ Health, Vol. 43, No.11, Nov 2014, 1486-1496.
16. Esen, et al. Factors affecting success and abstinence within a smoking cessation clinic: A one-year follow-up study in Turkey. Tob. Prev. Cessation 2020;6 (December):71.
17. Argüder, E. et al. Factors Affecting the Success of Smoking Cessation. Türk Toraks Derg. 2013; 14: 81-87.
18. Kanatsız, B. et al. Evaluation of the Factors Affecting Success Rate and Medical Treatments In Smoking Cessation. Euras J Fam Med. 2017;6(2):65-71.
19. See, J. et al. Smoker motivations and predictors of smoking cessation: lessons from an inpatient smoking cessation programme. Singapore Med J. 2019;60 (11):583-589.
20. Global Adult Tobacco Survey: Country Report 2015. Department of Health-Philippines.
21. Lent, A. et al. Quit outcomes among clients through the state quitline: A retrospective observational study. BMC. 2018Public Health 18:1001.
22. Nair, U. et al. Quitline program utilization and cessation outcomes: A comparison of provider-referred clients by healthcare settings. Preventive Medicine Reports. 2019. 14:1008963.
23. Martins, R. et al. Factors motivating smoking cessation: a cross-sectional study in a lower-middle-income country BMC Public Health (2021) 21:1419.
24. Abdullah A. et al. Promoting smoking cessation among the elderly: what are the predictors of intention to quit and successful quitting? J Aging Health 2006; 18: 552e64.
25. Hu, Y. et al. Characteristics and Predictors of Abstinence Among Smokers of a Smoking Cessation Clinic in Hunan China. Front. Public Health 2021; 9:615817.
26. Yang, T. et al. Attitudes to smoking cessation and triggers to relapse among Chi-

nese male smokers. BMC Public Health.2006, 6:6.
27. Tan, M. and G. Agra. Smoking Behavior and Practices and Smoking Cessation in the General Population and Among Health Care Professionals in Metro Manila. Phil. J. Internal Medicine, 47: 129-135, May-June, 2009.
28. Hughes, J. and Carpenter, M. The feasibility of smoking reduction: an update. Addiction 2005;100:1074e89.
29. Robles, A. et al. The protective role of emotional intelligence in smoking relapse during a 12-month follow-up smoking cessation intervention. PLoS One. 2020; 15(6): e0234301.
30. Collins, S. et al. Preventing relapse following smoking. Current Cardiovascular Risk Rep 2010;4:421–8.
31. Iliceto, P. et al Predictors of success in smoking cessation among Italian adults motivated to quit. J Subst Abuse Treat. 2013;44(5):534-40.

Philippine Journal of Chest Diseases

Original Research

Association Between Smoking Status and Prognosis Among COVID-19 Patients Admitted at the Chinese General Hospital and Medical Center: A Cohort Study

Celene Marie R. Rey, MD and Tommy Yau, MD, FPCCP
Chinese General Hospital and Medical Center, Manila Philippines
Corresponding Author: *Dr. Celene Marie R. Rey (celenemarierey@yahoo.com)*

ABSTRACT

BACKGROUND: The SARS-COV2 was a cause of an outbreak of respiratory illness that came to be known in Wuhan, Hubei Province, China, in December 2019. The outcome of this viral disease is prolonged hospital stay, intensive care unit (ICU) admission, dependence on invasive mechanical ventilation, respiratory failure, and mortality. Several factors were already well-studied and recognized in conjunction with their association with prognosis during COVID-19 including old age, cardiovascular diseases, and diabetes. One important factor to investigate is the smoking status and the risks of COVID-19 outcomes among Filipinos.

OBJECTIVES: To determine the association between smoking status and prognosis among COVID-19 confirmed patients admitted at Chinese General Hospital from March 2020 to December 2022 .

METHODS: We conducted a retrospective cohort study that included 389 COVID-19 patients admitted at the Chinese General Hospital and Medical Center from March 2020 to March 2022 diagnosed with COVID-19. Association between smoking status and the clinical outcomes of interests (mortality, ICU admission, respiratory failure, and length of hospital stay) was determined by logistic regression analysis .

RESULTS: There were more patients with greater severity among smokers than non-smokers. Those ≥15 pack-year smokers had 22.94 times increased odds of mortality compared to non-smokers (95% CI 0.81 to 7.14, p = 0.115). Those who were ≥15 pack-year smokers had 39.72 times the odds of ICU admission compared to non-smokers (95% CI 11.33 to 139.18, p<0.001). Patients who were <15 pack-year smokers had 4.09 times the odds of ICU admission (95% CI 1.13 to 14.77, p = 0.031) compared to non-smokers. Patients who were ≥15 pack-year smokers had 111.55 times the odds of respiratory failure compared to non-smokers (95% CI 37.43 to 332.49, p<0.001). Lastly, patients who were <15 pack-year smokers had 7.13 times the odds of respiratory failure compared to non-smokers (95% CI 2.95 to 17.25, p<0.001).

CONCLUSION: The findings from this study support evidence that suggests an association between smoking and COVID-19 complications and disease progression. Smoking is an important risk factor for severity, in-hospital mortality, and morbidity of COVID-19.

KEYWORDS: *COVID-19, SARS-CoV2 virus, cigarette smoking, prognosis*

INTRODUCTION

COVID-19 is a coronavirus outbreak caused by SARS-CoV2 virus that initially appeared in Wuhan, Hubei Province, China in December 2019, but it has already evolved into a pandemic spreading rapidly worldwide. As of February 3, 2022, the outbreak of the coronavirus disease had been confirmed in over 220 countries and territories. The virus had infected over 385 million people worldwide, and the number of deaths had reached 5.7 million.[1] A number of researches have published risk factors for poor outcome in patients with COVID-19 which include older age, male sex, hypertension, diabetes, cardiovascular disease, and respiratory disease. COVID-19 can cause severe disease leading to hospitalization in intensive care units (ICU) and potentially death, especially in the elderly with comorbidities. According to the Centers for Disease Control and Prevention (CDC), 8 out of 10 deaths reported in the USA occurred in adults 65 years old and above.[2]

Another possible risk factor is smoking since it affects a person's overall health and damages nearly every organ of the body. Recent meta-analyses were performed and found that smokers have double the odds of COVID-19 progression risk globally. One of these was by Umnuaypornlert et al. where, based on 40 studies included in the meta-analysis, it was shown that both current smoking and former smoking significantly increased the risk of disease severity (OR 1.58, 95% CI 1.16 to 2.15, p=0.004; and OR 2.48, 95% CI 1.64 to 3.77, p<0.001; respectively) with moderate appearance of heterogeneity. Similarly, current smoking and former smoking also significantly increased the risk of death (OR=1.35, 95% CI 1.12 to 1.62, p=0.002; and OR 2.58, 95% CI 2.15–3.09, p<0.001; respectively) with moderate appearance of heterogeneity.[3]

Currently, there remains a distinct lack of clarity and high-quality evidence from our local data regarding the relationship between smoking status and prognosis of patients who tested positive for COVID-19. According to the Department of Health (DOH), the country's case fatality rate (CFR) as of December 7, 2021 is currently at 1.61% and is below the global average of 2.0%. This Philippine CFR was markedly lower than the 9% CFR reported in the Nikkei COVID-19 Recovery Index press release. The Department added that after cases and deaths peaked in September 2021, both have continuously declined after, along with the monthly case fatality rates. In October 2021, there were 4,348 deaths and a CFR of 1.84%, and a slightly lower figure for November 2021 with 838 deaths and a CFR of 1.81%.[4] As of January 2022, there are 57,999 deaths out of 3.67 million of COVID 19 cases in the Philippines.[5]

Therefore, due to the lack of local data, this retrospective study aims to evaluate the effect of smoking status on the prognosis of patients with COVID-19 admitted in a tertiary private hospital in the Philippines. Also, we wanted to compare the demographic and clinical characteristics of patients by in-hospital morbidity and mortality, and establish the association between smoking status and in-hospital morbidity and mortality.

METHODS

Study Design

The researcher utilized a retrospective cohort design. Participants included were COVID-19 patients admitted at the Chinese General Hospital and Medical Center from March 2020 to March 2022. Data was collected via retrospective review of medical charts from June to July 2022.

Study Setting

The study took place at the Chinese General Hospital and Medical Center, a tertiary private hospital located in Blumentritt, Manila, Philippines. Since the start of the pandemic, an average of 275 COVID-19 patients per month have been admitted.

Study Population

Adult COVID-19 patients admitted at the Chinese General Hospital and Medical Center from March 2020 to December 2022

Inclusion Criteria

- age over 18 years old

- confirmed positive for COVID-19 based on RT PCR done at Chinese General Hospital regardless of severity
- available data on smoking status
    * ≥15 pack -year smoker
    * <15 pack-year smoker
    * Non-smoker

Exclusion criteria

- Incomplete data
- Discharged against medical advice

Data Collection

The following data were obtained and reviewed from the medical charts and recorded: age, sex, comorbidities (i.e., hypertension, cardiovascular diseases, diabetes mellitus, chronic obstructive pulmonary disease (COPD), cancer, asthma or pulmonary tuberculosis (PTB), COVID severity on admission, oxygen requirement of the participants and those admitted at ICU. Clinical outcomes were obtained from medical charts including in-hospital mortality, in-hospital morbidity, and length of stay.

Operational Definition of Variables

1. In-hospital mortality – Patient died during hospital stay based on medical charts. Categorized as yes or no.
2. In-hospital morbidity – Patient developed any of the following conditions during hospital stay based on medical charts. Categorized as yes or no.
    - Mechanical ventilator use
    - ICU admission
    - Septic shock
3. Length of stay – the number of days from admission to discharge based on medical charts.
4. Smoking status on admission based on medical records.
5. Smoker – Patient's current smoking status based on self-report at the time of admission. The frequency of EGFR mutations is not significantly different between patients with non-small cell lung cancer who never smoked and those who smoked cigarettes up to 15 pack years.6 Categorized as non-smokers, <15 pack-year smokers, and ≥15 pack-year smokers
6. COVID-19 severity on admission based on medical records, following the definition given by the Department of Health, Philippines7
    - Mild
    - Moderate
    - Severe
    - Critical
7. Comorbidities – Patient's self-reported comorbidities at the time of admission obtained from medical charts such as diabetes mellitus, hypertension, lung disease (asthma, PTB), and cancer

Sample Size

Minimum sample size requirement was computed using R version 4.0.3. A minimum sample size of 244 is needed to achieve 80% power with 5% level of significance (two-sided) in a logistic regression analysis to detect a change in probability of mortality from a baseline value of 0.26 for non-smokers to 0.35 for smokers (Farsalinos, et. al., 2021). This sample size was increased to 373 to adjust for other co-variates of interest in a multiple regression with an expected R-squared of 0.40.

Statistical Analysis

The clinical and demographic profile and outcomes of patients with COVID-19 admitted in Chinese General Hospital from March 2020 to March 2022 were summarized by descriptive statistics. Non-normally distributed (age) and discrete numerical (length of hospital stay) variables were described as median and interquartile range. Categorical variables (sex, comorbidities, vaccination status, disease severity, mortality, ICU admission, and respiratory failure) were described as frequency and percentage. The clinical and demographic profiles were compared between three exposure groups, i.e., ≥15 pack-year smoker, <15 pack-year smoker, and non-smoker, by Kruskal-Wallis H test, chi-square or Fisher exact test of homogeneity, as appropriate, to determine the homogeneity of the characteristics between the three groups.

Fisher's exact test was used to compare cate-

gorical variables. Univariate analysis was performed for qualitative variables and reported as odds ratios (OR) with 95%confidence intervals (CI). Given the multiplicity of variables, only factors with a p value of <0.01 on the mentioned univariate analysis in the smoker cohort were entered into the multivariate analysis (binary logistic regression) to define independent risk factors for the principal outcome and focusing on the smoking status (≥15pack year smoker, <15 pack year smoker, or never). Mortality analysis was performed using Kaplan-Meier estimates and log-rank tests were used to compare factors. Two-sided p values of <0.05 were accepted as statistically significant.

The association between smoking status and the clinical outcomes of interests: mortality, ICU admission, respiratory failure, and length of hospital stay, was determined by logistic regression analysis. Among the different clinical outcomes of interest, length of hospital stay, being a numerical variable, was dichotomized by median split method into <10 days and ≥10 days for this analysis. For each outcome of interest, an initial univariable logistic regression was performed to screen for possible confounding variable among the different clinical and demographic profile. Those with p-value of <0.200 were included in the multivariable logistic regression. Significant confounding variables were confirmed by backward elimination model building using change-in-estimate criterion of 10%. Data analysis was performed using Stata version 17. Missing values were neither replaced nor imputed. Hypothesis testing were evaluated against a significance level of α =0.05.

RESULTS

A total of 389 patients met the enrolment criteria and were included in the study. There were 208 (53%) male and 181(46%) female patients. The majority of patients (199/389; 51%) were <15 pack-year smokers, while 120 (31%) were non-smokers, and only 70 (18%) were ≥15 pack-year smokers. The median age was 54 years. Table 1 shows the summary measures for age, comorbidities, and severity. In the overall cohort, the most frequent comorbidities were hypertension and diabetes mellitus. The character-

Table 1. Clinical profile of the participants of the study (N=389)

Clinical Profile	Full cohort	≥15 pack-year smoker	<15 pack-year smoker	Non-smoker	p-value
	n = 389	n = 70	n = 199	n = 120	
Age, *median (IQR)*	54 (25)	68 (24)	50 (25)	52.5 (25.5)	<0.001
Sex, *n*					0.001
Male	208 (53.5%)	51 (72.9%)	104 (52.3%)	53 (44.2%)	
Female	181 (46.5%)	19 (27.1%)	95 (47.7%)	67 (55.8%)	
Comorbidities, *n (%)*					
Hypertension	167 (42.9%)	51 (72.9%)	72 (36.3%)	44 (36.7%)	<0.001
Diabetes mellitus	106 (27.3%)	36 (51.4%)	46 (23.1%)	24 (20%)	<0.001
Cancer	16 (4.1%)	1 (1.4%)	9 (4.5%)	6 (5%)	0.519
Asthma	43 (11%)	1 (1.4%)	19 (9.6%)	23 (19.2%)	0.001
Pulmonary tuberculosis	89 (22.9%)	31 (44.3%)	25 (12.7%)	33 (27.5%)	<0.001
Vaccinated, *n (%)*	31 (8.3%)	5 (7.4%)	17 (8.8%)	9 (8%)	0.922
COVID-19 Severity, *n (%)*					<0.001
Mild	105 (27%)	0	16 (8%)	89 (74.2%)	
Moderate	162 (41.7%)	8 (11.4%)	130 (65.3%)	24 (20%)	
Severe	71 (18.3%)	28 (40%)	40 (20.1%)	3 (2.5%)	
Critical	51 (13.1%)	34 (48.6%)	13 (6.5%)	(3.3%)	

istics of the participants between the exposure groups were heterogenous with different comorbidities. Comparing smoking patterns, as shown in Table 1, patients with COVID-19 in the ever smoker group had a significantly higher proportion of diabetes with p value <0.05. There were more males among smokers than non-smokers. There were less patients with asthma among smokers than non-smokers. Among COVID-19 smokers of more than 15 pack-years, COVID-19 severity was classified as critical in 48.6%, severe in 40%, moderate in 11.4%, and mild in zero patients.

Table 2 shows the outcomes of the study participants with regard to the exposure smoker only. The total number of in-hospital mortality was 58 patients, in which most of them were from the ≥15 pack-year smoker group, followed by <15 pack-year smoker group (7%). Most of those admitted at ICU were from ≥15 pack-year smokers (51.4%), followed by <15 pack years (7.5%). The same trend was seen with the number of patients who had respiratory failure (≥15 pack-year smokers: 87.1%), <15 pack-year smokers: 26.6%, and non-smokers: 5%).

Following this, a multivariate analysis was performed. After adjusting for confounding factors, ≥15 pack-year smokers had a greater odds of death from all causes (OR 22.94, 95%CI 8.04 to 65.45, p<0.001) when compared with non-smokers. They also had a significantly higher odds of having complications of COVID-19 infection, being admitted to ICU, and having respiratory failure. Likewise, smokers with <15 pack-years had an increased odds of death compared to non-smokers (OR 2.40, 95% CI 0.81 to 7.14, p=0.115), but this independent risk was not as strong as that observed in the current smokers' group. It also showed that <15 pack-year smokers had a statistically significant higher odds of ICU admission and respiratory failure as compared to non-smokers. There was no sufficient evidence to conclude that smoking status was associated with length of hospital stay.

Table 3. Association of smoking with the different clinical outcomes of interest, among COVID-19 patients using multivariate analysis

Clinical outcomes	OR	95% CI	p-value
In-hospital mortality			
Non-smoker	Reference		
<15 pack-year smoker	2.40[a]	0.81, 7.14	0.115
≥15 pack-year smoker	22.94[a]	8.04, 65.45	<0.001
ICU admission			
Nonsmoker	Reference		
<15 pack-year smoker	4.09[b]	1.13, 14.77	0.031
≥15 pack-year smoker	39.72[b]	11.33, 139.18	<0.001
Respiratory failure			
Non-smoker	Reference		
<15 pack-year smoker	7.13[c]	2.95, 17.25	<0.001
≥15 pack-year smoker	111.55[c]	37.43, 332.49	<0.001
Length of hospital stay ≥10 days			
Non-smoker	Reference		
<15 pack-year smoker	1.51[d]	0.71, 3.24	0.285
≥15 pack-year smoker	1.16[d]	0.38, 3.59	0.793

[a]*Adjusted for the following confounder/s: age, pulmonary tuberculosis*
[b]*Adjusted for the following confounder/s: pulmonary tuberculosis*
[c]*Adjusted for the following confounder/s: age*
[d]*Adjusted for the following confounder/s: vaccination, COVID-19 disease severity*

Table 2. Multivariate analysis for in-hospital mortality

Clinical outcomes	Full cohort	≥15 pack-year smoker	<15 pack-year smoker	Non-smoker
	n = 389	n = 70	n = 199	n = 120
In-hospital mortality, *n*	58 (14.9%)	39 (55.7%)	14 (7%)	5 (4.2%)
ICU admission, *n*	54 (13.9%)	36 (51.4%)	15 (7.5%)	3 (2.5%)
Respiratory failure, *n*	120 (30.9%)	61 (87.1%)	53 (26.6%)	6 (5%)
Length of hospital stay, *median (IQR)*	10 (9)	16 (12)	11 (8)	6 (3)

Statistically significant p-value: p<0.05
** Composite endpoint of ICU admission, respiratory failure or length of hospital stay*

DISCUSSION

Previous researches have shown that smoking is associated with higher mortality and complication rates in patients with COVID-19. The aim of this study was to gather Philippine local data in the setting of a private tertiary hospital in terms of the association of smoking with the prognosis of COVID-19, and additional data with regard to comparing ≥15 pack-year smokers, <15 pack-year smokers, and non-smokers.

In another meta-analysis conducted by Patanavanich and Glantz where a total of 11,590 patients with COVID-19 from 19 studies were included, it was shown that in the overall cohort, 18.4% of the patients developed disease progression. Results between smokers and non-smokers were compared, and smokers were found to present with a higher rate of disease progression (29.8%) in contrast with non-smokers (17.6%), with a twofold increased odds for smokers (OR 1.91, 95%CI 1.42 to 2.59, p=0.001).[11]

In this study, the severity of disease was evaluated. Different confounding variables were taken into consideration. In all patients with COVID-19, the median age of smokers was only 3 years older than never smokers which may not have clinical significance. There was a statistically significant greater number of smokers among males, with which there were more patients with greater severity.

LIMITATION AND RECOMMENDATIONS

The study has several limitations such as recall and documentation biases on smoking history and COVID-19 clinical histories. Hospital-based studies have several limitations such as poor data quality and difficulty in collecting the history of smoking in an emergency room scenario.

CONCLUSION

After adjusting for significant confounding variables, smokers who smoked more than 15 pack-years have 22.94 times higher odds of dying, 39.72 times higher odds of ICU admission, and 111 times the odds of having respiratory failure compared to non-smokers.

Comparing <15 pack-year smokers with the non-smokers, they have 4 times the odds of ICU admission and 7 times the odds of respiratory failure compared to non-smokers. The findings from this study support evidence that suggests the association of smoking with COVID-19 complications and disease progression. Smoking is an important risk factor for severity, in-hospital mortality and morbidity of COVID-19. Public awareness with regard to smoking cessation and its importance is recommended based on this study.

CONCLUSION

7. Elflein, J. Number of coronavirus (COVID-19) cases worldwide as of February 3, 2022, by country: https://www.statista.com/statistics/1043366/novel-coronavirus-2019ncov-cases-worldwide-by-country/
8. National Center for Health Statistics Centers for Disease Control and Prevention https://www.cdc.gov/nchs/nhis/tobacco/tobacco_glossary.htm August, 2017
9. Umnuaypornlert A, Kanchanasurakit S, Lucero-Prisno DEI, Saokaew S. Smoking and risk of negative outcomes among COVID-19 patients: A systematic review and meta-analysis. Tob Induc Dis. 2021 Feb 4;19:09. doi: 10.18332/tid/132411. PMID: 33551713; PMCID: PMC7857247.
10. Department of Health: https://doh.gov.ph/press-release/PH-CASE-FATALITY-RATE-REMAINS-BELOW-2%25-GLOBAL-AVERAGE Dec 2021
11. Republic of Philippines Department of Health: https://doh.gov.ph/covid19tracker February 2022
12. Janjigian, Y. Y., McDonnell, K., Kris, M. G., Shen, R., Sima, C. S., Bach, P. B., Rizvi, N. A., & Riely, G. J. (2010). Pack-years of cigarette smoking as a prognostic factor in patients with stage IIIB/IV nonsmall cell lung cancer. Cancer, 116(3), 670–675.
13. Republic of the Philippines Department of Health: Interim Guidelines on the COVID-19 Disease Severity Classification and Management: July 2020
14. Li Y-C, Bai W-Z, Hashikawa T. The neuroin-

vasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients. J Med Virol 2020;92:552–5. 10.1002/jmv.25728
15. Garufi G, Carbognin L, Orlandi A, et al.. Smoking habit and hospitalization for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-related pneumonia: The unsolved paradox behind the evidence. Eur J Intern Med2020;77:121–2. 10.1016/j.ejim.2020.04.042
16. Qiu F, Liang C-L, Liu H, et al.. Impacts of cigarette smoking on immune responsiveness: up and Down or upside down? Oncotarget2017;8:268–84. 10.18632/oncotarget.13613
17. Patanavanich R, Glantz SA. Smoking is associated with COVID-19 progression: a meta-analysis. Nicotine Tob Res 2020;22:1653–6. 10.1093/ntr/ntaa082
18. Mahabee-Gittes, Mendy, A, Merianos A et al. Assessment of Severe COVID-19 Outcomes using measures of Smoking Status and Smoking Intesity: Int J Environ Res Public Health. 2021 Sep; 18(17): 8939.
19. Smith J, Sausville E et Al Cigarette Smoke Exposure and Inflammatory Signaling Increase the Expression of the SARS-CoV-2 Receptor ACE2 in the Respiratory Tract; Dev Cell. 2020 Jun 8; 53(5): 514–529.e3.Published online 2020 May 16. doi: 10.1016/j.devcel.2020.05.012
20. Farsalinos, K etal Smoking prevalence among hospitalized COVID-19 patients and its association with disease severity and mortality: June 2020
21. Zhang, H, Ma, S. et al Association of smoking history with severe and critical outcomes in COVID-19 patients: A systemic review and meta-analysis February 2021
22. Kozak R, Prost K, Yip L, et al. . Severity of coronavirus respiratory tract infections in adults admitted to acute care in Toronto, Ontario. J Clin Virol 2020; 126: 104338.
23. Paleiron, N, Mayet, A et al. Imapct of Tomabcco Smoking on the Risk of COVID-19: A Large Scale Retrospective Cohort Study 2021 Aug 4;23(8):1398-1404.
24. Mehra MR, Desai SS, Kuy S, Henry TD, Patel AN. Cardiovascular disease, drug therapy, and mortality in COVID-19. New Engl J Med. 2020. doi: 10.1056/NEJMoa2007621.
25. Alqahtani JS, Oyelade T, Aldhahir AM, et al. Prevalence, severity and mortality associated with COPD and smoking in patients with COVID-19: a rapid systematic review and meta-analysis. PLoS One. 15 (5):e0233147.

Meta-analysis on the Diagnostic Value of Virtual Bronchoscopic Navigation (VBN)-assisted Radial Endobronchial Ultrasound (r-EBUS) versus r-EBUS Alone for the Biopsy of Peripherally-located Solitary Pulmonary Nodules

Mohamad Alisar Abdullatif, MD; Richard Boado, MD; Paul Rilhelm Evangelista, MD, FPCCP
Lung Center of the Philippines, Quezon City
Corresponding Author: *Dr. Mohamad Alisar Abdullatif (djal_dhek07@yahoo.com.ph)*

ABSTRACT

BACKGROUND: Solitary pulmonary nodules (SPN) are a diagnostic challenge for physicians especially when the lesion is located peripherally. Radial endobronchial ultrasound (r-EBUS) is a known alternative to CT scan-guided trans-thoracic lung biopsy with less complication rate but inferior diagnostic yield. Virtual bronchoscopic navigation (VBN) can be used in combination with EBUS when getting a biopsy sample for SPN.

OBJECTIVES: To determine if VBN + r-EBUS increases the diagnostic yield among patients with peripherally-located solitary pulmonary nodules versus r-EBUS alone when doing a biopsy.

METHODS: We conducted a a database search for randomized controlled trials comparing the diagnostic yield between VBN + EBUS vs EBUS alone among patients with SPN. Four studies satisfying the inclusion criteria were evaluated by two investigators for study design and baseline characteristics, potential bias, and heterogeneity. Random effects model meta-analysis was performed.

RESULTS: With an overall risk ratio estimate of 1.1 [1.00, 1.21] at 95% CI, there is no significant difference in the diagnostic yield statistically between VBN + r-EBUS vs r-EBUS alone but there is a trend towards a better yield for the combined group. The complication rate has an overall risk ratio of 0.72 at 95% CI [0.31, 1.64]. This again shows a trend towards benefit with the combined group. For the total examination time and positioning time, both showed negative overall mean difference (-3.34 at 95% CI -6.24, 0.44 and -3.52 at 95% CI -4.48, -2.57 respectively) in favor of the combined group.

CONCLUSION: The diagnostic yield showed no significant difference but suggests a small but statistically significant increase in the risk of outcome in the VBN + r-EBUS versus r-EBUS alone with some uncertainty in the estimate. It is a safe procedure and offers less total examination time and positioning time when compared to r-EBUS alone.

KEYWORDS: *Solitary pulmonary nodules (SPN), radial endobronchial ultrasound (r-EBUS), virtual bronchoscopic navigation (VBN)*

INTRODUCTION

Solitary pulmonary nodule (SPN) is a discrete, single lung opacity measuring less than 3 cm. Most cases are incidental finding during a routine chest CT scan for lung cancer screening or indications other than the respiratory system and pose a diagnostic challenge to clinicians since most patients are asymptomatic. Often, they are benign, but in the absence of biopsy, differentiation between benign and malignant lesion is difficult. Cases that are found to be malignant are usually in their early potentially curable stage. [1,2]

Getting a biopsy sample can be particularly difficult when these lesions are located peripherally since most SPNs are detached from the pleura. There is no gold standard procedure for getting a biopsy, but many centers rely on trans-thoracic lung biopsy (TTNA) under CT guidance, and it had stayed for many years as a standard of care for SPN for its high diagnostic yield. Diagnostic sensitivity or diagnostic yield as operationally defined in this study is the likelihood that a biopsy sample is adequate and can provide the histopathologic information needed to establish the diagnosis of SPN regardless if it is benign or malignant. The problem with TTNA is its high risk for complications which has led to the development of new bronchoscopic modalities such as radial endobronchial ultrasound (r-EBUS), electromagnetic navigation bronchoscopy (ENB), and Virtual Bronchoscopic Navigation (VBN). [3,4]

Endobronchial ultrasound guided transbronchial needle aspiration (EBUS-TBNA), a minimally invasive procedure, has become part of the workup for centrally-located pulmonary lesions or mediastinal tumors. It is particularly useful in diagnosing lung cancer and mediastinal lymph node sampling for staging. There are two types: the common linear (Convex) EBUS with attached ultrasound transducer at the tip of the bronchoscope which allows the performer to view masses in close contact with the airway in real-time; and radial EBUS which allows the performer to access peripheral pulmonary nodules not accessible by a regular bronchoscope by inserting a miniature ultrasound probe through the instrument channel of a standard bronchoscope.[5,6]

In a meta-analysis done by Muhammad S. Ali et al. (2017) evaluating the diagnostic yield and other performance characteristics of r-EBUS (57 studies with a total of 7872 lesions included from 2002 to 2016), the overall diagnostic yield was high at 70.6% (95% CI: 68-73.1%). It was even higher when the lesion size is more than 2 cm, malignant in nature, and with bronchus sign on chest CT scan. The overall complication rate was very low at 2.8%.[4]

Complication is less when radial EBUS guided trans-bronchial approach for biopsy (r-EBUS+TBNB) is compared to CT guided trans-thoracic biopsy. Although it has a good diagnostic yield, it is still inferior to the latter (pooled value of 75% (98% confidence interval [CI]) vs 93% (98% confidence interval [CI]). The recommendation on the same study done by Yeji Han et al. (2018) was to do a percutaneous approach for PPL ≤ 2 cm (pooled diagnostic yield: 92%, 95% CI: 88-95 versus 66%, 95% CI: 55-76), but consideration of trans-bronchial approach maybe reasonable when the lesion size is greater than 2 cm (diagnostic yield improved to 81%, 95% CI: 75-85) given its better safety profile[13]. In another study by Wei Wang et al. (2018), same finding of inferiority for overall diagnostic accuracy (65% vs 85%) with r-EBUS vs CT guided biopsy.[14]

Virtual bronchoscopy is a new technology for diagnosing PPL. It provides a real-time path navigation within the lungs for lung biopsy via virtual animation created thru 3d reconstruction of pre-procedural CT scan images side-by-side with live bronchoscopic views. It guides the bronchoscopist to the target lesion, shortening the bronchoscope arrival time, and increases the diagnostic yield in doing trans-bronchial lung biopsy (TBNA) when done with EBUS.[8]

Ishida et al. (2017) performed a multicenter prospective RCT involving 199 patients who were randomly assigned to VBN assisted EBUS and non-VBN assisted. The diagnostic yield revealed 80.4% vs 67.0%; p = 0.032 favoring the combined group. The positioning time and the total duration of the procedure were reduced also in the combined group. Only one complication (pneumothorax) was noted in the non-VBN group.[22]

Chen et al. (2016) also evaluated this earlier claim of increased diagnostic yield through a randomized controlled trial of 184 patients with SPN and compared VBN+EBUS with EBUS only. Findings revealed that the combined procedure did not improve diagnostic yield (72.04% vs 69.23%), contrary to the earlier study mentioned. Mean operation time was less with the combined group (45±10) min vs (55±10) min, affirming the findings of Ishida et al. In general, VBN+EBUS was well tolerated and no severe procedure-related complications were reported such as pneumothorax and bleeding.[20]

Another study done by Bo et al. (2019) confirmed earlier findings of Chen et al. and concluded that there is no significant difference in the diagnostic yield between VBN+EBUS vs EBUS alone (72.3% vs 74.3%). The same holds true for the total bronchoscope operation time, but the positioning time is less in the VBN+EBUS group (7.96 ± 1.18 min in the combined group versus 11.92 ± 5.37 min in the EBUS group, $p < 0.05$).[21]

Xu et al. (2019) on the other hand confirmed the 2011 study by Ishida et al. in 115 patients with SPN who underwent transbronchial lung biopsy. It was found out that when the lesion is ≤ 2 cm, the diagnostic yield is improved to 80% (P=.41) with the combined group compared to doing EBUS alone [53.6% (P=.41)]. The positioning time conforms with the result of earlier studies at 5.67 ± 2.48 min vs 8.65 ± 2.23 min, P = .015 favoring the combined group. There was no significant difference in the examination time and rate of complications between the two groups.[13]

Although a retrospective controlled study but worthy of mention, latest among the studies reviewed was the one done by Liu et al. (2020) where 236 patients with peripheral lung cancer (nodule diameter 8-30mm diagnosed through HRCT) from three different centers were enrolled between October 2018 to December 2019. Those who underwent VBN + EBUS were included in the observation group, and those who underwent EBUS-GS were included in the control group. Findings of the study revealed no significant difference in the diagnostic yield and total operating time between the two groups.

Question remains whether this added expense for the patient and institution for doing the combined procedure over EBUS alone equates to less complication and better diagnostic yield. The other issue is whether it does decrease the number of procedures to be done in a patient with SPN to arrive at a definitive histopathologic diagnosis by avoiding doing both TBNA and TTNA.

This study will attempt to answer to the earlier question of possible added benefit with VBN + EBUS. The results will help guide doctors and hospitals with regard to procuring these modalities in aid of clinical decision-making for SPN.

Upon searching PubMed, Cochrane library, Embase, and CT.gov, four randomized controlled trials published were seen but with no meta-analysis yet done comparing VBN + EBUS vs EBUS alone hence this study was pursued. A search for unpublished data with the same nature of study was not done during the conduct of this study.

METHODS

Criteria for considering studies for this review

We included all published randomized controlled trials comparing the diagnostic value of VBN + EBUS vs EBUS among patients with

SPN. Participants were adults ≥18 years old diagnosed with peripheral SPN on chest CT scan regardless of their comorbidities. Interventions were VBN combined with r-EBUS and r-EBUS only. The outcome measures involve a primary outcome (diagnostic yield) and secondary outcomes (complication rate, total examination time, and positioning time). All studies included should at least satisfy the primary but not necessarily the secondary outcomes.

Search Methods

We searched PubMed (MEDLINE), Embase, Cochrane library, and ClinicalTrials.gov using the Boolean language. Maximum sensitivity search strategy for the expansion of study variables was done using the operational term "OR". Search result for both the population and interventions were intersected, and then narrowed by filtering (study design, English language). The actual search was done on October 1, 2020. We included studies published between 2011 to 2019. The search terms included the following: free text - navigational bronchoscopy, virtual bronchoscopic navigation, virtual bronchoscopy, endobronchial ultrasound or EBUS, solitary pulmonary nodule, small pulmonary nodule, peripherally located nodule; mesh – solitary pulmonary nodule, bronchoscopy.

+ EBUS and EBUS alone as comparator, and diagnostic yield as an outcome and not necessarily the secondary outcomes. Exclusion criteria were; non-comparative studies evaluating the diagnostic yield VBN + EBUS, non-RCT trials (we only included randomized controlled trials in this study), and studies involving SPN more than 30mm in size.

Full text of studies that met the inclusion/ exclusion criteria were reviewed independently by two trained investigators. Disagreement was resolved by a third-party investigator (research adviser). Included studies along with their study characteristics were recorded.

Two reviewers extracted the data independently. Study characteristics such as setting, location, intervention groups, randomization, treatments, inclusion and exclusion criteria, and participants characteristics as well as the clinical outcomes such as diagnostic yield, positioning time, total examination time, and complication rate will be extracted and recorded. Disagreement was resolved by a third party (adviser).

The two authors independently assessed the risk of bias using the template from the Cochrane

PubMedSearchHistory

Search numb	Query	Sort By	Filters	Search Details	Results	Time
9	((ebus) OR (endobrc		Randomized Controlled Trial	("ebus"[All Fields] OR (("endobronchial"	9	18:22:06
8	((ebus) OR (endobronchial ultrasound)) AND (((VBN			("ebus"[All Fields] OR (("endobronchial"	183	18:22:01
7	((VBN) OR (navigational bronchoscopy)) OR (virtual I			"VBN"[All Fields] OR (("navigability"[All	637	18:21:46
6	virtual bronchoscopic navigation			("virtual"[All Fields] OR "virtuality"[All F	136	18:21:31
5	navigational bronchoscopy			("navigability"[All Fields] OR "navigable'	515	18:21:10
4	VBN			"VBN"[All Fields]	155	18:20:55
3	(ebus) OR (endobronchial ultrasound)			"ebus"[All Fields] OR (("endobronchial"[	4,007	18:20:48
2	endobronchial ultrasound			("endobronchial"[All Fields] OR "endobr	3,755	18:20:36
1	ebus			"ebus"[All Fields]	1,950	18:20:24

Figure 1. PubMed search history

Data Collection and Analysis

Retrieved citation titles and abstracts were evaluated if they meet the inclusion criteria. The inclusion criteria were; studies whose population includes only patients with SPN measuring ≤ 30mm, interventions involving VBN

Handbook for Systematic Reviews of Interventions (see appendix A). ROB-2 tool was used, and we evaluated for random sequence generation and allocation concealment for selection bias, blinding of outcome assessment for detection bias, incomplete outcome data for attrition bias,

and selective reporting for reporting bias. Disagreements were resolved by a third party (research adviser).

We used ratio/percentage for the diagnostic yield and complication rate and means (in minutes) ± standard deviation for positioning time and total procedure time. Statistical analysis was performed using the Review Manager 5.4. Random effects model was used for the meta-analysis on the assumption that true size effect will be similar but not identical among the studies included. This model represents the lack of knowledge about why real, or apparent, intervention effects differ by considering the differences as if they were random.

The researcher recognizes possible sources of heterogeneity such as; the intervention being operator dependent, experience of the centers/ hospitals involved in the studies, and differences in the procedure methodology. Heterogeneity was measured using the I^2 statistic, chi-square, p value, and visual inspection of Forest plot. We considered substantial heterogeneity if the I2 is ≥ 50% or chi square p-value is <0.1.

- 0% to 40%: might not be important
- 30% to 60%: may represent moderate heterogeneity
- 50% to 90%: may represent substantial heterogeneity
- 75% to 100%: considerable heterogeneity

(Note that the overlapping ranges and the equivocation "may" imply acknowledgement that the thresholds are both arbitrary and uncertain.)

We assessed for reporting bias using the funnel plot which is a simple scatter plot of the intervention effect estimates from individual studies against some measure of each study's size or precision. Precision of the estimated intervention effect increases as the size of the study increases. Effect estimates from small studies will therefore scatter more widely at the bottom of the graph, with the spread narrowing among larger studies. Statistical analysis was performed using Review Manager 5.4. Sensitivity analysis by study design and risk of bias were done if there is evidence of small-study effects. This depends on between study heterogeneity and if publication bias was identified.

RESULTS

Description of Studies

The study selection process is depicted in Figure 2 PRISMA Flow Diagram. Database search using PubMed, Cochrane library, Embase, and Clinical Trial.gov yielded 70 reference studies. Duplicates totaling 30 were removed, and the 40 remaining were initially screened for eligibility using title and abstract which eliminated another 31 references. The nine remaining studies were screened using their full text whether the inclusion and exclusion criteria were met. A final of four studies meeting the inclusion criteria were included in the meta-analysis, with a total of 1163 patients included.

All of the studies included were randomized controlled trials published between 2011 and 2019, and all except for the study done by Ishida et al. were conducted in China. Two studies (Chen et al and Xu et al) were conducted in single centers, while the remaining two were multicenter studies. Majority of the patients were male, and the mean and median age were tabulated on Table 1. The primary outcomes were reported in all four studies, while the secondary outcomes were also reported in all studies except Chen et al. which did not include the positioning time in his reported outcomes.

Five studies were excluded from a total of 9 studies using full text review for not satisfying the intervention. One study satisfied all the interventions and outcomes but was excluded because it was a retrospective study.

Risk of Bias of Included Studies

The following were used to assess the risk of bias: random sequence generation and allocation concealment for selection bias, blinding of participants and personnel for performance bias, blinding of outcome assessment for detection bias, incomplete outcome data for attrition bias, and selective reporting for reporting bias.

Table 1. Study Characteristics

Author, Year Published, Study Design, Location	Population (PPN ≤ 30mm)	Age	Sex (% male)	Intervention	Comparator	Outcome
Ishida et al. 2017, RCT, Japan	194	Median Age of 69 (21-85)	121 (62.4%)	VBN + r-EBUS (n=99)	r-EBUS only (n=95)	Diagnostic yield, Complication rate, Examination time, Positioning time
Chen et al. 2016, RCT, China	184	Mean Age of 62 ± 10.5	117 (63.6%)	VBN + r-EBUS (n=93)	r-EBUS only (n=91)	Diagnostic yield, Examination time,
Bo et al. 2019, RCT, China	670	Mean Age of 57.14 ± 11.46	409 (61%)	VBN + r-EBUS (n=334)	r-EBUS only (n=336)	Diagnostic Yield, Complication rate, Examination time, Positioning time
Xu et al. 2019, RCT, China	115	Mean Age of 56.7 ± 11.8	52 (45.2%)	VBN + r-EBUS (n=55)	r-EBUS only (n=60)	Diagnostic Yield, Complication rate, Examination time, Positioning time

Assessment of the studies was done using the template from the Cochrane Handbook for Systematic Reviews of Interventions with an overall assessment of no serious risk and none of the studies was seriously flawed. A graph and summary of the risk of bias assessment generated using Review Manager 5.4 is found on Figure 3.

Random Sequence Generation (Selection Bias)
All studies used randomization during the selection of the patients which minimized selection bias. Chen et al. used random number method, while Bo et al. used computer for randomization. Ishida et al. randomized the participants based on lesion size (mishidaean diameter <2 cm or 2-3 cm) and bronchoscopists used a randomized block design to ensure that these factors were balanced in the study arms.

Allocation Concealment (Selection Bias)
Allocation concealment was observed in all three studies to minimize foreknowledge of the next allocation by the participants thereby preventing bias. Although it was not elaborated, but it can be inferred from the method of random sequence generation from the different studies mentioned above, except for Xu et al. which did not elaborate on the means of randomization.

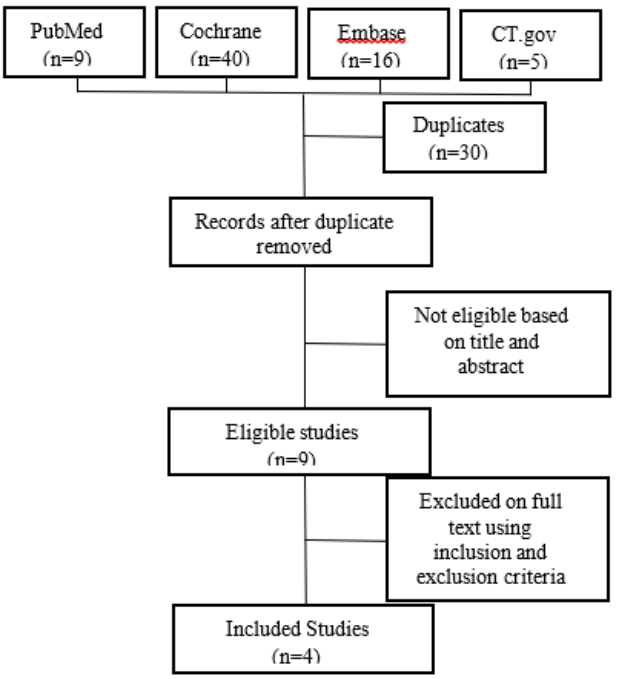


Figure 2. Flow diagram showing the study selection process for meta-analysis

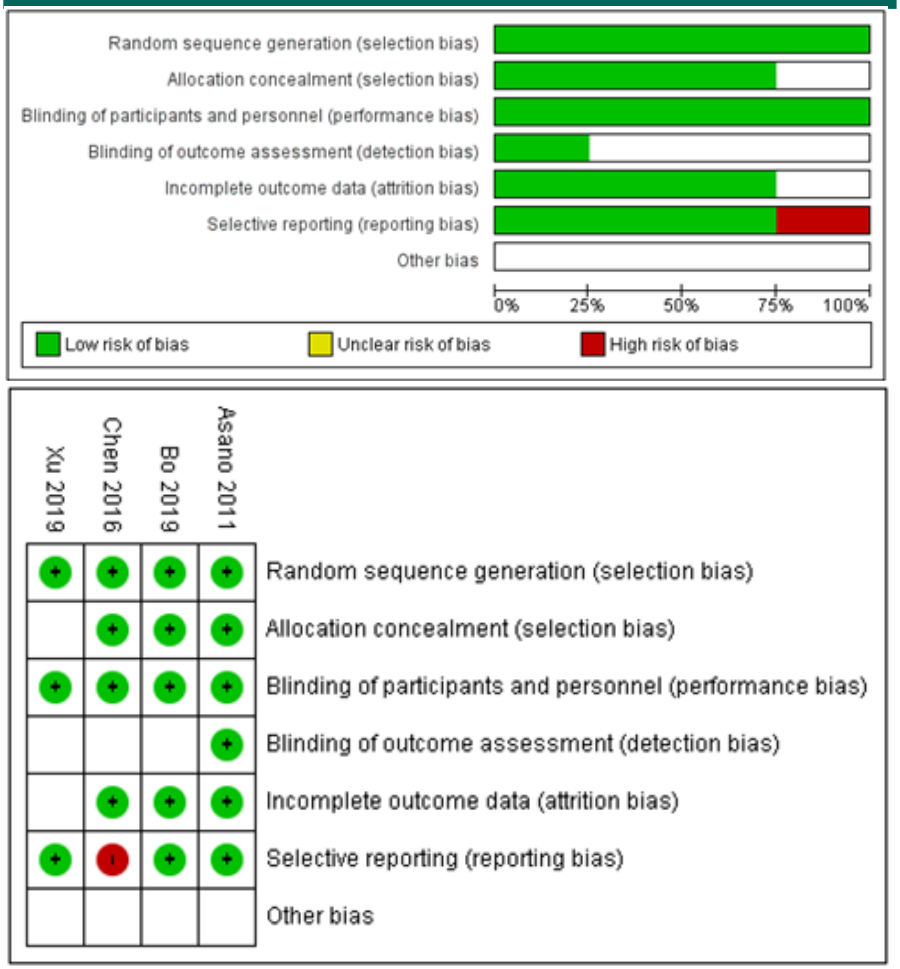


Figure 3. Risk of bias graph (top) and summary (bottom): review authors' judgement about each risk of bias item for each included study

Blinding of Participants and Personnel (Performance Bias)

Blinding of both the participants and the personnel was not possible due to the procedural nature of the studies.

Blinding of Outcome Assessment (Detection Bias)

In the study done by Ishida et al., the pathologist who read the specimen was blinded to the randomization of the study groups. The remaining 3 studies had unclear means of outcome assessment.

Incomplete Outcome Data (Attrition Bias)

All four studies did not report significant drop-out, thus minimizing attrition bias.

Selective Reporting (Reporting Bias)

One study was judged to have report selection bias because it did not elaborate on the bleeding complications of 12 study participants and concluded directly that the study had no bleeding complications on the bases of the absence of hemoptysis.

Effects of Intervention

The findings of the four included studies are summarized in Table 2. Ishida et al. reported an increased diagnostic yield with VBN + EBUS. While the other three studies did not find any significant difference statistically, all of them presented increased diagnostic yield, with a mean diagnostic yield of the combined group above that of the control group. VBN + r-EBUS

group has a pooled diagnostic yield of 75.9%, while the r-EBUS group has 70.44%. Short of statistical computation, based on the data summarized in Table 2, among patients with solitary pulmonary nodules, VBN + EBUS may improve the diagnostic yield in doing biopsy compared to doing EBUS alone.

Secondary Outcomes

Complication rates were reported in all studies except for one with unclear reporting as assessed by the investigator. Both arms showed a low complication with VBM + EBUS, showing an incidence of 9/488 (1.844%) versus 13/491 (2.65%) for EBUS alone, as shown in Table 3 and Figure 4, with an overall risk ratio of 0.72 at 95% CI [0.31, 1.64]. This again shows a trend towards benefit with the conclusion that the VBN combined with EBUS does not increase the rate of complications. In the study done by Ishida et al., the only reported complication was mild pneumothorax in a single patient in the r-EBUS group. In the study done by Xu et al., the combined group had pneumothorax which was controlled by oxygen inhalation after 5 days, and bleeding (20 ml) which was controlled by injection of thrombin and epinephrine. Finally, the study done by Bo et al. had 4 incidences of hemorrhage and 7 pneumothoraces, 1 needing intervention for the r-EBUS group, and 3

Table 2. Summary of outcomes from the 4 studies com paring VBN + r-EBUS vs EBUS alone

	Diagnostic Yield	Complication Rate	Total Examination Time	Positioning Time
Asano et. al (2011) RCT, n=194	↑	↔	↓	↓
Bo et. al (2019) RCT, n=670	↔	↔	↔	↓
Chen et. al (2016) RCT, n=184	↔	↔	↓	-
Xu et. al (2019) RCT, n=115	*↔	↔	↔	↓

Legend:
↑ *Increased with VBN + r-EBUS*
↓ *Decreased with VBN + r-EBUS*
↔ *No significant difference between VBN + r-EBUS vs r-EBUS alone*
* *Further analysis revealed increased diagnostic yield when the lesion is ≤ 20mm*

Primary Outcome (Diagnostic Yield)

Diagnostic yield was available as an outcome for all four studies. The total number of participants was 1163, distributed into 581 in the combined group and 582 in the r-EBUS group. Table 3 shows the individual diagnostic yield (in ratio). With an overall risk ratio estimate of 1.1 [1.00, 1.21] at 95% CI (also shown on figure 4) and a Forest plot that touches 1, there is no significant difference statistically between the two interventions but there is a trend towards a better diagnostic yield for the combined [441/581 (75.9%) versus 410/582 (70.44%) for r-EBUS alone].

Table 3. Diagnostic yield (ratio of events / total) with corresponding weight and risk ratio at 95% CI

	VBN + r-EBUS		r-EBUS			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
Asano 2011	80	99	64	95	22.1%	1.20 [1.01, 1.42]
Bo 2019	248	334	243	336	42.6%	1.03 [0.94, 1.13]
Chen 2016	67	93	63	91	19.4%	1.04 [0.86, 1.25]
Xu 2019	46	55	40	60	15.8%	1.25 [1.01, 1.55]
Total (95% CI)		**581**		**582**	**100.0%**	**1.10 [1.00, 1.21]**
Total events	441		410			

hemorrhage and 5 pneumothoraxes, 3 needing intervention to control the pneumothorax for the combined group. None of the bleeding complications required intervention for both groups.

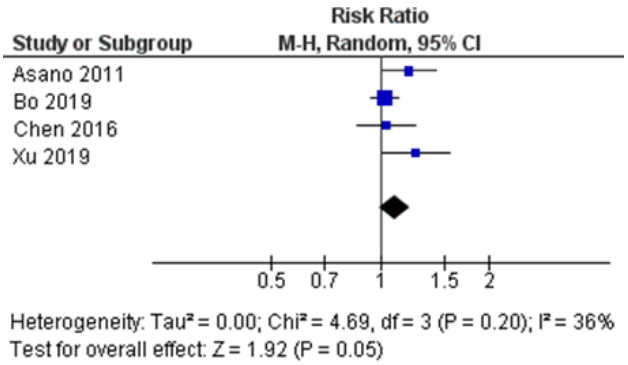


Figure 4. Forest plot showing the diagnostic yield of the different studies. Random effects model was used, with an overall risk ratio of 1.1[1.1, 1.21] at 95% CI. There is no statistically significant difference between VBN + r-EBUS vs EBUS alone since the confidence interval touches 1.

Table 4. Complication rate (ratio of events / total) with corresponding weight and risk ratio at 95% CI

	VBN + r-EBUS		r-EBUS			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
Asano 2011	0	99	1	95	6.7%	0.32 [0.01, 7.76]
Bo 2019	8	334	11	336	84.3%	0.73 [0.30, 1.80]
Xu 2019	1	55	1	60	9.0%	1.09 [0.07, 17.02]
Total (95% CI)		**488**		**491**	**100.0%**	**0.72 [0.31, 1.64]**
Total events	9		13			

Ishida et al. reported the positioning time and total examination time in median and range format, favoring the combined group with reduced time of 8.1 (2.8±39.2) vs 9.8 (2.3±42.3) min, p=0.045, and 24.0 (8.7±47.0) vs 26.2 (11.6±58.6) min, p=0.016. The other three

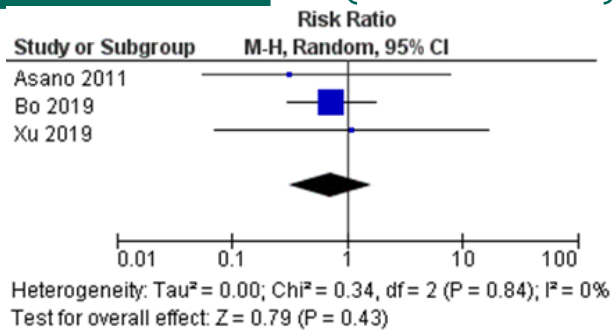


Figure 5. Forest plot showing the complication rates of the different studies. Random effects model was used, with an overall risk ratio of 0.72 [0.31, 1.64] at 95% CI. There is no statistically significant difference between VBN + r-EBUS vs EBUS alone since the confidence interval touches 1.

studies were reported in mean and standard deviation as seen in table 5 and figure 6 for the total examination time. All 3 studies showed a negative mean difference meaning that the combined modalities decreased the total examination time, with an overall mean difference of -3.34 at 95% CI -6.24, 0.44 minutes in favor of the combined group. The total examination time was less with VBN + r-EBUS versus EBUS only.

Only 2 studies reported the positioning time in means and standard deviations format, namely, Bo et al. (7.96 ± 1.18 min in the combined group vs 11.92 ± 5.37 min in the EBUS group, $p < 0.05$) and Xu et al. (5.67 ± 2.48 min in the combined group vs 8.65 ± 2.23 min in the EBUS group, P=.015) both reported less time required to

Table 5. Mean Total Examination Time of the different studies with their corresponding mean difference at 95% CI

	VBN + r-EBUS			r-EBUS				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Bo 2019	28.34	5.65	334	29.06	6.4	336	36.2%	-0.72 [-1.63, 0.19]
Chen 2016	45	10	93	55	10	91	27.3%	-10.00 [-12.89, -7.11]
Xu 2019	20.59	2.12	55	21.53	2.12	60	36.5%	-0.94 [-1.72, -0.16]
Total (95% CI)			**482**			**487**	**100.0%**	**-3.34 [-6.24, -0.44]**

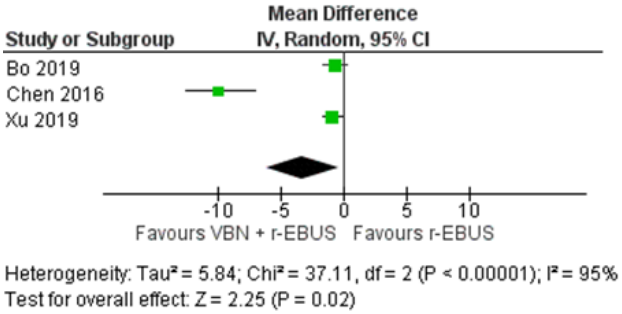


Figure 6. Forest plot showing the mean total examination time of the different studies. Random effects model was used, with an overall mean difference of -0.34 [-6.24, -0.44] at 95% CI favoring VBN + rEBUS

reach biopsy position with the VBN + r-EBUS group compared to r-EBUS alone with mean difference of -3.52 at 95% CI -4.48, -2.57 in favor of the combined group (see Table 6, Figure 7).

studies. The value of Higgins I2 heterogeneity index for diagnostic yield was 36% (df=3 [p=0.2], chi2=4.69) demonstrating insignificant heterogeneity between studies (see Figure 4). We removed one study to adjust the diagnostic yield and still found no significant change between the two interventions (see Figure 8).

The three studies which reported on the complication rate were also analyzed for sensitivity. With an I2=0%, (df=2 [p=0.84], Chi2=0.34) shown in figure 5, the studies were homogenous. Removal of the study to evaluate for the adjustment of the complication rate did not change the I2 (see Figure 9).

Table 6. Mean Positioning Time of the different studies with their corresponding mean difference at 95% CI

Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Bo 2019	7.96	1.18	334	11.92	5.37	336	55.5%	-3.96 [-4.55, -3.37]
Xu 2019	5.67	2.48	55	8.65	2.23	60	44.5%	-2.98 [-3.84, -2.12]
Total (95% CI)			**389**			**396**	**100.0%**	**-3.52 [-4.48, -2.57]**

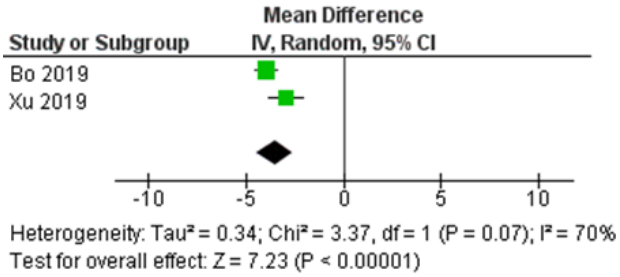


Figure 7. Forest plot showing the mean positioning time of the different studies. Random effects model was used, with an overall mean difference of -0.52 [-4.48, -2.57] at 95% CI favoring VBN + r-EBUS

Subgroup Analysis

A subgroup analysis would have been ideal by dividing the participants into subgroups (lesion size or location) but it was not available in the full text of the studies.

Sensitivity Analysis

Sensitivity analysis was done for all the four

There was considerable heterogeneity in the total examination time between the three studies (I2=95%, df=2 [p<0.00001], Chi2=37.11) as shown in Figure 6. This is evident because when we removed Chen et al. in the sensitivity analysis which adjusted our mean examination time, the I2 value decreased significantly to 0% (see figure 10). Several factors that may have contributed to the heterogeneity include but are not limited to; experience of the hospital and operator in doing the procedure, differences in the procedural methodology of the studies (number of biopsies taken; Chen et al. included doing brushing, washing of guide sheet, lavage, and repositioning of the ultrasonogram for repeat sampling), and differences in the definition (procedure start from entry into the trachea vs carina) although this can be negligible (seconds). Despite the heterogeneity, the direction of the treatment

effect is the same for all 3, and that they favor the combined group. Since only 2 studies reported on the positioning time in mean and standard deviation, the investigator saw it inappropriate to make a sensitivity analysis for this outcome.

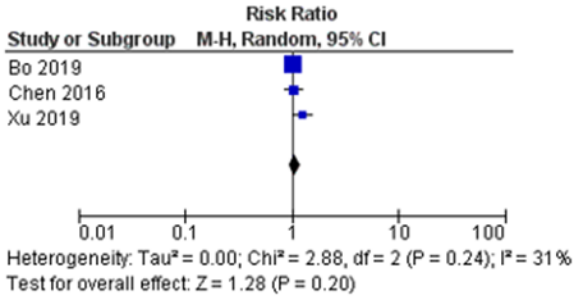


Figure 8. VBN + r-EBUS vs r-EBUS alone: diagnostic yield sensitivity analysis with removal of one study

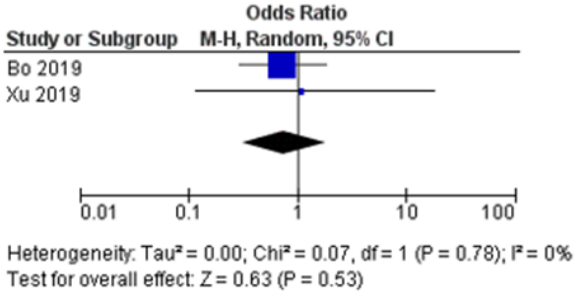


Figure 9. VBN + r-EBUS vs r-EBUS alone: complication rate sensitivity analysis with removal of one study

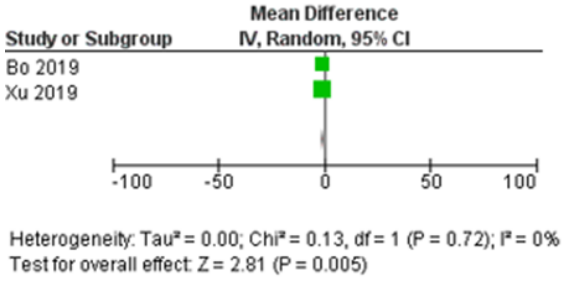


Figure 10. VBN + r-EBUS vs r-EBUS alone: diagnostic yield sensitivity analysis with removal of one study

DISCUSSION

Summary of Findings

The main results of this meta-analysis are as follows: the diagnostic yield of VBN + r-EBUS did not differ significantly from r-EBUS alone, but there was a trend towards better diagnostic yield for the combined group; the complication rate between the two groups did not differ significantly; and the total examination time and positioning time was less with the combined group (see Table 7).

Overall Completeness and Applicability of Evidence

Although CT scan guided TTLB remains the gold standard for diagnosing peripherally-located pulmonary nodules, risk of complications especially when dealing with smaller nodules detached from the chest wall is always a concern[13]. Radial endobronchial ultrasound has been a good alternative to this, with a very good safety profile, but its inferior diagnostic yield has pushed us more to explore additional modalities[7,13]. Virtual bronchoscopic navigation, being a relatively new technology to most centers, can be a complementary procedure to radial EBUS in improving its diagnostic accuracy. This was the initial finding of a randomized controlled trial done by Ishida et al. in Japan in 2017, but has been challenged by the more recent three studies. The most of recent of which (Xu et al. 2019) although concluded no difference in the accuracy between VBN + r-EBUS and r-EBUS alone, further observation noted superior diagnostic yield with the combined group when the lesion is ≤ 20mm (80.0% vs 53.6%, P=.041).

Part of the limitations of this study was reflected in our findings in the secondary outcomes. Both for the positioning time and procedure time, the significant level of heterogeneity was obvious because the study of Chen et al. included (in addition to 5-8 biopsy samples) brushing, washing, and lavage of the biopsy area, and repositioning of the ultrasound to collect again the same samples, compared to the other two studies which were limited only to 3-5 biopsies[13,20,21]. Although the differences in the definition of the total

Table 7. Summary of findings using GRADE methodology

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	De-sign	Risk of bias	Inconsis-tency	Indirect-ness	Impreci-sion	Other considera-tions	VBN + r-EBUS	EBUS alone	Rela-tive (95% CI)	Abso--lute		
Diagnostic Value (assessed with: Ratio/Percentage)												
4	Rando-mized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	441/581 (75.9%)	410/582 (70.4%)	RR 1.1 (1.00 to 1.21)	70 more per 1000 (from 0 more to 148 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Complication Rate (assessed with: Ratio/Percentage)												
4	Rando-mized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	9/488 (1.8%)	13/491 (2.6%)	RR 0.72 (0.31 to 1.64)	7 fewer per 1000 (from 18 fewer to 17 more)	⨁⨁⨁⨁ HIGH	IMPORTANT
Total Examination Time (measured with: Mean with SD; range of scores: 20.59-45; Better indicated by lower values)												
4	Rando-mized trials	no serious risk of bias	serious[1]	no serious indirectness	no serious imprecision	none	482	487	-	MD 3.34 lower (6.24 to 0.44 lower)	⨁⨁⨁⨁ HIGH	IMPORTANT
Positioning Time (measured with: Mean with SD; range of scores: 5.67-7.96; Better indicated by lower values)												
2	Rando-mized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	389	396	-	MD 3.52 lower (4.48 to 2.57 lower)	⨁⨁⨁⨁ HIGH	IMPORTANT

procedure time (Be et al. – begins upon entry into the trachea and ends upon completion of the procedure; Xu et al. – begins upon entry into the carina and ends upon exit into the glottis) and positioning time (Bo et al. – begins upon entry into the trachea and ends upon confirmation of the location of SPN with the EBUS; Xu et al. – begins upon entry into the carina and ends upon confirmation of the location of SPN with the EBUS) among the studies seems like an attractive source of heterogeneity, the difference could be negligible since the time it takes to pass the bronchoscope from the trachea to the carina usually lasts only for few seconds.[13,21] The total examination time difference of 1-10 minutes favoring the combined group is significant when doing any invasive procedure because it equates to lesser exposure to infection, anesthesia, and overall complication. Addition of another procedure to EBUS theoretically should increase the examination time but our findings say otherwise.

Quality of Evidence

The strength of evidence for the different outcomes was assessed using GradePro and is presented in the summary of findings table (see Table 7) using GRADE methodology. For the diagnostic yield, the strength of evidence was moderate due to the inconsistency of the result since VBN + r-EBUS is favored by one study (Ishida et al.), while the remaining three studies found no significant difference between the two interventions. It is also important to note that

although Xu et al. found no significant difference, analysis of lesions less than 20mm revealed better diagnostic yield favoring the combined group.

Potential Biases in the Review Process

The database search was limited to 4 sites and the studies included were those with English translation. The available published RCTs also were all from Asia, and the results may not reflect the same findings with non-Asian population.

Agreements and disagreements or reviews

This is the first meta-analysis done comparing VBN + r-EBUS vs r-EBUS alone based on our database search. Although only 1 out of 4 studies favored the combined group to have increased diagnostic yield, the individual means of VBN + r-EBUS group is increased in all four studies. Using Forest Plot analysis and risk ratio computation at 95% CI, there was a trend towards better diagnostic outcomes with the combined group.

For the secondary outcomes, there was no disagreement between the studies regarding the complication rate and positioning time. But for the total examination time, 2 studies favored the combined group, while the other two found no significant difference between the two interventions. Our statistical findings again using Forest Plot analysis and mean difference at 95% CI favoreds the combined group.

Conclusion

There was a trend towards a better diagnostic yield when we combined virtual bronchoscopic navigation with radial EBUS compared to radial EBUS alone. It is a safe procedure and offers less total examination time and positioning time when compared to EBUS alone.

RECOMMENDATIONS

The investigators of this study believe that further studies, preferably RCTs, are required to strengthen our findings. The investigators also recommend doing meta-analysis comparing diagnostic yield of VBN + r-EBUS among patients with SPN ≤ 30mm vs patients with ≤ 20mm.

FUNDING

Funding of this study was shouldered by the investigators. Data was sourced from the published articles of the studies included, of which the investigators would also like to acknowledge the authors of the 4 studies.

ACKNOWLEDGMENTS

The authors would like to thank Dr. Cecilia Jimeno, Dr. Virginia Delos Reyes, and Dr. Racquel Ibanez for serving as co-advisers in making this meta-analysis.

REFERENCES

1. Wyker A, Henderson WA. Solitary Pulmonary Nodule. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan. 2020 Mar 12.
2. Cruickshank A, Steiler G, Ameer F. Evaluation of the solitary pulmonary nodule. Intern Med J. 2019 Mar;49(3):306-315.
3. Kemp SV. Navigation Bronchoscopy. Respiration. 2020;99(4):277-286.
4. Ali MS, Trick W, Mba BI, Mohahnaney D, Sethi J, Musani AI. Radial endobronchial ultrasound for the diagnosis of peripheral pulmonary lesions: A systematic review and meta-analysis. 2017 Apr;22(3):443-453.
5. Labarca G, Caviedes I, Folch E, Majid A, Fernandez-Bussy S. Endobronchial ultrasound-guided transbronchial needle aspiration. Rev Med Chil. 2017 Sep;145(9):1165-1171.
6. Fielding D, Kurimoto N.Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration for Diagnosis and Staging of Lung Cancer. Clin Chest Med. 2018 Mar;39(1):111-123.
7. Bo L, Li C, Pan L, Wang H, Li S, Li Q, Bai C, Zeng Y, Nan Y, Wang Y, Huang H, Zhou R, Zhou H, Liu W, Sun J, Liu Z, Jin F. Diagnosing a solitary pulmonary nodule using multiple bronchoscopic guided technologies: A prospective randomized study. Lung Cancer. 2019 Mar;129:48-54.

8. Khan AN, Al-Jahdali HH, Irion K, Arabi M, Koteyar SS. Solitary pulmonary nodule: A diagnostic algorithm in the light of current imaging technique. Avicenna J Med. 2011 Oct-Dec; 1(2): 39–51.
9. Holin SM, Dwork RE, Glaser S, Rikli AE, Stocklen JB. Solitary pulmonary nodules found in a community-wide chest roentgenographic survey; a five-year follow-up study.*Am Rev Tuberc. 1959 Apr; 79(4):427-39.*
10. Swensen SJ, Jett JR, Hartman TE, Midthun DE, Sloan JA, Sykes AM, Aughenbaugh GL, Clemens MA. Lung cancer screening with CT: Mayo Clinic experience.*Radiology. 2003 Mar; 226(3):756-61.*
11. Gohagan J, Marcus P, Fagerstrom R, Pinsky P, Kramer B, Prorok P, Writing Committee, Lung Screening Study Research Group.Baseline findings of a randomized feasibility trial of lung cancer screening with spiral CT scan vs chest radiograph: the Lung Screening Study of the National Cancer Institute. *Chest. 2004 Jul; 126(1):114-21.*
12. International Early Lung Cancer Action Program Investigators., Henschke CI, Yankelevitz DF, Libby DM, Pasmantier MW, Smith JP, Miettinen OS. Survival of patients with stage I lung cancer detected on CT screening. *N Engl J Med. 2006 Oct 26; 355(17):1763-71.*
13. Xu C, Yuan Q, Wang Y, Wang W, Chi C, Zhang Q, Yu L, Zhang X.Usefulness of virtual bronchoscopic navigation combined with endobronchial ultrasound guided transbronchial lung biopsy for solitary pulmonary nodules. Medicine (Baltimore). 2019 Feb;98 (7):e14248.
14. Balamugesh T. and Herth F. J. Endobronchial ultrasound: A new innovation in bronchoscopy. Lung India. 2009 Jan-Mar; 26(1): 17
15. Han Y, King HJ, Kong KA, Kim SJ, Lee SH, Ryu YJ, Lee JH, Kim Y, Shim SS, Chang JH. Diagnosis of small pulmonary lesions by transbronchial lung biopsy with radial endobronchial ultrasound and virtual bronchoscopic navigation versus CT-guided transthoracic needle biopsy: A systematic review and meta-analysis. PLoS One. 2018 Jan 22;13 (1):e0191590.
16. Wang W, Yu L, Wang Y, Zhang Q, Chi C, Zhan P, Xu C. Radial EBUS versus CT-guided needle biopsy for evaluation of solitary pulmonary nodules. Oncotarget. 2018 Mar 13; 9 (19): 15122–15131.
17. De Wever W, Vandecaveye V, Lanciotti S, Verschakelen JA.Multidetector CT-generated virtual bronchoscopy: an illustrated review of the potential clinical indications. European Respiratory Journal 2004 23: 776-782; DOI: 10.1183/09031936.04.00099804
18. Polverosi R, Vigo M, Baron S, Rossi G. Evaluation of tracheobronchial lesions with spiral CT: comparison between virtual endoscopy and bronchoscopy. *Radiol Med (Torino)* 2001;102:313–319.
19. Aquino SL, Vining DJ. Virtual bronchoscopy. *Clin Chest Med* 1999;20:725–730.
20. Chen Zhongbo, Jin Yanping, Yu Yiming, et al. The value of virtual navigation combined with bronchial ultrasound in the diagnosis of peripheral pulmonary nodules[J]. Chinese Journal of Tuberculosis and Respiratory, 2016 ,39(7): 509-513. DOI: 10.3760/cma.j.issn.1001-0939.2016.07.004
21. Bo L, Li C, Pan L, Wang H, Li S, Li Q, Bai C, Zeng Y, Nan Y, Wang Y, Huang H, Zhou H, Liu W, Sung J, Liu Z, Jin F.Diagnosing a solitary pulmonary nodule using multiple bronchoscopic guided technologies: A prospective randomized study. Lung Cancer. 2019 Mar;129:48-54.
22. Ishida T, Asano F, Shinagawa N, Sukoh N, Anzai M, Kanazawa K, Tsuzuku A, Morita. Virtual bronchoscopic navigation without X-ray fluoroscopy to diagnose peripheral pulmonary lesions: a randomized trial. S.BMC Pulm Med. 2017 Dec 11;17(1):184. doi: 10.1186/s12890-017-0531-2. PMID: 21749984. PMCID: PMC3221323.
23. Yong Liu, Feng Wang, Qun-Cheng Zhang, Zhao-Hui Tong. Value of virtual bronchoscopic navigation and transbronchial ultrasound-guided sheath-guided exploration in diagnosis of peripheral lung cancer. World J Clin Cases. Aug 26, 2020; 8(16): 3450-3457. doi: 10.12998/wjcc.v8.i16.3450

Philippine Journal of Chest Diseases

Original Research

Successful Treatment of an Endobronchial Hamartoma Through Flexible Bronchoscopic Electrosurgery: A Case Report

Raymond Philip Huang, MD, Marie Krisca Liu, MD, DPCCP and Albert L. Rafanan, MD, FPCCP
Chong Hua Hospital, Cebu City, Philippines
Corresponding Author: *Dr. Raymond Philip Huang (rayphilhuang5@gmail.com)*
PAPER PRESENTED IN THE FOLLOWING FORUM: American Thoracic Society 2021 Convention (Abstract Presentation)

ABSTRACT

BACKGROUND: Pulmonary hamartomas are rare benign tumors with an incidence of 0.025 to 0.32% within the adult population. Hamartomas are composed of mesenchymal elements such as cartilage, fat, fibrous tissue, and epithelial elements. They are found in the lung parenchyma with only 1.4% occurring endobronchially.

OBJECTIVES: To discuss the case of a pulmonary hamartoma located endobronchially in a 50-year-old male presenting with obstructive changes on spirometry test and to correlate the case with existing literature with regard to clinical presentation, histopathology, and treatment.

THE CASE: We present a case of a 50-year-old male, with a right upper lobe infiltrate. He had occasional cough and right chest pain during respiratory tract infections. He was treated for pulmonary tuberculosis 7 years ago. Physical exam was normal. Imaging tests revealed an endobronchial tumor. He was referred to our institution for further management. Bronchoscopy revealed a large fungating polypoid mass with almost complete obstruction of the right upper lobe (RUL). Biopsy revealed an endobronchial hamartoma. Endobronchial resection of the hamartoma via flexible bronchoscopic electrocautery was performed resulting in reduction of the endobronchial hamartoma obstruction of the RUL lumen from 90 % to 10%, with visualization of the RUL apical, posterior and anterior subsegments. After four months, a repeat bronchoscopy showed growth of the residual tumor obstructing the right upper lobe posterior subsegment. A repeat bronchoscopy with electrocautery was done. Residual tumors were removed with 100% patency of the RUL and its subsegments.

CONCLUSION: Our case demonstrates the successful resection of an endobronchial hamartoma by flexible bronchoscopic electrosurgery which has become an alternative method for resection of benign endobronchial tumors particularly in our locality due to its cost-effectiveness and ease of use.

INTRODUCTION

Most tumors of the endobronchial tree are malignant with benign tumors representing less than 1%. Pulmonary hamartomas are the most common of these benign tumors with an incidence of 0.025% to 0.32%.[1] Pulmonary hamartomas are usually located parenchymally in which patients are asymptomatic. However, hamartomas can also be located endobronchially which is found in 1.4% of cases. [1] These patients may present with symptoms such as cough, fever, dyspnea and chest pain which are related to tracheobronchial obstruction. Endobronchial hamartoma originates from primitive mesenchymal tissues which includes cartilage, fat, bone and muscle tissues.[1] Bronchoscopic removal is the first line approach for the treatment of endobronchial hamartomas.[2] Bronchotomy or lung parenchymal resection through thoracotomy may be reserved for cases of irreversible lung damage secondary to chronic tracheobronchial obstruction.[3] Our case presents a 50-year-old male with an endobronchial hamartoma initially presenting with non-specific symptoms and a spirometry result showing mild obstructive changes who was successfully treated using electrosurgery through flexible fiberoptic bronchoscopy.

THE CASE

A 50-year-old male consulted due to occasional chronic cough and chest pain during episodes of respiratory tract infection. His spirometry test showed a mild obstructive ventilatory defect on routine annual physical examination in his company. Past medical history revealed pulmonary tuberculosis (TB) treated with 6 months of anti-TB medications last 2013 and multinodular non-toxic goiter s/p total thyroidectomy last 2013. Patient is a non-smoker, no known allergies and works as a bottling mechanic in a manufacturing factory. Patient has no history of asthma.

On physical examination, patient is sthenic and has normal nutrition with a BMI of 25.23 kg/m^2, afebrile with stable vital signs and an oxygen saturation of 98% at room air. Patient has equal chest expansion and clear lung fields. There were no lymphadenopathies noted. Upon work-up, laboratories were unremarkable. Chest X-ray showed a chronic inflammatory process in the right upper lobe shown in Figure 1. CT scan of the chest showed a soft tissue nodule in the right upper lobe bronchus as shown in Figure 2. MRI of the chest showed similar results. Both the CT scan and MRI did not reveal calcifications or adipose tissue.

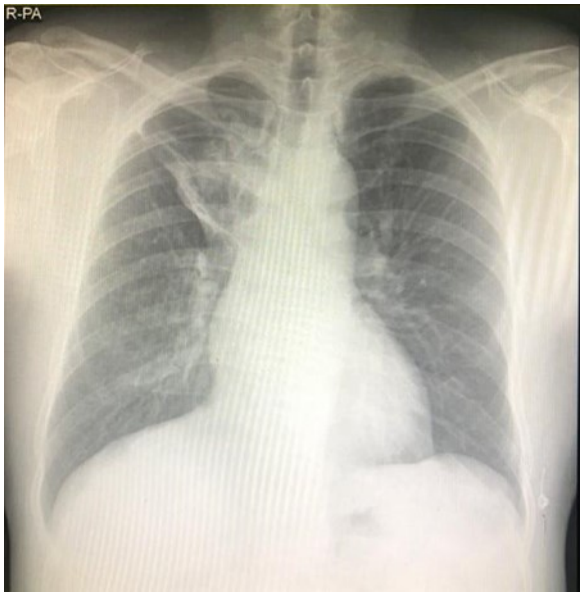
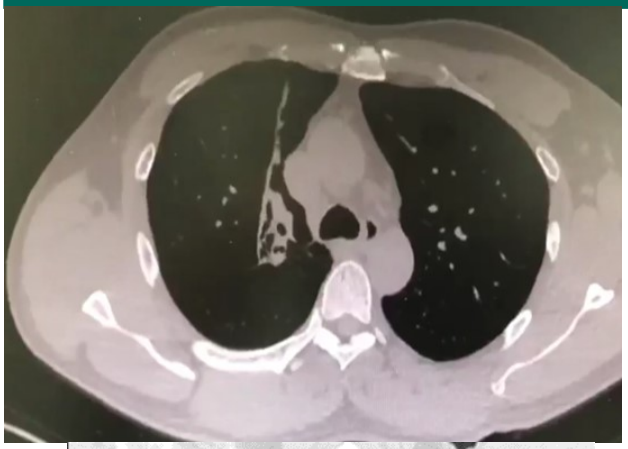


Figure 1. Chest roentgenogram showing fibrosis and mild bronchiectatic changes in the right upper lobe

As the mass was centrally located in the RUL bronchus, flexible fiberoptic bronchoscopy was performed instead of a percutaneous needle lung biopsy which revealed a smooth fleshy mass obstructing the right upper bronchus shown in Figure 3. Electrosurgical removal of the mass was done shown in Figure 4. There was minimal bleeding during the procedure and hemostasis was achieved with cauterization of the base of the lesion. Frozen section of the mass was not performed at the time of the procedure due to unavailability. Histopathology of the mass showed mesenchymal elements consisting of cartilage, fat and myxoid connective tissue consistent with hamartoma located endo-



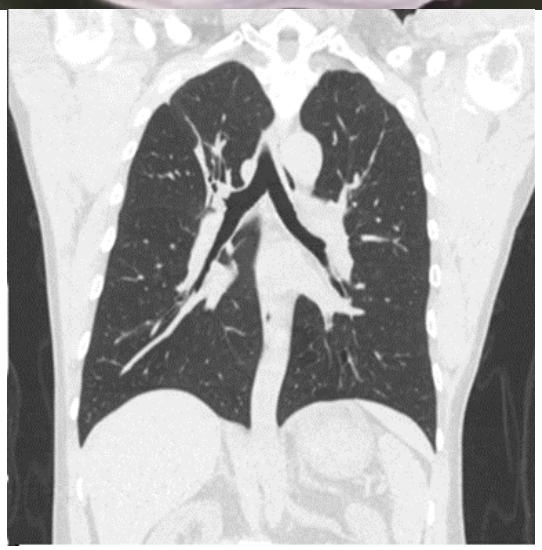


Figure 2. CT scan of the chest showing the nodule in the right upper lobe bronchus

bronchially. Patient had no complications post-procedure and had close follow-up as outpatient. Four months after the resection, CT scan showed recurrence of the mass at the right upper lobe bronchus. Patient underwent repeat bronchoscopy which revealed recurrence of the endobronchial mass shown in Figure 5. Electrosurgical snaring was done which resulted in complete resection of the mass shown in Figure 6. Repeat histopathology of the mass revealed a benign mesenchymal tumor composed of mature adipose tissue admixed with myxoid to fibroblastic stroma with tiny fragments of chondroid or cartilaginous tissue and one fragment which contains smooth muscle consistent of an endobronchial hamartoma. Patient was monitored closely as outpatient with no recurrence.

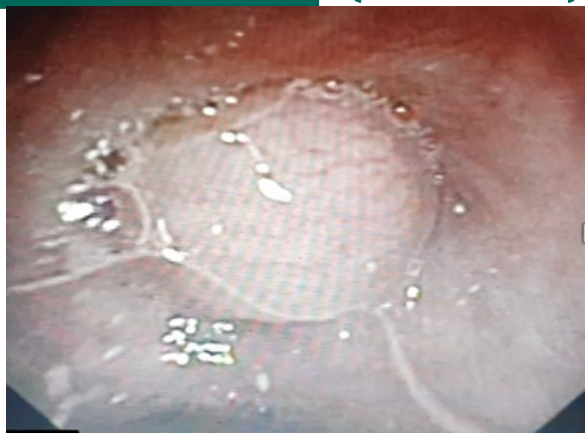


Figure 3. Gross appearance of the endobronchial mass on flexible bronchoscopy

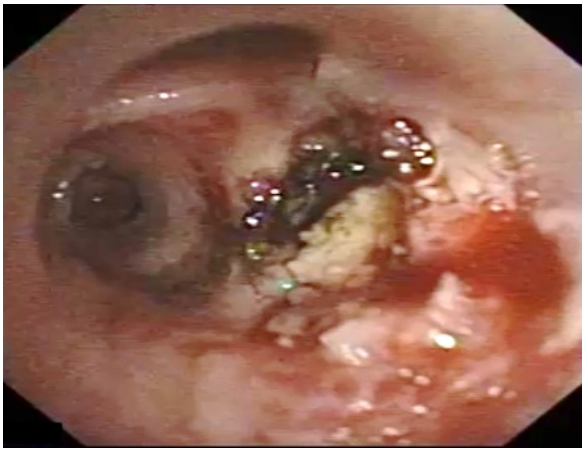


Figure 4. Lesion removed using electrocautery through flexible bronchoscopy with residual tissue causing obstruction of the posterior segment of the right upper lobe

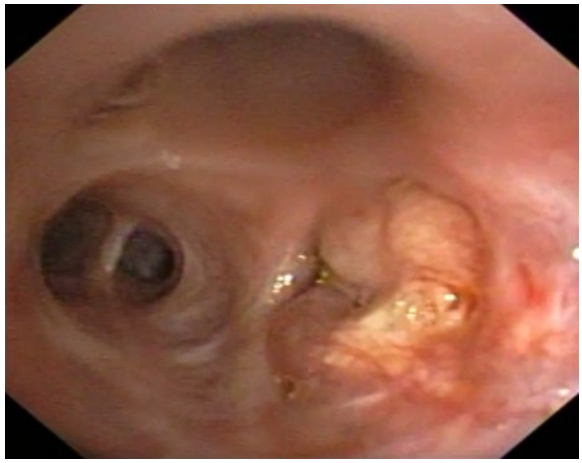


Figure 5. Residual lesion obstructing the posterior segment of the right upper lobe on repeat bronchoscopy after 4 months

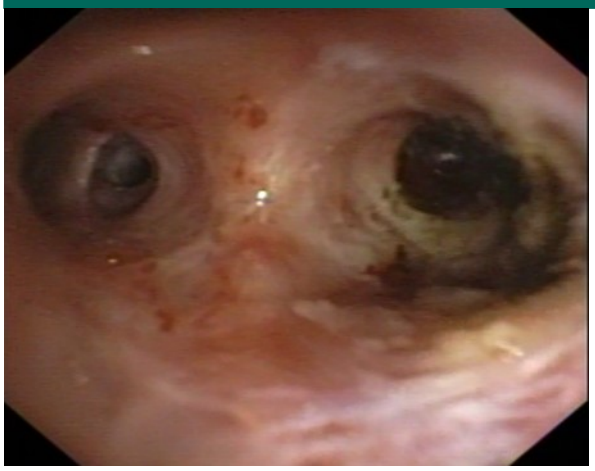


Figure 6. Complete removal of the endobronchial hamartoma

DISCUSSION

Pulmonary hamartoma is a rare tumor with an incidence of 0.025% to 0.32% constituting approximately 8% of all benign lung neoplasms.[1] The term *hamartoma* was first coined by Albrecht in 1904 describing a tumor like lesion which developed from an abberant growth.[4] Goldsworthy in 1934 described hamartoma as a benign lung tumor which originated from neoplastic transformation of primitive mesenchymal cells that differentiates into chondroid, adipose and smooth muscle cells.[5] It is composed of at least two mesenchymal elements. Parenchymal hamartomas usually contain chondroid, fibroblastic, fatty and osseous tissues. Only 1.4% of the pulmonary hamartomas are located endobronchially making this case exceptionally rare.[1] They are more common in males with a peak incidence of 6^{th}-7^{th} decade of life. Endobronchial hamartomas are usually composed of chondroid, fatty, and fibroblastic elements. Genetic rearrangement of chromosome band 12q15 is commonly found in pulmonary hamartoma.[6] Symptoms of hamartoma depend on the location of the tumor. If located peripherally or in the lung parenchyma, patients can be asymptomatic and can be diagnosed incidentally through imaging. If located endobronchially, they can present as persistent cough due to irritation of the bronchial mucosa. Endobronchial hamatomas can also present as bronchial obstruction resulting in fever, cough, dyspnea and wheezing. In our patient, he did not present with persistent cough, dyspnea, or wheezing but he had bronchial obstruction as evidenced by his spirometry result.

Radiographic imaging particularly chest X-ray may show non-specific findings and may relate to obstructive changes such as pneumonia, atelectasis, or bronchiectasis. Bateson and Abott radiographically described hamartomas as well-delineated masses with lobulated borders and speckled or "popcorn"-like calcifications.[4] In our patient, chest X-ray showed an inflammatory process compatible with pulmonary tuberculosis with fibrosis and mild bronchiectatic changes and signs of volume loss in the right upper lobe. Chest CT scan typically shows fat tissue alternating with foci of calcifications. On gross examination, endobronchial hamartomas are seen as sessile or pedunculated, polypoid nodules located within the lumen of a bronchus. In our patient, the mass was seen as a smooth fleshy structure obstructing the right upper bronchus. Histologically, parenchymal hamartomas are predominantly composed of cartilage and variable amounts of fibromyxoid connective tissue, fat, bone, and smooth muscle. In endobronchial hamartoma, fat tissue may be more abundant than other types of tissues. In our patient, histopathology of the mass removed by endobronchial electrocautery showed adipose tissue with myxoid to fibroblastic stroma, chondroid or cartilagenous tissue, and smooth muscle.

The treatment of endobronchial hamartoma is individualized depending on the size of the lesion, location, rate of growth, and patient's symptoms.[7] Asymptomatic patients with slow tumor growth of less than 2.5 cm in diameter can be managed conservatively with close follow-up with appropriate imaging.[1] However, tumor removal is recommended for large, fast-growing endobronchial tumors. Surgical intervention by lung resection or bronchotomy is the

conventional treatment of choice for benign lung tumors including hamartomas.[3] A review by Abdel Hady et al. in 2017 showed that bronchoscopy is now the first line of treatment in patients with symptomatic endobronchial hamartomas with surgical resection reserved for cases with severe lung damage secondary to chronic obstruction.[2] An endoscopic ultrasound may be utilized for diagnostic and surgical planning.[8] Rigid bronchoscopy was documented to be successful in removal of benign endobronchial tumors. Moreover, laser treatment through rigid bronchoscopy is considered the gold standard treatment for patients with symptomatic bulky masses.[1] Its disadvantage, however, is the requirement for general anesthesia and limited accessibility to tumors located in the trachea and main bronchi.[3] Fiberoptic flexible bronchoscopy, on the other hand, only requires local anesthesia and has more access to distal airways making this method more readily available. Endoscopic electrosurgery which includes the use of probes and snares, although widely used in gastroenterology, is an unusual method to pulmonologists. Several reports have documented the use of electrosurgery or electrocautery through flexible bronchoscopy. Electrosurgery utilizes electric current to cause tissue destruction and coagulation.[9] The procedure is cost-effective, has a short duration and is performed under sedation without the need for intubation.[3] Complications of electrosurgery include bleeding, perforation, and burning.[1] In our patient, electrosurgery of the endobronchial mass was done through flexible bronchoscopy without such complications. Recurrence, however, is common in bronchoscopic electrosurgery because of its limitation in removing the tumor base, making a sessile polyp less suitable for the procedure than a pedunculated polyp. In our patient, recurrence was noted four months after bronchoscopic electrosurgery. A study by Aktas et al. (2018), showed that bronchoscopic removal followed by cryotherapy at the root of the lesion can prevent recurrences by destroying the remaining tumor cells in the bronchial wall.[10] Cryotherapy creates a cytotoxic effect on tumor tissues due to formation of intracellular and extracellular ice crystals. Cryotherapy is capable of destroying tumor cells at a depth of 10mm with a rigid probe and at a depth of 3mm with a flexible probe. In our patient, cryotherapy was not done but bronchoscopic electrosurgery was repeated with cautery of the tumor base. There was no recurrence of the mass during follow-up. Other bronchoscopic methods of endobronchial mass removal include YAG laser and argon plasma coagulation. This report highlights the successful resection of an endobronchial hamartoma by flexible fiberoptic bronchoscopic electrosurgery.

CONCLUSION

Endobronchial hamartoma is a rare benign lung tumor. Genetic rearrangement of chromosome band 12q15 is responsible for the development of such condition. Endobronchial hamartomas are composed of at least two mesenchymal elements but mostly composed of fatty tissue. In the absence of chronic post-obstructive lung damage, patients may be asymptomatic. Patients may also present with chronic cough, wheezing, dyspnea, and recurrent pneumonia in cases of bronchial obstruction. Chest X-ray may show non-specific findings related to post-obstructive changes. Chest CT scan may show fat tissue with calcifications. Treatment may be conservative in asymptomatic patients. However, in patients with chronic obstructive symptoms and recurrent pneumonia, flexible bronchoscopic removal and even lobectomy in cases with irreversible lung damage may be involved. Our case report adds to the limited literature on successful removal of endobronchial hamartoma through flexible bronchoscopic electrosurgery especially in our local setting.

REFERENCES

1. Mondello, B., Lentini, S. Buda, C. et al. Giant endobronchial hamartoma resected by fiberoptic bronchoscopic electrosurgical snaring. Journal of Cardiothoracic Surgery. 2011

6:97
2. Abdel Hady, S., Elbastawisy, S., Hassaballa, A., Elsayed, H. Is surgical resection superior to bronchoscopic resection in patients with symptomatic endobronchial hamartoma?. Interactive cardiovascular and thoracic surgery 24 (2017) 778-782.
3. Kim, J.H., Jeong, G.M., Park, K.H. et al. Large endobronchial hamartoma successfully resected by snare through flexible bronchoscopy. Ann Thorac Surg 2015; 100: 1107-09
4. Jain, S., Agrawal, D., Shah, T., Udwadia, Z.F. Resection of an endobronchial hamartoma by electrocautery and argon plasma ablation via fiberoptic bronchoscopy. The Indian Journal of Chest Diseases and Allied Sciences. 2006; Vol 48
5. Altin, S., Dalar, L., Karasulu, L. et al. Resection of giant endobronchial hamartoma by electrocautery and cryotherapy via flexible bronchscopy. Tuberkuloz ve toraks. 2007 February 55 (4): 390-394
6. Ahmed, S., Arshad, A, Mador, M.J. Endobronchial hamartoma: a rare structural cause of chronic cough. Respiratory Medicine Case Reports. 2017 August 22 (22) 224-227
7. Liu, C., Wang, J., Zhu, Y., Chen, C. Successful use of snare electrocautery via flexible fiberoptic bronchoscopy for removal of an endobronchial hamartoma causing chronic lung atelectasis and mimicking malignancy. Therapeutic advances in respirtatory disease. March 20, 2017. 11(12) 435-438.
8. Insler, J. E., Seder, C. W., Furlan, K., Mir, F., Reddy, V. B., & Gattuso, P. (2021). Benign Endobronchial Tumors: A Clinicopathologic Review. Frontiers in Surgery, 8, 644656. https://doi.org/10.3389/fsurg.2021.644656
9. O' Connell, O., Rodriguez-Vial, M., Ost, D., Jimenez, C., Grosu, H. Bronchoscopic management of a benign obstructing pedunculated tumor. Ann Am Thorac Soc. Aug 7, 2015. 12 (11): 1715-1717.
10. Aktaş, Z., Yılmaz, A., Öztürk, A., & Karataş, M. (2018). Can we prevent recurrences in the endoscopic treatment of endobronchial hamartomas? Tuberkuloz Ve Toraks, 66(4), 312–316. https://doi.org/10.5578/tt.67434
11. Saadi MM, Barakeh DH, Husain S, Hajjar WM. Large multicystic pulmonary chondroid hamartoma in a child presenting as pneumothorax. Saudi Med J. 2015 Apr;36 (4):487-9.
12. Gjevre JA, Myers JL, Prakash UBS. Pulmonary hamartomas. Mayo Clin Proc 1996; 71: 14-20.
13. Haridas, N., Mehta, A., Mohammed, T.S., Nair, I.R. Young man with nonresolving pneumonia. Egyptian Journal of Bronchology. 2018 12: 367-369.
14. Poonja, Z., Sobey, A., Weinkauf, J.G. Endobronchial hamartoma. J Bronchol Intervent Pulmonol. 2013 July 20 (3)
15. Sang, D.L., Young, W.K., Sung, K.H., et al. Endobronchial hamartoma- a case report. The Korean Journal of Internal Medicine. 1988 January 3 (1).
16. Kim, H.R., Choi, K.H., Jeong, E.T., Hwang, K.I. Resection of an endobronchial hamartoma by cryotherapy. Korean J intern Med. 2016 31: 805-806.
17. Van De Bosch, J.M.M., Wagenaar, S.S., Corrin et al. Mesenchymoma of the lung (so called hamartoma): a review of 154 parenchymal and endobronchial cases. Thorax 1987; 42: 790-793

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) 8924 9204