LUNG CENTER OF THE PHILIPPINES

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WHAT'S INSIDE

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CLINICAL RESEARCH DEPARTMENT

The Clinical Research Department (CRD) oversees all research projects at the Lung Center of the Philippines (LCP). It receives, evaluates and coordinates all research activities. It establishes policies and guidelines for the development, writing, presentation and approval of research proposals. Thru its Technical Review Board (TRB), it provides guidance and technical expertise on protocol development, including sample size calculation and statistical analysis plan. It spearheads institutional researches and coordinates with other national and international agencies for clinical trials, student undergraduate and graduate research, and collaborative research. It runs the TB Research Team at the LCP's National Center for Pulmonary Research (NCPR) as well as spearheads the Lung Cancer Registry to gather and collate the comprehensive local data on pulmonary tuberculosis and lung cancer, respectively. It maintains the Clinical Research Facility (CRF), an establishment that provides room, space and storage facilities for clinical trials and research.

The CRD publishes the Scientific Proceedings, the official journal of the LCP, to share local relevant educational material in the field of pulmonary medicine. The Scientific Proceedings Journal publishes original clinical investigations, epidemiological studies, case reports, review articles, evaluation of diagnostic and surgical techniques, and latest updates on management guidelines.

In 2019, the CRD started to align with the vision and strategic direction of the LCP on research. The current challenges involve providing resources to support priority programs and projects with other departments to undertake institutional research on advanced procedures to support new clinical pathways, programs and policies and contribute to impact healthy lungs and healthy environment.

The department likewise is aligned with the National Unified Health Research Agenda 2021–2025 on [1] responsive health system [2] research to enhance and extend healthy lives [3] holistic approaches to health and wellness [4] health resiliency [5] global competitiveness and innovation in health and [6] research in equity and health.

In order to achieve these proposed strategic directions, the CRD reviews its accomplishment using the perspectives of the Balanced Scorecard in [1] learning and growth [2] internal business processes [3] customer satisfaction and [4] financial perspective. From these perspectives, the CRD hopes to monitor the outcomes of all action plans and to evaluate the implementation of such plans.

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Registration of researches to be conducted at the LCP : processes all applications for Institutional Research, Clinical Trials, Student Undergraduate Research, Graduate Research and Collaborative Research.

Technical Review Board (TRB) : provides review of research protocols based on its technical merits.

Clinical Research Facility: provides rental for room space, investigational product storage and archiving of completed research.

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The **Scientific Proceedings**, the official journal of the Lung Center of the Philippines, is an open-access, English language, medical science journal, published biannually by the Lung Center of the Philippines. The journal intends toshare local relevant scientific findings in the field of respiratory medicine through publication of high quality original clinical investigations, epidemiological studies, case reports, review articles, evaluations of diagnostic and surgical techniques, and the latest updates on management guidelines. The journal's target audience are clinicians, surgeons, specialists, laboratorians, scientists, and researchers working on pulmonary medicine. The Scientific Proceedings does not charge any subscription, review, or manuscript processing fees.

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Scientific Proceedings

CONTENTS

THE CRUCIAL ROLE AND RESPONSIBILITIES OF THE RESEARCH ADVISER

Jubert P. Benedicto, MD, FPCCP
Editor-in-Chief

You, as a researcher, have already selected a topic... or at least you have narrowed down your choices and crafted a "ripe research idea". However, you do not know how to proceed further in the research process. You might be overwhelmed by what such an idea may need to be ensured so that it will be feasible (and can be done during your training period). You may be uncertain if similar studies may have been done already. What makes your idea unique or innovative or worth pursuing? **YOU NEED A GOOD RESEARCH ADVISER**.

As consultants, trainees have approached us to be their research adviser. But have you ever wondered what this title *really* entails? What are its repercussions? Aside from appearing during a session with the Technical Review Board or having your name appear in the by-line potentially as one of the co-authors, do you know the specific expectations from you? Needless to say, a research adviser is one of the critical personnel in ensuring that well-crafted research is adequately performed, and a well-written manuscript should result from this endeavor.

Ideally, a formal conforme should be signed by the potential adviser. This officially secures their commitment in ensuring that their presence will be consistent and palpable all throughout the steps in doing research. This means they will be readily available and accessible from conception and development of the idea or topic, its revisions, presentation to statistician and technical body, actual performance of the research, writing of the paper, publication, and in exploring options to share the results of the study. It is assumed that the adviser is a researcher as well- therefore one will be knowledgeable in the intricacies of the whole cycle. He or she can readily empathize with the trainee and can offer advice at strategic points of the study. His or her steady presence should guide, inspire, ensure completion, and catapult the idea into reality.

To the consultant: *Do you have the time? Are you certain that you can work together with the trainee with deadlines that need to be observed? Are you ready for such an integral role? Are you willing to edit and guide the final written version of your study?* Remember, you are expected to do these on top of your other tasks (as a clinician, administrator, or both).

Not everyone is capable of being an *effective* research adviser. The knee-jerk reaction is to accept the trainee's offer. However, some fall short of the expected tasks and not all roles are satisfactorily fulfilled. Unfortunately, this results in a poorly conceived or conducted study, a subpar manuscript that undergoes tremendous revisions (or worse, deemed not fit for publication), unsatisfactory presentation, and possible rejections for presentation in scientific conferences.

The literature has consistently articulated the main responsibilities of a research adviser.

Consistently, the general roles are the following:

- Full development of the research proposal.
- Reviews methodology to ensure feasibility of the study (including timelines and costs)
- Willingness to help or assist the student in the overall conduct of the research.
- Guidance in the analysis of the results, crafting of discussion, and making the conclusion and recommendations.
- Finalization of the main paper including making it compliant to targeted poster or oral presentation and be publication ready.
- Checking of grammar and thought content of the written output.
- Must be present in ALL presentation days to the relevant bodies.

Not all were made to be advisers. Majority are developed into one. From what I witness, most effective advisers evolve into one after being conscientious researchers themselves. They experienced what it was to need and be collaborative with a "teacher", "expert", "counselor", and possibly a "research friend". It made the entire process quite bearable and to a certain extent, fulfilling.

Certain qualities stand out that a good research adviser possesses. He or she should be knowledgeable in the field of interest (quite logical), fostering and encouraging free discussion and being nonjudgmental, approachable, engaging, firm yet understandable, open to ideas, and flexible especially with allotment of time and schedule.

We all acknowledge the value and premium in having excellent advisers in all our studies.

For trainees, search them out and do not be afraid to ask and strike an agreement with them. Afterall, churning out good studies require efforts both ways. To potential research advisers, really "bite into your role". *This requires time and effort*. It cannot be taken lightly. Bear in mind that your interaction with the trainees will have implications (good or bad) in their training years and further professional life. Let us take this crucial role seriously.

EDITORIAL POLICIES

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The **Scientific Proceedings**, the official journal of the Lung Center of the Philippines, is an open-access, English language, medical science journal, published by the Lung Center of the Philippines. Its policies are guided by the latest version of the International Committee of Medical Journal Editors (ICMJE) **"Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals."**

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The **Scientific Proceedings** intends to share local relevant scientific findings in the field of respiratory medicine through publication of high quality original clinical investigations, epidemiological studies, case reports, review articles, evaluations of diagnostic and surgical techniques, and the latest updates on management guidelines. The journal's target audience are clinicians, surgeons, specialists, respiratory therapists, laboratorians, scientists, researchers working on pulmonary medicine, and policy makers.

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ORIGINAL ARTICLE

DEVELOPMENT AND DETERMINATION OF RELIABILITY OF TAGALOG VERSION OF THE INSOMNIA SEVERITY INDEX IN PATIENTS WITH INSOMNIA AT THE SLEEP CLINIC OF THE LUNG CENTER OF THE PHILIPPINES

Faye Karissa Lourdes M. Bautista MD, FPCP, FPCCP, Katherine C. Paras MD, FPCP, FPCCP
Maria Cecilia I. Jocson, MD, FPCP, FPCCP

ABSTRACT

Background. A quick screening tool to detect cases of insomnia in the Filipino population, written in the vernacular is currently lacking. It will be helpful for physicians to recognize insomnia early and initiate the appropriate treatment.

Objective. This study aimed to produce a Tagalog version of the Insomnia Severity Index (ISI) Questionnaire, to examine its internal consistency, and measure the test-retest reliability in a subset of patients with insomnia from a sleep clinic in a tertiary government hospital.

Methodology. This was a single-center, cross sectional study done at the Lung Center of the Philippines from February 2019 to May 2023. The study was divided into two stages from November 2019 to March 2020 and continued from November 2022 to May 2023. The English version of the ISI was translated into Tagalog, then translated back into English. Pilot testing of the pre-final version was carried out among 30 healthy non-insomnia patients, who were randomly selected. Based on any comments for revisions, a final version of questionnaire was developed. The final version of the translated questionnaire was then used to screen the severity of insomnia in 79 insomnia subjects. The internal consistency was measured using Cronbach's alpha. The relationship of each ISI item to the total instrument score was examined using item-total correlations. Test--retest reliability between the ISI scores of study subjects taken at baseline and after two weeks was described using intraclass correlation coefficient (ICC) and its mean differences illustrated using Bland-Altman Plot analysis.

Results. In total, 79 subjects filled out the baseline questionnaires (test), whereas 73 subjects (92.4%) filled out the follow-up questionnaires during the (retest). Among the 79 insomnia participants, 59.4% (n=47) were females, and 40.5% (n=32) were young adults aged (18-35 years) The mean age of the participants was 42.78 years (SD 15.76). The mean ISI score was 16.1 (SD 5.25) indicating moderate insomnia. The Tagalog version of the ISI had an excellent internal consistency at 0.917. All corrected item total correlations were at α = more than 0.4 indicating high discriminant value. The ISI translated version likewise presented a very good test-retest reliability, (α = 0.878). ICC = 0.782 (CI = 0.685-0.852). Test and Retest items have moderate agreement.

Conclusion. The Tagalog version of the ISI is a consistent, and reliable tool for screening Filipino patients coming into our clinics for problems about insomnia.

Keywords. *Sleep, insomnia, insomnia severity index, Tagalog version, translated questionnaire*

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INTRODUCTION

Insomnia is the most prevalent sleep disorder in the general population and is commonly encountered in medical practices. Insomnia is defined as the subjective perception of difficulty with sleep initiation, duration, consolidation, or quality that occurs despite adequate opportunity for sleep, and that results in some form of daytime impairment.[1] Insomnia can largely affect several daytime cognitive functions such as attention, concentration, and memory[2] that can decrease performance and efficiency at work[3] and increase the risks of injuries and traffic accidents[4] and of falls in older adults.[5]

Reported prevalence estimates for insomnia of any duration or severity range from 30% to 50% for the general population.[6–9] The Asian Sleep Research Society (ASRS) reported that insomnia is also highly prevalent in three Asian countries (Thailand, Taiwan, and Philippines) with overall prevalence of 52%.[10] Despite its high prevalence and significant morbidity, insomnia often remains unrecognized and untreated, partly due to several barriers to assessment.

The assessment of insomnia is multidimensional and should ideally include a clinical evaluation and be complemented by self-report questionnaires and daily sleep diaries. The Insomnia Severity Index (ISI) is a brief instrument that was designed to assess the nature, severity, and impact of insomnia and monitor treatment response in adults. It is widely used with other insomnia populations and has validated criteria to define both treatment response and treatment remission.[11] The ISI is composed of seven items assessing sleep onset, sleep maintenance, early morning awakening, interference with daily functioning, perceived prominence of impairment attributed to the sleep problem, concerns about sleep problems, and satisfaction with sleep patterns.[12] Perceived severity of each item is rated on a 0–4 scale. A total score ranging from 0 to 28 is obtained from summing the seven ratings.

The ISI was developed in English and has been translated into several languages; currently there is no Tagalog version of ISI. This study aims to develop a Tagalog version of the ISI using standard translation procedures, and to verify its reliability as a screening measure of insomnia in a Filipino population using internal consistency, item analysis and test-retest reliability.

METHODOLOGY

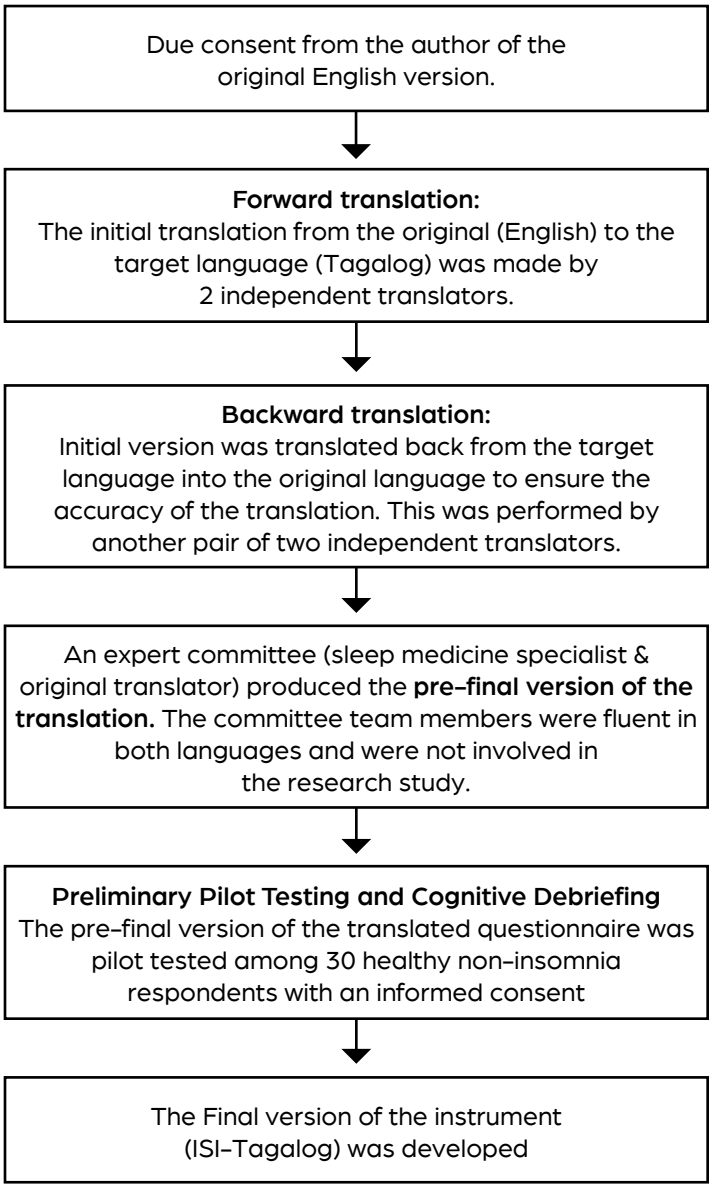

Figure 1. *STAGE 1 process of translation and pilot testing*

Study Setting

This was a single-center, cross sectional study conducted in the Sleep Disorders Laboratory of the Lung Center of the Philippines from November 2019 to May 2023. There were 2 stages in this study. First stage was the development of the translated version from November 2019 until March 2020. The study was halted during the pandemic and was reopened when the restrictions were lifted. The second stage: Data collection and questionnaire administration, commenced from November 2022 to May 2023.

Questionnaire Translation–Back translation

The Insomnia Severity Index written originally in the English Language was translated into the Tagalog version by at least 2 independent and expert groups of translators and was back translated into the English language. This was the pre–final version of the questionnaire which was then used for pilot–testing among a group of 30 healthy non–insomnia subjects. Comments and suggestions highlighting clarity, readability, instruction, assumptions, and the time it took to complete the questionnaire were collated and considered during the questionnaire revision. The final version of the Tagalog ISI questionnaire was administered in the target population.

STAGE 1: Questionnaire Translation

A. Translation of the ISI into Tagalog (Forward and Back Translation)

1. Due consent from the author of the original English version was requested through https://eprovide.mapi-trust.org/my-eprovide/my-requests/new?origin=request.

2. The initial translation from the original (English) to the target language (Tagalog) was made by at least 2 independent translators from Sentro ng Wikang Filipino University of the Philippines Manila.

   The Sentro ng Wikang Filipino–UP Diliman is a devolved language center of the UP System, which takes lead in the establishment of tutorial (coordination with Learning Resource Center) and translation services to develop and promote the widest possible use of Filipino and other Philippine languages, particularly as communication tool for research in the health sciences. The Center, which is non–degree–granting, consisted of a director, a university research associate, and a student assistant. It has a committee of advisers and/or consultants representing each college from the health sciences, namely, Medicine, Nursing, Dentistry, Pharmacy, Public Health, Allied Medical Professions, National Teacher Training Center for the Health Professions and the College of Arts and Sciences. One translator was made aware of the concepts the questionnaire intended to measure and was tasked to produce a version, whereas a second naive translator, who was unaware of the objective of the questionnaire, produced a second version of the translation so that subtle differences in the original questionnaire were detected. Discrepancies between the two translators were discussed and resolved between the two, thus forming the "initial translation" version.

3. The initial translation was then independently back–translated (i.e., translated back from the target language into the original language) to ensure the accuracy of the translation. As with the forward translation, the backward translation was performed by another set of two independent translators from the Department of English and Comparative Literature of University of the Philippines Diliman.

4. To avoid bias, back–translators were not informed of the concepts the questionnaire was intended to assess.

5. An expert committee (sleep medicine specialist & original translators) produced the pre–final version of the translation. These individuals were fluent in both languages and were not involved in the research study. The pre–final Tagalog version of ISI was obtained after completion of these standard procedures.

Pilot Testing and Cognitive Debriefing

A sample size of 30 healthy patient volunteers for the pilot testing was based on about 5% anticipated problems to be detected in the questionnaire. After completing the translated pre–final version of the questionnaire, the respondents were asked to elaborate what they thought on each questionnaire item and what their corresponding response meant. At this stage, the primary purpose of the pilot test was to determine any problems that concerned clarity, readability, instruction, assumptions, and length of time it took to complete the questionnaire. Comments from the volunteers were considered in revising the Tagalog version. The final version of the instrument in the target language was the result of all the iterations described above.

Study Implementation using the Final Version

STAGE 2: Administration of the Final Version of Tagalog Insomnia Severity Index.

Cronbach's alpha	0.9
Precision	0.05
Significance level (α)	0.05
Number of items (k)	7
Drop–out	0.1
Sample size	42
Sample size (with drop–out)	47

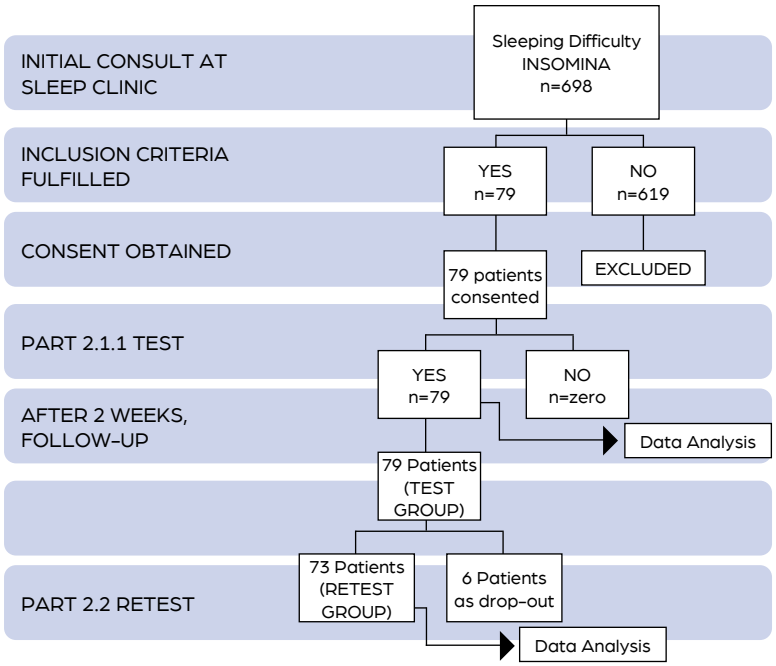

Figure 2. *Steps taken for the stage 2 of study implementation*

Sample Size Computation

A minimum sample size of 42 patients satisfying the inclusion/exclusion criteria were randomly selected to enroll in the study to have an 80% chance of detecting, as significant at the 5% level, the reliability of Insomnia Severity Index – Filipino as a reliable tool in assessing the nature, severity and impact of insomnia based on expected Cronbach's alpha of 0.90.[13]

The recommended estimate of minimum required sample size was computed using a formula for Cronbach's alpha. Given that the computation was based on the assumption that the Tagalog version will yield a Cronbach's alpha as high as 90%, conclusions based on the results will be applicable to this group of subjects unless the power of applicable statistical tests on actual study data are ≥80%.

Participants

Subjects were asked to complete the final version of translated ISI at baseline. Based on study inclusion and exclusion criteria, out of the 698 subjects who consulted the sleep lab from November 2022 to May 2023, 79 people with insomnia were included in the final evaluation via convenience sampling. The inclusion criteria of the study were as follows: people (1) with self-reported insomnia defined by an ISI score of at least 8; (2) aged 15 years and older with no uncontrolled major health problems; and (3) clinically stable at the time of study enrollment. The exclusion criteria for the study were as follows: people with (1) poor mental health or a (2) self-reported current diagnosis of major depression or psychiatric disease that prevented participation in the survey as assessed by the investigator (3) subjects who did not consent to participate (4) subjects not adept with using the Filipino language.

Measures

Insomnia Severity Index

The ISI assesses the nature, severity, and impact of insomnia during the previous 2 weeks. Its seven items address (1) difficulty falling asleep, (2) difficulty staying asleep, (3) problems waking too early, (4) sleep dissatisfaction, (5) interference of sleep problems with daytime functioning, (6) noticeability of sleep difficulties to others, and (7) level of distress caused by sleep difficulties. Each item is rated using a 5-point Likert scale ranging from 0 (none) to 4 (very severe). Total scores range from 0 to 28, and higher scores indicate greater insomnia severity.[14]

Ethical approval

Study approval was obtained from the Institutional Ethics Review Board of the Lung Center of the Philippines twice to address the gap between the two stages of the study implementation.

Statistical analysis

Data were analyzed using IBM SPSS version 29. Data quality and missing data were assessed using descriptive statistics (means, SDs, frequencies, and percentages). No missing data were identified for the variables included in this study. All tests were two-tailed, and a type I error rate of a < 0.05 was considered statistically significant.

The reliability of the ISI was determined by estimating internal consistency using Cronbach's alpha. The relationship of each ISI item to the total instrument score was measured by item-analysis and represented using item-total correlation. The test-retest reliability was measured using intraclass coefficient and was graphically represented by Bland-Altman Plot.

RESULTS

Study Sample

Table 1 below shows the profile of patients included in the study. The study population for the second stage consisted of 79 adults (Mage = 42.78 years, SD = 15.76; range: 15–78 years; 59.4 % females). 40.5% belonged under the young adult age category from 18–35 years of age. 73 subjects (92.4%) filled out the follow-up questionnaires during the retest. 88% were Catholic. Half of the study subjects were married and employed, and 60 percent lived within NCR. 69% of subjects complained of chronic insomnia problems and only 34% had a concurrent Obstructive Sleep Apnea. The mean ISI score was 16.1 indicating moderate insomnia.

Table 1. *Demographic and clinical characteristics of patients with insomnia*

Characteristic	All Patients n, [%]
Age in years	
Young adults (18–35)	32, [40.5]
Middle-aged adults (36–55)	26, [32.9]
Older adults (≥56)	21, [26.6]
Gender	
Male	32, [40.5]
Female	47, [59.5]
Religion	
INC	3, [3.8]
Catholic	70, [88.6]
Non-Christian	1, [1.3]
Others	4, [6.3]
Marital status	
Single	36, [45.6]
Married	41, [51.9]
Widow/Widower	2, [2.5]
Residence	
Outside NCR	19, [24.1]
Within NCR	60, [75.9]
Occupation	
Unemployed	26, [32.9]
Employed	53, [67.1]
Diagnosis	
Acute insomnia	10, [12.7]
Chronic insomnia	69, [87.3]
Comorbid conditions	
OSA	27, [34.2]
No OSA	52, [65.8]

Data presented count (percent). Mean ISI score 16.1 SD 5.25)

Internal consistency, item analysis and correlation of the items of the translated version.

It can be observed that in the 2nd column on Table 2, all corrected item total correlations are well above the margin of 0.4, hence, each item has very good discrimination. Higher total-item correlations in a test result in a higher value of coefficient alpha. The corrected total item correlation is used to define the association of the item with the total score on the other items. Items of 0.4 and above indicate very good discrimination.

The Cronbach's alpha if item was deleted from the questionnaire is found in the third column in the table and represented each item's reliability if that item was to be removed from the instrument. The Cronbach's alpha of the instrument was measured at 0.917. The values of each item, except Q3 (Problems waking up too early/"Masyado maagang nagigising"), when omitted from the instrument would decrease the instrument's alpha. Question 3 also would have made only a slight but tolerable difference as well. Therefore, all items were worthy of retention in the instrument.

Table 2. *Cronbach's alpha and Item-total correlation of the Insomnia Severity Index – Tagalog*

Item	Corrected Item Total Correlation	Cronbach's alpha if item deleted
Difficulty falling asleep (Nahihirapang makatulog)	0.790	0.899
Difficulty staying asleep (Paputol-putol ang tulog)	0.765	0.902
Problems waking up too early (Masyado maagang nagigising)	0.553	0.922
Satisfaction with current sleep pattern (Kuntento sa kasalukuyang lagay ng pagtulog)	0.770	0.902

Item	Corrected Item Total Correlation	Cronbach's alpha if item deleted
Noticeable to others in impairing quality of life (Kapansin-pansin sa ibang tao ang epekto ng problema sa pagtulog)	0.685	0.910
Distressed about current sleep problem (Nababahala o Nalulungkot sa kasalukuyang lagay ng pagtulog)	0.855	0.891
Extent to interfere with daily functioning (Nakakahadlang o Nakakapekto ang hirap sa pagtulog sa pang-araw-araw na Gawain)	0.794	0.899

Note: Reliability Statistics of the instrument, Cronbach's Alpha = 0.917

Test-retest reliability of the translated version of the ISI done 2 weeks apart

The results obtained showed moderate levels of agreement between the test group and retest group of the translated version, where ICC=0.782 (CI = 0.685-0.852). The Cronbach's alpha of 0.878 also indicated good reliability in the test-retest scores.

The Bland-Altman plot of the translated version of the instrument is seen below Figure 3. The mean difference and the average of ISI scores from both the test and retest groups, were plotted in the X and Y axis. All the differences were close to zero and were within the limits of agreement.

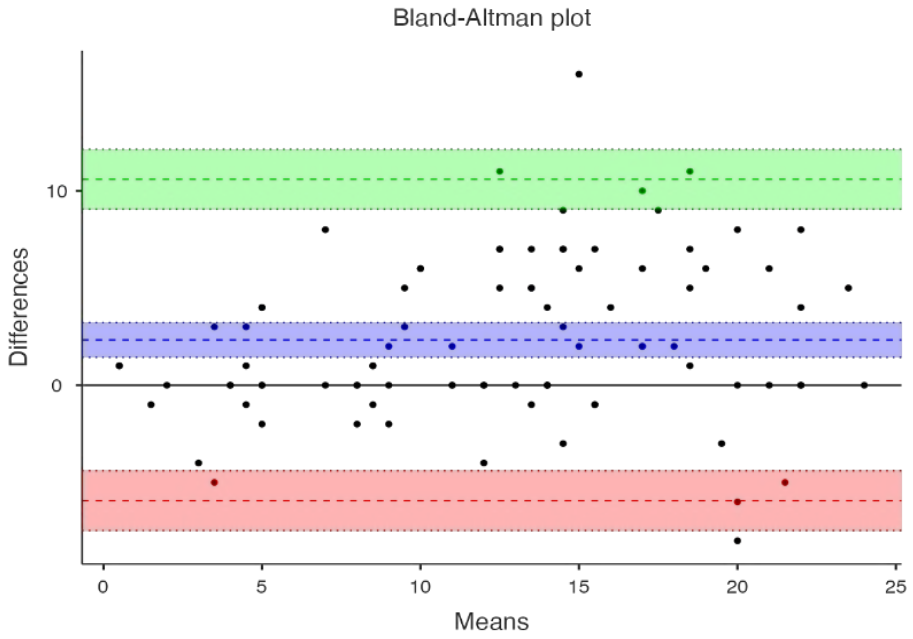

Figure 3. *Bland-Altman Plot showing moderate agreement between measures*

DISCUSSION

Method of Translation

To prepare the measuring instruments such as questionnaires for cross-cultural research, the method of forward translation to the vernacular is employed.[11] The aim of this process is to achieve different language versions of the instrument, written in English, which are conceptually equivalent in each of the target countries/ cultures. However, cross-cultural translation has its own set of limitations. Contextual and semantic errors may occur during translation, and these may distort the original meaning. To achieve a good quality translated version of questionnaire, use of multiple methods of translation such as forward translation, backward translation and consensus translation are desirable whenever possible.[12,14]

Breslin's back-translation method is the most widely used translation procedure in cross-cultural translation.[15] However, it is not the gold standard, and a combination of various translation methods is more appropriate to use.[16] A multi-step translation method was employed in our study to ensure that the items in the questionnaire are conceptually equivalent to the English version of the ISI.

ISI has been translated and validated in Spanish, French, Arabic, Hindi, German, Korean, Chinese, Iranian, Italian and Swedish. To our knowledge, this is the first study to evaluate the reliability and validity of the Tagalog version ISI among people with insomnia.[17-25]

The objective of our study was to translate the original ISI scale written in English into the Tagalog version. The acceptability of this version was good, as demonstrated by the zero-refusal rate and the absence of missing data. The COVID-19 pandemic and associated disruptions have had a major impact, which transcended even the implementation of many researches. Many traditional research activities were suspended, other than COVID-19-related and other essential research. Such was our experience, since there was a lack of subjects during that time, and for safety concerns, the study was temporarily halted. With the resumption of offices, we have sought permission again from the IRB to reopen the study and was duly granted.

Reliability

Reliability is the extent to which a questionnaire, test, observation, or any measurement procedure produces the same results on repeated trials.[26] It gives an estimation of the temporal stability or consistency of scores over time or across raters. Causes of differences in measurement can arise from between the raters/observers or from the instrument or from the intrinsic stability of the item being measured[27] Measurements are reliable to the extent that they are repeatable and that any random influence that tends to make measurements different from occasion to occasion or circumstance to circumstance is a source of measurement error.[28]

Therefore, reliability, when applied to research methods, has two distinct meanings. The first one refers to stability over time, the second to internal consistency. A reliable measurement tool should be able produce similar or the same results consistently if it measures the same "end point". A measure can be reliable without being valid, but a measure cannot be valid without being reliable. The same ideas regarding reliability and its significance were kept in mind in the construction of this study.[29]

Internal Consistency and Item Analysis

In this study, internal consistency, item analysis and test-retest reliability as measures of reliability were used. Internal consistency reflects the extent to which the questionnaire items are inter-correlated, or whether they are consistent in measurement of the same construct. Internal consistency is commonly estimated using the coefficient alpha, also known as Cronbach's alpha. Cronbach's $\alpha = 0$ indicates no internal consistency (i.e., none of the items are correlated with one another), whereas $\alpha = 1$ reflects perfect internal consistency (i.e., all the items are perfectly correlated with one another). In practice, Cronbach's alpha of at least 0.70 has been suggested to indicate adequate internal consistency. A rule of thumb for interpreting alpha for dichotomous questions or Likert scale questions is: $\alpha \geq 0.9$ as excellent, $0.8 \leq \alpha < 0.9$ as good, $0.7 \leq \alpha < 0.8$ as acceptable, $0.6 \leq \alpha < 0.7$ as questionable, $0.5 \leq \alpha < 0.6$ as poor and $\alpha < 0.5$ as unacceptable.[30]

The mean Cronbach's alpha value for the T-ISI ($\alpha = 0.91$), indicates excellent internal consistency. The internal consistency of the Tagalog version was satisfactory and comparable with previous studies that also found values above 0.6. The translated version of the Insomnia Severity Index in Hindi also showed comparable internal consistency (Cronbach's $\alpha = 0.91$), as well as the Chinese ($\alpha = 0.91$) and Korean versions ($\alpha = 0.92$). It appears to have better outcome compared to the Arabic ($\alpha = 0.84$) and the French versions ($\alpha = 0.70$).

In an item analysis, the relationship of each item to each other and to the total construct is measured. The corrected total item correlation is often used to define the association of the item with the total score on the other items. It can be observed that in Table 2, all corrected item total correlations are well above the margin of 0.4, hence, each item therefore has very good discrimination. In addition, all items, when deleted have a minute difference to the total alpha coefficient, thereby all items are worthy of retention in the instrument. So, each item evaluated an attribute distinct from the construct of the measurement scale.[31]

Test-Retest Reliability

Test-retest reliability, or reproducibility, is a method that evaluates a tool's reliability by administering it to the same group of people, in the same way, on two or more different occasions.[32]

In our study, the test-retest reliability for the total score of the ISI done during the test was compared to the retest group completed after 2 weeks using the intraclass coefficient (ICC), Cronbach's Alpha and Bland-Altman plot. The ICC can range from 0-1, with 0 indicating no reliability and 1 indicating perfect reliability. In terms of reliability, if ICC ≥ 0.9 this means that there is almost perfect agreement, and if ICC is 0.8 it means that there is moderate agreement.[33] Put simply, ICC can be used to determine if items can be rated reliably by different raters. The results obtained moderate agreement with the test group and retest group of the translated version, where ICC = 0.782 (CI = 0.685-0.852). The Cronbach's alpha of 0.878 was also measured

and indicated high reliability and temporal stability in the test-retest scores. The findings are comparable to the ICC from the previous studies on the other translated versions of Both the French (ICC = 0.84, CI = 0.78–0.89) and Iranian versions had an ICC N 0.75.

The Bland-Altman Plot is also a simple and accurate way to quantify agreement between two variables and may help clinicians to compare a new measurement method against a reference standard. It is also a frequently applied technique in studies that investigate the agreement between two methods of the same medical measurement.[34] It is usually represented as a scatterplot in which the X-axis represents the average, and the Y-axis represents the difference of two measurements.

In the Bland-Altman plot of the translated version of the instrument, the average of almost all the differences was close to zero and was within the limits of agreement. The difference between the responses did not increase or decrease as the average increased. The variability was consistent across the graph. Very few outliers were detected (two outliers) with the translated version.

CONCLUSION

We found that the Tagalog version of ISI is a reliable instrument for assessing insomnia severity. It has good internal consistency; items have high item-total correlation. Test-retest reliability scores have moderate agreement. Likewise, the ease of administration, and the brevity of the questionnaire make it a helpful means to assess the self-reported insomnia symptoms of our patients (e.g., daytime fatigue, sleep dissatisfaction, and functional impairment) that are otherwise difficult to measure objectively.

LIMITATIONS

Our study was subject to some limitations. First, it was conducted at a sleep center in the Philippines and so was limited to our patients; however, since the questions of the Tagalog ISI did not have local characteristics, there were no regional differences. Second, we did not include any healthy controls without sleep problems, and additional studies that include such participants are needed. Third, we did not strictly assess for the presence of other comorbid disorders, such as psychiatric disorders, cancer, cardiovascular diseases which may affect patient's quality of sleep.

FUNDING

This study was self-funded, and the authors did not have any financial conflicts of interest.

CONFLICT OF INTEREST

None declared.

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APPENDICES

APPENDIX A. Tagalog Version of the Insomnia Severity index Questionnaire

Indeks sa Pagsukat ng Tindi ng Insomnia

May pitong tanong ang Insomnia Severity Index, o Indeks sa Pagsukat ng Tindi ng Insomnia. Susumahin ang pitong kasagutan upang makuha ang kabuuang iskor. Matapos makuha ang kabuuang iskor, tingnan ang 'Mga Panuntunan para sa Pag–iiskor/Interpretasyon' sa ibaba para malaman kung gaano katindi ang iyong hirap sa pagtulog.

BILUGAN ang numerong pinakaangkop na naglalarawan sa iyong sagot sa bawat tanong.

Sukatin ang KASALUKUYANG (HULING 2 LINGGO) TINDI ng iyong insomnia o hirap sa pagtulog.

Problema sa Insomnia (Para sa #1–3)
0 – Hindi 1 – Hindi Malubha 2 – Katamtaman 3 – Malubha 4 – Napakalubha

1. Nahihirapang makatulog – 0 1 2 3 4

2. Paputol–putol ang tulog – 0 1 2 3 4

3. Masyadong maaga nagigising – 0 1 2 3 4

4. Gaano ka KAKUNTENTO / HINDI KAKUNTENTO sa iyong KASALUKUYANG lagay ng pagtulog?
   0 – Sobrang kuntento
   1 – Kuntento
   2 – Medyo Kuntento
   3 – Hindi Kuntento
   4 – Sobrang Hindi Kuntento

5. Napapansin ba ng ibang tao ang epekto sa iyong buhay ng problema mo sa pagtulog?
   0 – Hindi Kapansin–pansin
   1 – Napapansin nang Kaunti
   2 – Medyo Kapansin–pansin
   3 – Kapansin–pansin
   4 – Sobrang Kapansin–pansin

6. Gaano ka NABABAHALA / NALULUNGKOT sa iyong kasalukuyang problema sa pagtulog?
   0 – Hindi Nababahala
   1 – Nababahala nang Kaunti
   2 – Medyo Nababahala
   3 – Nababahala
   4 – Sobrang Nababahala

7. Sa kasalukuyan, gaano NAKAHAHADLANG / NAKAAAPEKTO ang inosmnia sa pang-araw-araw mong gawain (halimbawa, pagkahapo sa umaga, sumpong o mood, kakayahan na magtrabaho o gumawa ng pangkaraniwang gawain, konsentrasyon, memorya, at iba pa)?
   0 – Hindi Nakahahadlang
   1 – Nakahahadlang nang Kaunti
   2 – Medyo Nakahahadlang
   3 – Nakahahadlang
   4 – Sobrang Nakahahadlang

Mga Panuntunan para sa Pag-iiskor/Interpretasyon:

Sumahin ang mga iskor ng mga sagot mo sa pitong tanong (Mga Sagot sa Tanong 1 + 2 + 3 + 4 + 5 +6 + 7) = _____ ang iyong kabuuang iskor

Kategorya ng Insomnia Batay sa Iskor:
   0–7 = Walang Insomnia
   8–14 = Mahinang Insomnia
   15–21 = Katamtamang Insomnia
   22–28 = Malubhang Insomnia

APPENDIX B. DEFINITION OF TERMS
Chronic Insomnia Disorder
A to F must be met

A. Sleep disturbance/ complaint	1. Difficulty initiating sleep 2. Difficulty maintaining sleep 3. Waking up earlier than desired 4. Resistance to going to bed on appropriate schedule 5. Difficulty sleeping without parent or caregiver intervention
B. Associated Consequences	C. Fatigue/malaise D. Attention, concentration, or memory impairment E. Impaired social, family, occupational or academic performance F. Mood disturbance, irritability G. Daytime sleepiness H. Behavioral problems (hyperactivity, impulsivity, aggression) I. Reduced motivation, energy, initiative J. Proneness for errors, accidents K. Concerns about or dissatisfaction with sleep
C. Adequate Opportunity	Cannot be explained purely by inadequate opportunity or circumstances
D. Frequency	Sleep disturbance and associated daytime symptoms occur at least 3x/ week
E. Duration	At least 3 months
F. Relationship to other condition	Not better explained by another sleep disorder, co-existing mental disorder or medical condition and not attributed to the physiologic effects of a substance

Acute Insomnia Disorder
A to F must be met

A. Sleep disturbance/ complaint	6. Difficulty initiating sleep 7. Difficulty maintaining sleep 8. Waking up earlier than desired 9. Resistance to going to bed on appropriate schedule 10. Difficulty sleeping without parent or caregiver intervention
B. Associated Consequences	M. Fatigue/malaise N. Attention, concentration, or memory impairment O. Impaired social, family, occupational or academic performance P. Mood disturbance, irritability Q. Daytime sleepiness R. Behavioral problems (hyperactivity, impulsivity, aggression) S. Reduced motivation, energy, initiative T. Proneness for errors, accidents U. Concerns about or dissatisfaction with sleep
C. Adequate Opportunity	Cannot be explained purely by inadequate opportunity or circumstances
D. Frequency	Sleep disturbance and associated daytime symptoms occur at least 3x/ week
E. Duration	Less than 3 months
F. Relationship to other condition	Not better explained by another sleep disorder, co-existing mental disorder or medical condition and not attributed to the physiologic effects of a substance

Insomnia Severity Index – is a 7-item self-report questionnaire assessing the nature, severity, and impact of insomnia. The usual recall period is the "last month" and the dimensions evaluated are: severity of sleep onset, sleep maintenance, and early morning awakening problems, sleep dissatisfaction, interference of sleep difficulties with daytime functioning, noticeability of sleep problems by others, and distress caused by the sleep difficulties.

Reliability – It is the stability or consistency of scores over time or across raters. As measurement error is present in content sampling, changes in respondents, and differences across raters, the consistency of a questionnaire can be evaluated using its internal consistency, test-retest reliability, and inter-rater reliability, split-half reliability.

Cronbach's Alpha – Cronbach's alpha is a measure of the internal consistency or reliability between several items, measurements, or ratings. The value of Cronbach's alpha ranges from zero to one with the higher values implying the items are measuring the same dimension. In contrary, if the Cronbach's alpha value is low (near to 0), it means some or all of the items are not measuring the same dimension

Internal Consistency – reflects the extent to which items within an instrument measure various aspects of the same characteristic or construct.

Item-Total Correlation – An item-total correlation test is performed to check if any item in the set of tests is inconsistent with the averaged behaviour of the others, and thus can be discarded. The analysis is performed to purify the measure by eliminating "garbage" items prior to determining the factors that represent the construct

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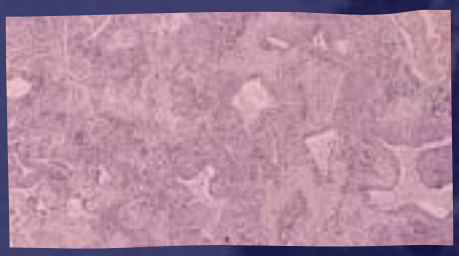

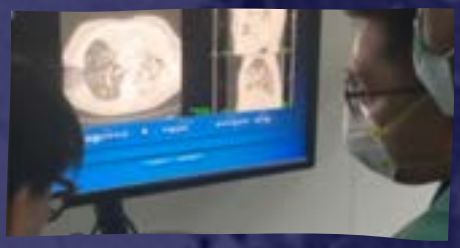

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ORIGINAL ARTICLE

PRESUMPTIVE PERIPHERAL ARTERIAL DISEASE AMONG PATIENTS WITH OBSTRUCTIVE SLEEP APNEA: ITS PREVALENCE AND ASSOCIATION WITH CLINICAL AND POLYSOMNOGRAPHIC PARAMETERS

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ABSTRACT

Objective. Obstructive sleep apnea (OSA) is a sleep breathing disorder characterized by episodes of breathing pauses, causing hypoxemia and sleep fragmentation. Peripheral arterial disease (PAD) is an atherosclerotic process of the lower extremity arteries leading to arterial obstruction and consequent arterial insufficiency. The proponents aimed to determine the prevalence of presumptive PAD among patients with OSA using the polysomnogram. We also sought to determine if there was a significant difference in the polysomnographic profiles of those with and without presumptive PAD.

Methodology. This was a single-center, prospective cross-sectional study conducted at the Lung Center of the Philippines from November 2022-April 2023. A total of 136 patients diagnosed with OSA with ABI measurements were included. Clinical and polysomnographic parameters were gathered, reviewed, and analyzed for association with PAD.

Results. Majority of the subjects were male (72.8), 36-55 age range (44.1), obese (61.0) and non-smokers (64.7). Bulk of the subjects had a high waist and neck circumference. Hypertension was present in 95 subjects. 92.1% of subjects have severe OSA with a severe oxygen desaturation index and poor sleep efficiency. The prevalence of presumptive PAD among OSA subjects was 15.44%. There was no significant difference between the clinical and polysomnographic profiles of subjects with and without presumptive PAD; however, apnea duration was longer among presumptive PAD patients, but it was not statistically significant (p = 0.557). Having poor sleep efficiency (p= 0.006) statistically increased the risk for presumptive PAD.

Conclusion. The prevalence of presumptive PAD among patients diagnosed with OSA using polysomnogram at the Lung Center of the Philippines was 15.44%. There was longer apnea duration among presumptive PAD patients. Having poor sleep efficiency can significantly increase the risk for PAD among OSA patients. Screening for PAD appears to be important among OSA patients.

Keywords. *Obstructive Sleep Apnea, peripheral artery disease, ankle brachial index, polysomnography, Sleep efficiency*

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INTRODUCTION

Obstructive sleep apnea is a sleep breathing disorder characterized by repetitive episodes of breathing pauses, with resultant hypoxemia and sleep fragmentation.[1,2] It is a common yet frequently overlooked medical disorder and often associated with cardiovascular complications. These hypoxic-driven awakening reactions result in activation of the sympathetic nervous system, causing significant increases in plasma catecholamines and blood pressure, even at daytime.[3]

Peripheral arterial disease is an atherosclerotic process of the lower extremity arteries leading to peripheral arterial obstruction and causes symptoms as a result of reduced arterial blood flow and consequent arterial insufficiency.[4] In the general population, the percentage of patients being asymptomatically or symptomatically affected by PAD averages 20 %.[5,6] The easiest and accurate non-invasive method for the diagnosis of PAD is the determination of the ankle-branchial index (ABI). It is the ratio of the systolic blood pressure measured at the ankle over the systolic blood pressure measured at the brachial artery. An ABI of ≤0.90 has been demonstrated to have high sensitivity and specificity for the identification of PAD.[7]

Nagagoshi et al. was able to demonstrate that obstructive sleep apnea was associated with greater prevalent PAD among black participants and self-reported OSA was associated with two-fold increase in newly diagnosed PAD.[8] A high prevalence of obstructive sleep apnea among patients undergoing revascularization due to severe PAD was noted by Utriainen.[9]

Data on the effect of OSA on PAD is sparse; however, their mutual pathophysiological dependence could be inferred based on the development of CAD and heart failure in OSA patients. The repetitive hypoxia during OSA causes oxidative stress that in turn damages endothelial tissue, promotes endothelial dysfunction and aggravates inflammatory processes.[10] Metabolic dysregulation is closely associated with OSA. Taken together, a growing body of evidence exists indicating that obstructive sleep apnea by itself is atherogenic. Obstructive sleep apnea affects myocardial function, coronary vessels and coronary arteries. Atherosclerosis has been proposed as an intermediate between sleep apnea and incident cardiovascular disease events. Since PAD represents a manifestation of atherosclerosis in the vascular bed of the lower extremity arteries and considering the above-mentioned OSA-induced pathophysiology, causality may not only exist for CAD, but also for PAD.

OBJECTIVE

This study was conducted to determine the prevalence of presumptive peripheral artery disease among patients diagnosed with obstructive sleep apnea using the polysomnogram at the Lung Center of the Philippines Sleep Laboratory from November 2022-April 2023. Specific objectives included:

1. To determine if there was a significant difference in the profiles of those with and without peripheral artery disease among adult patients diagnosed with obstructive sleep apnea: based on physical characteristics and comorbidities; and
2. To determine if there was a significant difference in the polysomnographic profiles of those with and without peripheral artery disease among adult patients diagnosed with obstructive sleep apnea: severity of sleep apnea, O2 desaturation, apnea duration and sleep efficiency

METHODOLOGY

Study Design and Setting

This was a single-center, prospective cross-sectional study conducted at the Lung Center of the Philippines from November 2022-April 2023.

Study Population and Subjects

Population

This study included patients who underwent diagnostic and split night polysomnogram at the Lung Center of the Philippines and diagnosed with Obstructive Sleep Apnea

1. Diagnosed with obstructive sleep apnea of any severity
2. Adults ≥18 years old
3. Signed written informed consent

Exclusion Criteria

1. Presence of significant Central Sleep Apnea during polysomnogram
2. Presence of Cheyne-Stokes Breathing during polysomnogram
3. Heart Failure NYHA III or IV based on history, 2D echo, if available, and clinical signs and symptoms of heart failure
4. Renal artery stenosis based on any one of the following:
   a. History of prior diagnosis
   b. Imaging studies (Ultrasound, CT or MR angiography, digital subtraction angiography)
   c. Presence of abdominal bruits, both systolic and diastolic, heard over the flank area

Subject Selection

All patients referred to the Lung Center of the Philippines Sleep Laboratory meeting the inclusion and none of the exclusion criteria were included in the study. An informed consent was obtained by the investigator prior to any study related procedures.

Study Design

All patients referred to the Lung Center of the Philippines Sleep Laboratory and Sleep Disorders Clinic for diagnostic and split night polysomnography were invited and asked by the investigator for their willingness to participate in the study. Those who agreed to participate in the study were asked by the investigator to sign the informed consent.

Subjects were asked for their preferred language when reading and understanding the informed consent. Ample time was given to the subject to read, understand and sign the informed consent. They were allowed to ask questions regarding the informed consent. The study participants were also given relevant information about what the study is about; the risks and benefits of taking part; how long the study took place; and the investigator and IERB chair contact information and the institution's approval number. They were informed that only the investigators, institution and IERB will have access to their records, and that their name and other information that can directly identify them were stored securely and separately from the research information collected from them. They knew that utmost confidentiality was provided. They can also withdraw their information by contacting the investigators. If they agreed to participate, they can sign or initial the consent form.

When the informed consent was signed, subjects were asked to complete a questionnaire via a physician–facilitated interview either face to face or virtually. This was followed by a brief physical examination including ABI determination to be done at the research site (LCP Sleep Laboratory) when the subject arrives for their scheduled polysomnography or after their interview when it was done via face to face. The following physician's facilitated interview using questionnaires included the following information: general questionnaire regarding demographic and clinical data and co–morbidities as well as Epworth Sleepiness Scale. If a subject was positive for Peripheral Arterial Disease based on their ABI score, they were advised to seek consultation with a vascular specialist or be referred back to their main attending physician with the polysomnography pushing through as referred. When a patient was tested positive for OSA of any severity and met all inclusion criteria and not any of the exclusion criteria, they were included in the study and their data obtained by the investigator for analysis. Otherwise, they will be excluded from the study. Interview and physical examination research data of those subjects who are excluded were destroyed/disposed of and deleted in a manner that leaves no possibility for reconstruction of information. However, their information and physical examination data that belongs to the sleep laboratory were retained at the sleep laboratory for documentation and safe keeping.

The purpose for gathering initially patient information and physical examination prior to conducting the polysomnography was to avoid trouble on the part of the patient of going back to the sleep laboratory to do those procedures since most of the follow up on these patients were done virtually. It is a protocol itself of the Lung Center of the Philippines Sleep Laboratory and Sleep Disorders Clinic to gather patient information and physical examination prior to their scheduled polysomnography. All this information was discussed with the subjects.

Data Collection

The following physician's facilitated interview using questionnaires were filled–up and completed:

1. General questionnaire regarding demographic and clinical data and co– morbidities
2. Epworth Sleepiness Scale.

A brief physical examination was conducted after the questionnaires were administered.

1. Vital Signs (Blood pressure, pulse rate, oxygen saturation)
2. Anthropometrics (Height, weight, BMI, neck circumference, waist circumference, hip circumference)
3. Mallampati Grade
4. Tonsillar Grade

Ankle Brachial Index Determination Technique

The ABI is performed by measuring the systolic blood pressure from both brachial arteries and from both the dorsalis pedis and posterior tibial arteries after the patient has been at rest in the supine position for 10 minutes. The systolic pressures are recorded with a handheld 5– or 10–mHz Doppler instrument. Standard blood pressure cuff can be used at the ankle. As with arm pressures, the blood pressure cuff is appropriately sized to the patient's lower calf (immediately above the ankle). Measurement will begin with the right arm, then the right leg, then the left leg, and finally the left arm, as the blood pressure may drift during the exam, and the two arm pressures at the beginning and end of the exam provide for some quality control.

Measuring the brachial pressure

The patient should be in the supine position. Place the blood pressure cuff on the arm, with the limb at the level of the heart. Place the ultrasound gel in the antecubital fossa over the patient's brachial pulse. Place the transducer of the handheld Doppler on the gel, and position the transducer to maximize the intensity of the signal. Inflate the cuff to about 20 mmHg above the expected systolic blood pressure of the patient. The Doppler signal should disappear. Then slowly deflate the cuff, approximately 1 mmHg/sec. When the Doppler signal re–appears, the pressure of the cuff is equal to the brachial systolic pressure. Record the brachial systolic pressure.

Measuring the ankle pressures

Place the cuff immediately proximal to the malleoli. Place ultrasound gel on the skin overlying the dorsalis pedis (DP)

and posterior tibial (PT) arteries in the foot. The Doppler signal of the DP can often be found slightly lateral to the midline of the dorsum of the foot. Using a standard hand-held Doppler probe and the ultrasound gel, locate the signal from the DP. Slowly move the Doppler until the strongest signal is heard. To measure the systolic pressure at the DP artery, inflate the cuff until you no longer hear the signal. Then slowly deflate using the same technique used in the arms until the Doppler signal re-appears. Record the measurement.

Next, measure the systolic pressure of the PT artery. The PT signal is detected posterior to the medial malleolus. Once again, using the Doppler with ultrasound gel, locate the signal, and follow the process described above to measure the PT systolic pressure. Repeat both measurements on the opposite leg.

Calculating the ABI

An ABI is calculated for each leg. The ABI value is determined by taking the higher pressure of the 2 arteries at the ankle, divided by the brachial arterial systolic pressure. In calculating the ABI, the higher of the two brachial systolic pressure measurements is used. In normal individuals, there should be a minimal (less than 10 mm Hg) interarm systolic pressure gradient during a routine examination. Calculated ABI values should be recorded to 2 decimal places.

Formula: ABI = highest foot pressure/highest brachial pressure

Statistical Analysis

To test for independence of proportions of the characteristics to PAD, the Fisher Exact test was performed for dichotomous data: gender, waist circumference, neck circumference, ESS, comorbidities, and medications; while Pearson chi-square for age, BMI, Mallampati, Tonsillar, Blood Pressure, Waist-to-hip ratio, and smoking status.

Fisher's exact test was used to compare proportion in sleep efficiency, Pearson chi-square for apnea/hypopnea index and oxygen desaturation index, while point-biserial test for lowest oxygen saturation, longest apnea duration, and heart rate.

Binomial logistics regression (univariable and multivariable) was used in determining the crude odds ratio as well as the adjusted odds ratio of the variables potentially associated with PAD. Odds-ratio and 95% confidence interval were estimated. Statistical significance was based on p-value ≤ 0.05. STATA v14 was used in data processing and analysis.

Limitations of the Study

There are several possible limitations of this study that should be taken into consideration. Pulse detection may be affected by pulse intensity. The presence of pedal edema can also affect the assessment. To ensure consistency of the measurements, only the primary investigator measured the ABI using a calibrated device.

Risks and Benefits

Benefits

This study screened and identified the presence of peripheral arterial disease among OSA patients without prior history of PAD. Early detection of PAD is a critical step in the management and prevention of complications of PAD such as cardiovascular events and coronary disease.

Risks

This study utilized non-invasive procedures to determine the presence of obstructive sleep apnea and peripheral arterial disease. The polysomnogram is an elective, painless and non-invasive procedure. The most common side effect is skin irritation caused by the adhesive used to attach test sensors to the skin. The ankle brachial index is also a painless, non-invasive procedure. Patients may feel some discomfort when the blood pressure cuffs inflate on their arm and ankle. But this discomfort is temporary and should stop when the air is released from the cuff.

ETHICAL CONSIDERATIONS

This study was conducted after the approval by the Technical Review Board (TRB) and Institutional Ethics Review Board (IERB) of the Lung Center of the Philippines. The study was in accordance with the ethical standards set by International Conference on Harmonization (ICHGCP) guidelines, to protect the rights of research participants, enhance research validity, and maintain scientific integrity.

The study's process of informed consent was tailored to inform the subject of rights, risks, and benefits when participating. The informed consent form (ICF) contained information in an understandable language to the subject. A copy of the approved ICF was provided to the subject for them to read and were asked if they had any questions. The study participants were also given relevant information about what the study is about; the risks and benefits of taking part; how long the study will take; and the investigator and IRB chair contact information and the institution's approval number. They were also informed that their data were kept confidential, and they are free to stop filling in the survey at any point for any reason. They can also withdraw their information by contacting the investigators. If they agree to participate, they can sign the consent form. Even if the procedures only have minimal risk, medical care and compensation were given to the subjects in case of a serious injury related to the study procedure. The subject has the right of free participation in this study, and they have the right to know that they are free to withdraw from the study at any given point. Only the investigators, institution and IERB have access to the

participants' records. The name of the subjects and other information that can directly identify them were stored securely and separately from the research information that identify the participants. The benefits of participating in this study is that the subjects were able to know if they have presumptive PAD on top of obstructive sleep apnea which warrants early management in order to prevent it from worsening. Subjects who were positive for peripheral arterial disease were referred back to their main attending physician or referred to a vascular specialist. The subjects were anonymous and only their clinical data, comorbidities, Epworth sleepiness scale, physical examination findings and polysomnographic results were shared but did not directly identify them.

The questionnaires, procedures and interviews to be administered to the subject did not contain any sensitive information that can harm the subject psychologically, socially, physically and legally.
Proper research communication was done on this study.

RESULTS

A total of 136 patients satisfied the inclusion criteria and were included in the study. The bulk of the patients were in the 36–55 age range (44.1%). The majority were males (72.8%) and obese (61%), with a Mallampati Score of 4 (44.9%) and a tonsillar grade of 2 (69.1%). Most of the patients had uncontrolled blood pressure (88.2%). Fifty-five-point one percent of the subjects have a waist circumference considered high risk for cardiometabolic disease (greater than 40 inches in males and greater than 35 inches in females), and half (50%) of the subjects have a waist to hip ratio of >1 in men and 0.85 in women which are considered high risk for comorbidities. Most of the patients (58.1%) also had a neck circumference at risk for OSA (>17 inches in males and >16 inches in females). Fifty-point seven percent of the subjects are clinically sleepy (ESS >10). The majority of the subjects were non-smokers (64.7%). Hypertension was present in 95 subjects (69.9%). Most patients do not have diabetes mellitus (76.5%) and dyslipidemia (75.7%). Coronary artery disease was not seen in 95.6% of the subjects. Only a small percentage of the subjects were diagnosed with chronic obstructive pulmonary disease (2.2%) and heart failure (1.5%). Stroke and TIA were mostly absent in the subjects (0.7%). Six-point six percent of subjects used aspirin, while 25.7% were taking statins.

Table 1 shows characteristics of patients with Obstructive Sleep Apnea according to presence of peripheral artery disease. Data were presented as count (percent). The overall prevalence of PAD among OSA subjects was 15.44% (n=21). There was no significant difference in demographic profiles, comorbidities, physical examination and sleepiness score.

Table 1. *Characteristics of patients with Obstructive Sleep Apnea according to presence of Peripheral Artery Disease*

Characteristic	All n = 136	PAD Present ABI < 0.9 n = 21	PAD Present ABI < 0.9 n = 115	*p*-value
Age in years				**.769**
18–35 (Young adults)	45 (33.1)	6 (28.6)	39 (33.9)	
36–55 (Middle-aged adults)	60 (44.1)	9 (42.9)	51 (44.3)	
>56 (Older adults)	31 (22.8)	6 (28.6)	25 (21.7)	
Gender				**.594**
Male	99 (72.8)	14 (66.7)	85 (73.9)	
Female	37 (27.2)	7 (33.3)	30 (26.1)	
Body mass index in kg/m2				**.942**
Underweight	1 (0.7)	0 (0)	1 (0.9)	
Normal	18 (13.2)	3 (14.3)	15 (13.0)	
Overweight	34 (25.0)	6 (28.6)	28 (24.3)	
Obese	83 (61.0)	12 (57.1)	71 (61.7)	
Mallampati				**.502**
Scale 1	7 (5.1)	0 (0)	7 (6.1)	
Scale 2	28 (20.6)	6 (28.6)	22 (19.1)	
Scale 3	40 (29.4)	5 (23.8)	35 (30.4)	
Scale 4	61 (44.9	10 (47.6)	51 (44.3)	
Tonsillar				**.831**
Grade 0	1 (0.7)	0 (0)	1 (0.9)	
Grade 1	11 (8.1)	1 (4.8)	10 (8.7)	
Grade 2	94 (69.1)	14 (66.7)	80 (69.6)	
Grade 3	27 (19.9)	5 (23.8)	22 (19.1)	
Grade 4	3 (2.2)	1 (4.8)	2 (1.7)	
Blood pressure in mmHg				**.714**
Controlled	16 (11.8)	3 (14.3)	13 (11.3)	
Uncontrolled	120 (88.2)	18 (85.7)	102 (88.7)	

Characteristic	All n = 136	PAD Present ABI < 0.9 n = 21	PAD Present ABI < 0.9 n = 115	*p*-value
Waist circumference in cm				**.635**
At-risk	75 (55.1)	13 (61.9)	62 (53.9)	
Not at-risk	61 (44.9)	8 (38.1)	53 (46.1)	
Waist-to-hip ratio				**.841**
Low	9 (6.6)	2 (9.5)	7 (6.1)	
Moderate	59 (43.4)	9 (42.9)	50 (43.5)	
High	68 (50.0)	10 (47.6)	58 (50.4)	
Neck Circumference				**.634**
At risk	79 (58.1)	11 (52.4)	68 (59.1)	
Not at-risk	57 (41.9)	10 (47.6)	47 (40.9)	
Epworth Sleepiness Scale				**.815**
≤10	67 (49.3)	11 (52.4)	56 (48.7)	
>10	69 (50.7)	10 (47.6)	59 (51.3)	
Smoking status				**.958**
Non-smoker	88 (64.7)	13 (61.9)	75 (65.2)	
Previous smoker	24 (17.6)	4 (19.0)	20 (17.4)	
Current smoker	24 (17.6)	4 (19.0)	20 (17.4)	
Comorbidities				**.120**
Hypertension				
-absent	41 (30.1)	3 (14.3)	38 (33.0)	
-present	95 (69.9)	18 (85.7)	77 (67.0)	
Diabetes mellitus				**.580**
-absent	104 (76.5)	15 (71.4)	89 (77.4)	
-present	32 (23.5)	6 (28.6)	26 (22.6)	
Dyslipidemia				**1.000**
-absent	103 (75.7)	16 (76.2)	87 (75.7)	
-present	33 (24.3)	5 (23.8)	28 (24.3)	
Coronary artery disease				**1.000**
-absent	130 (95.6)	20 (95.2)	110 (95.7)	
-present	6 (4.4)	1 (4.8)	5 (4.3)	
Chronic obstructive pulmonary disease				**.398**
-absent	133 (97.8)	20 (95.2)	113 (98.3)	
-present	3 (2.2)	1 (4.8)	2 (1.7)	
Heart failure				**1.000**
-absent	134 (98.5)	21 (100)	113 (98.3)	
-present	2 (1.5)	0 (0)	2 (1.7)	
CVD (Stroke, TIA)				**1.000**
-absent	135 (99.3)	21 (100)	114 (99.1)	
-present	1 (0.7)	0 (0)	1 (0.9)	

PAD: peripheral artery disease, ABI: ankle brachial index.

Majority of the subjects have severe obstructive sleep apnea (91.2%) with a severe oxygen desaturation index (70.6%). The mean lowest oxygen saturation of the subjects was 76.6% ± 11.9. The mean longest apnea duration was 52.8 seconds ± 21.8. Most of the subjects have a poor sleep efficiency (88.2%). The average heart rate in beats per minute of our subject was 71.1 ± 12.4.

Table 2 showed the polysomnographic profiles between subjects with presumptive PAD and those without, which revealed that there was no significant difference between the two groups. However, it was noted that presumptive PAD positive patients have longer apnea duration (78.0 ± 8.4) than negative patients (76.3 ± 12.5), though statistically not significant (0.557).

Table 2. *Polysomnographic profiles of adult patients with Obstructive Sleep Apnea according to presence of Peripheral Artery Disease.*

Sleep Parameters	All n = 136	PAD Present ABI < 0.9 n = 21	PAD Present ABI < 0.9 n = 115	*p*-value
Apnea Hypopnea Index in events/hour Moderate Severe Mild	 11 (8.1) 124 (91.2) 1 (0.7)	 1 (4.8) 20 (95.2) 0 (0)	 10 (8.7) 104 (90.4) 1 (0.9)	**.753**
Lowest oxygen saturation %	76.6 ± 11.9	78.0 ± 8.4	76.3 ± 12.5	**.557**
Oxygen desaturation index in events/hour (ODI) Normal Mild Moderate Severe	 9 (6.6) 14 (10.3) 17 (12.5) 96 (70.6)	 0 (0) 1 (4.8) 2 (9.5) 18 (85.7)	 9 (7.8) 13 (11.3) 15 (13.0) 78 (67.8)	**.339**
Longest apnea duration in seconds	52.8 ± 21.8	58.4 ± 30.9	51.9 ± 19.9	**.621**
Sleep Efficiency Good Poor	 16 (11.8) 120 (88.2)	 4 (19.0) 17 (81.0)	 12 (10.4) 103 (89.6)	**.273**
Heart rate in beats per minute	71.1 ± 12.4	69.9 ± 11.8	71.4 ± 12.6	**.612**

PAD: peripheral artery disease, ABI: ankle brachial index
Data presented as mean ± standard deviation, for lowest oxygen saturation, longest apnea duration, and heat rate, while count (percent) in terms of apnea/hypopnea index, oxygen desaturation index, and sleep efficiency.

Table 3. *Crude and Adjusted Odds Ratios for factors associated with Peripheral Arterial Disease*

Characteristic	Crude Odds Ratio (95% CI)	*p*-value	Adjusted Odds Ratio (95% CI)	*p*-value
Age in years 18–35 (Young adults) 36–55 (Middle-aged adults) >56 (Older adults)	 Reference 1.15 (0.38 – 3.49) 1.56 (0.45 – 5.38)	 0.809 0.481	 2.48 (0.36 – 16.91) 1.58 (0.12 – 21.32)	 0.353 0.732
Gender Male Female	 Reference 0.71 (0.26 – 1.92)	 0.494	 1.77 (0.16 – 20.06)	 0.644
Body mass index in kg/m2 Underweight Normal Overweight Obese	 Reference 0 0 0	 1.000 1.000 1.000	 	 ** ** **
Mallampati Scale 1 Scale 2 Scale 3 Scale 4	 Reference 0 1.39 (0.45 – 4.30) 0.73 (0.23 – 2.32)	 – 0.567 0.591	 	 ** ** **
Tonsillar Grade 0 Grade 1 Grade 2 Grade 3 Grade 4	 Reference 0 0.20 (0.01 – 4.72) 0.35 (0.03 – 4.12) 0.46 (0.03 – 6.06)	 0.000 0.200 0.404 0.551	 0.16 (0 – 344.69) 0.57 (0.01 – 49.64) 0.61 (0.00 – 98.40)	 0.638 0.806 0.850
Blood pressure in mmHg Controlled Uncontrolled	 ** **	 ** **	 ** **	 ** **
Waist circumference in cm At-risk Not at-risk	 Reference 0.72 (0.28 – 1.87)	 0.500	 0.09 (0.00 – 2.73)	 0.165

Characteristic	Crude Odds Ratio (95% CI)	*p*-value	Adjusted Odds Ratio (95% CI)	*p*-value
Waist-to-hip ratio				
Low	Reference			
Moderate	0.63 (0.12 – 3.53)	0.599	4.10 (0.11 – 152.38)	0.444
High	0.60 (0.11 – 3.33)	0.603	3.87 (0.08 – 190.03)	0.496
Neck Circumference				
At risk	Reference			
Not at-risk	1.32 (0.52 – 3.35)	0.565	0.28 (0.03 – 2.91)	0.288
Epworth Sleepiness Scale				
≤10	Reference			
>10	0.86 (0.34 – 2.19)	0.756	3.50 (0.63 – 19.50)	0.153
Smoking status				
Non-smoker	Reference			
Previous smoker	1.15 (0.34 – 3.93)	0.819	1.59 (0.13 – 20.16)	0.723
Current smoker	1.15 (0.34 – 3.93)	0.819	0.74 (0.07 – 8.14)	0.811
Comorbidities				
Hypertension				
-absent	Reference			
-present	2.96 (0.82 – 10.68)	0.097	8.27 (0.74 – 93.01)	0.087
Diabetes mellitus				
-absent	Reference			
-present	1.37 (0.48 – 3.88)	0.555	1.21 (0.13 – 11.14)	0.865
Dyslipidemia				
-absent	Reference			
-present	0.97 (0.33 – 2.89)	0.958		**
Coronary artery disease				
-absent	Reference			
-present	1.10 (0.12 – 9.92)	0.932	4.45 (0.09 – 214.19)	0.450
Chronic obstructive pulmonary disease				
-absent	Reference			
-present	2.83 (0.24 – 32.64)	0.406	15.51 (0.24 – 1006)	0.198
Heart failure				
-absent	Reference			
-present	0	0.999		**
CVD (Stroke, TIA)				
-absent	Reference			
-present	0	1.000		**
Apnea Hypopnea Index in events/hour				
Mild	Reference			
Severe	1.92 (0.23 – 15.87)	0.544	6.41 (0.05 – 827.96)	0.454
Moderate	0	1.000	6.191 (0.00 – 0.00)	1.000
Lowest oxygen saturation %	1.01 (0.97 – 1.06)	0.555	1.04 (0.95 – 1.14)	0.389
Oxygen desaturation index in events/hour (ODI)				
Normal	Reference			
Mild	0	0.999		**
Moderate	0	0.999		**
Severe	0	0.999		**
Longest apnea duration in seconds	1.01 (0.99 – 1.03)	0.619	1.03 (0.99 – 1.08)	0.152
Sleep Efficiency				
Good	Reference			
Poor	0.50 (0.14 – 1.72)	0.268	0.005 (0 – 0.21)	0.006*
Heart rate in beats per minute	0.99 (0.95 – 1.03)	0.610	1.01 (0.94 – 1.09)	0.744

OR: odds-ratio, CI: confidence interval; *significant, p<0.05, **Removed from model, p>0.2 in the univariate analysis

Table 3 shows the crude and adjusted odds ratio using binomial logistics regression to determine the variables associated with PAD.

Using univariate analysis, none of the clinical and polysomnographic variables posted a high risk of having PAD. All these associations did not show any statistical significance.

However, in using the multivariable regression analysis, only poor sleep efficiency (adjusted odds ratio 0.005, 95% confidence interval from 0 to 0.21 p= 0.006) posted a significant relationship to PAD.

DISCUSSION

In this study, we have demonstrated the following: 1). The overall prevalence of presumptive PAD among OSA patients was 15.44%, which translates to having an ABI </= 0.9. 2). The presence of poor sleep efficiency among OSA patients significantly increases the risk of presumptive PAD statistically. 3). There was longer apnea duration among presumptive PAD positive patients than negative patients, but it was statistically insignificant.

A recent systematic review by Aday et al. estimates that the global prevalence of PAD was 5.6% in 2015, indicating that ~236 million adults were living with PAD worldwide. The prevalence was higher in high-income countries than in low- and middle-income countries, but via population size, most individuals with PAD (72.9%) were in low- and middle-income countries. PAD prevalence also has increased from 2000 to 2015 by ~45% globally (~18% in high-income countries and ~58% in low- and middle-income countries.[11]

Compared with western studies, the prevalence rate of PAD among our confirmed OSA patients (18.26%) was lower from the studies done in Germany (98%),[12] but higher than in a study done in the USA (5.4%).[13] Another American meta-analysis study revealed a higher prevalence showing that 20.5% of OSA had PAD, using ABI as well as pulse wave velocity and duplex ultrasonography.[14] Among Latin American population, prevalence of PAD among OSA patients was lower than our subjects of only 4.7%, with increasing odds among moderate to severe OSA patients.[15] Another study in Finland found that 85% of patients with OSA were diagnosed with PAD, of whom 34% had severe OSA.[16]

Compared with Middle Eastern studies, a meta-analysis done in Saudi Arabia noted that PAD was present in 19.9% of patients with OSA using ABI, PWV and duplex ultrasonography which was higher than in our study subjects.[17] No articles were found yet regarding the prevalence of PAD among OSA patients in Asia.

In our study, it was noted that the presence of poor sleep efficiency among OSA patients significantly increases the risk of presumptive PAD statistically.

Sleep deprivation is a growing health concern. Short sleep durations are associated with development of vascular endothelial dysfunction that leads to increased cardiovascular disease risk and atherosclerotic plaques.

A study among Swedish population noted incident PAD risk was higher in those with short sleep (<5 hours; hazard ratio (HR), 1.74; 95% confidence interval (CI) 1.31–2.31) or long sleep (≥8 hours; HR 1.24; 95% CI 1.08–1.43), compared to individuals with a sleep duration of 7 to <8 hours/night.[18]

A study from Japan noted that poor sleep quality was independently associated with lower ABI in patients with essential hypertension.[19] A study in China examined the prevalence of LE-PAD and noted that patients with poor sleep quality had an OR of 1.41 (1.00 to 1.97) for having PAD.[20]

Another study from Korea noted that poor subjective sleep quality was associated with CAC in women but not in men, whereas the association between poor subjective sleep quality and brachial-ankle PWV was stronger in men than in women.[21]

Our study also noted that there was longer apnea duration among presumptive PAD positive patients than negative patients, but it was statistically insignificant.

No articles were found regarding the correlation between duration of apneic episodes on obstructive sleep apnea and presence of PAD; however, it appears that the longer the duration of the apneic event, the more hypoxemic would be, which would eventually lead to increased risk of vascular disease.

Study Limitations

Some limitations were identified in our study. Majority of subjects have severe OSA hence applicability to mild and moderate OSA are limited. It will also be prudent to include subjects with no OSA but were tested positive for PAD to serve as a control group.

Significance of the Study

OSA has a substantial effect on the development of PAD. The repetitive hypoxia during OSA causes oxidative stress that in turn damages endothelial tissue, promotes endothelial dysfunction and aggravates inflammatory processes, making OSA atherogenic leading to development of PAD. By identifying OSA patients at risk for CVD morbidity and mortality, it will allow improved CVD risk prediction. Early screening of PAD among OSA patients will enable early referral to a vascular specialist. Hence the presence of OSA along with its accompanying risk factors warrants a search for the presence of peripheral arterial disease.

CONCLUSION

Twenty-one out of 136 subjects, comprising 15.44% of the total sample exhibited PAD. It was significantly noted in the study that having poor sleep efficiency (p= 0.006) posted statistically significant relationships to PAD. There was longer apnea duration among presumptive PAD positive patients than negative patients, but it was statistically insignificant.

RECOMMENDATION

Based on the results together with the data from other studies, we suggest screening OSA patients for PAD, especially among those having a poor sleep efficiency and

long apnea duration. Increasing the sample size would help strengthen the association of PAD with other variables, especially apnea duration and oxygen desaturation.

FUNDING

This is a self-funded study.

CONFLICT OF INTEREST

None declared.

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APPENDICES

Appendix A. DEFINITION OF TERMS

(Operational Definition)

Dependent Variables

1. **Presumptive Peripheral Arterial Disease** – ankle brachial index of ≤0.90 measured using a handheld doppler device

Independent Variables

1. **Apnea Hypopnea Index**
   a. **Mild Obstructive Sleep Apnea**: AHI ≥ 5, but < 15 per hour
   b. **Moderate Obstructive Sleep Apnea**: AHI ≥ 15 to 30 per hour
   c. **Severe Obstructive Sleep Apnea**: AHI > 30 per hour
2. **Oxygen desaturation** – the lowest oxygen desaturation recorded during the diagnostic sleep study
3. **Sleep Efficiency** – total sleep time over total time in bed in percent
4. **Apnea duration** – duration of the longest apnea event during diagnostic sleep study in seconds

Modifiers

1. General Data
   a. **Age** – age of patient upon inclusion to the study
   b. **Gender** – being male or female as specified by the patient upon inclusion to the study
   c. **Smoking** – history of smoking either none, current or previous
2. Physical Exam
   a. **Vital Signs** – taken at time of inclusion to the study
      i. Blood Pressure – taken after 10 minutes of rest, measurement of both arms with the highest pressure recorded
      ii. Pulse Rate – radial pulse of patient
      iii. Oxygen saturation – measurement of patient's oxygen saturation level using a pulse oximeter
   b. **Waist Circumference** – screening measurement as index of central body fat distribution to identify obesity. Men and women who have waist circumferences greater than 40 inches (102 cm) and 35 inches (88 cm), respectively, are considered to be at increased risk for cardiometabolic disease (73)
   c. **Waist to Hip Ratio** – measurement of abdominal obesity is defined as a waist–hip ratio above 0.90 for males and above 0.85 for females
   d. **BMI** – body mass index; measure of body fat based on height and weight that applies; underweight(<18.5kg/m2); normal (18.5 to <25kg/m2); overweight (25.0 to <30.0kg/m2) Obese Class I (30.0–34.9); Obese Class II (35.0–39.9); Obese Class III (≥40)
   e. **Mallampati Classification** – an estimate of tongue size relative to oral cavity.
      i. Class I–complete visualization of the soft palate
      ii. Class II– complete visualization of the uvula
      iii. Class III–visualization of only the base of the uvula
      iv. Class IV–soft palate is not visible at all
   f. **Tonsillar grade** – reliable visual grading scale to grade tonsil size
      i. Grade I – In tonsillar fossa
      ii. Grade II – Visible beyond anterior pillars
      iii. Grade III – Extended ¾ of way to midline
      iv. Grade IV – Completely Obstructing airway
   a. **Neck Circumference** – screening measurement as index of upper body fat distribution to identify obesity. Neck circumference values of 17 inches or greater in men and 16 inches or greater in women are strongly correlated with the risk for obstructive sleep apnea.
   b. **Co–morbid conditions** – presence of other medical diseases upon inclusion to the study
   c. **Sleep Efficiency**– defined as the percentage of time spent asleep while in bed. A normal sleep efficiency is considered to be 85% or higher

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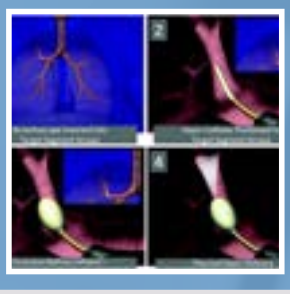

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ORIGINAL ARTICLE

SAFETY AND EFFICACY OF PRE-EMPTIVE INTRAVENOUS PARACETAMOL ON POST-OPERATIVE PAIN AMONG PATIENTS UNDERGOING UNI-PORTAL VIDEO ASSISTED THORACOSCOPIC SURGERY: A SINGLE-CENTER, DOUBLE-BLINDED, RANDOMIZED CONTROLLED TRIAL

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ABSTRACT

Objective. Video-Assisted Thoracoscopic Surgery (VATS) has become a standard approach for various thoracic surgical procedures due to its minimally invasive nature and reduced morbidity. However, ensuring adequate pain control is necessary for optimizing patient outcomes and overall satisfaction. Pre-emptive analgesia is a strategic approach to pain management that focuses on preventing or minimizing post-operative pain. This study investigates the potential benefits of administering intravenous paracetamol as pre-emptive analgesia before VATS, comparing its efficacy in pain relief, opioid consumption, side effects and length of hospital stay against standard post-operative pain regimen.

Methodology. This is a prospective, double-blind, randomized, controlled trial with a sample size of 58. All participants who met the inclusion criteria were randomly assigned in a 1:1 ratio to either treatment group (paracetamol) or the control group (normal Saline). This study assessed pain scores at various intervals, including PACU arrival, every 30 minutes for 2 hours, every 2 hours for 24 hours and every 4 hours for 48 hours post-operatively. Additionally, rescue doses, time to first rescue dose, side effects and length of hospital stay were evaluated.

Results. Upon PACU arrival, both groups exhibited a median pain score of 0, with 17% and 24% reporting mild pain in the treatment group and control groups respectively. The control group presented a higher percentage of moderate pain (18%) compared to that of the treatment group (4%). Significant differences in median pain scores were observed at 30 minutes, 1 hour and 1.5 hours post-operatively, favoring the treatment group. At 2 hours post-op, 46% in the treatment group reported no pain, contrasting with only 12% in the control group.

Throughout the study, the treatment group required fewer rescue doses (median score of 1 versus 4 in the control groups). Nausea was reported in 35% of the control group and 4% in the treatment group. Splinting was observed in 35% of the control group compared to 4% in the treatment group. No significant differences were found in the time to first rescue dose and length of hospital stay between the two groups.

Conclusion. Pre-emptive intravenous paracetamol results a to better pain management outcomes in VATS patients, potentially reducing post-operative pain, preventing development of chronic pain and lesser side effects.

Keywords: *Video-Assisted Thoracoscopic Surgery (VATS), intravenous paracetamol, pre-emptive analgesia, acute post-operative pain, tramadol*

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INTRODUCTION

Video-Assisted Thoracoscopic Surgery (VATS) is a minimally invasive surgical technique designed for diagnosing and treating a range of thoracic conditions including pulmonary, mediastinal and pleural pathologies. This employs small incisions allowing the reduction of surgical stress and post-operative pain. Despite these advantages, a significant number of patients still reports moderate to severe pain following the procedure. Acute post-operative pain, triggers a cascade of neuroendocrine, immune and inflammatory responses, resulting to a surged in stress hormones coupled with catabolism, immunosuppression and increase myocardial oxygen consumption that contributes to increase morbidity and mortality among post-operative patients. Moreover, uncontrolled acute post-operative pain increases the risk of it evolving into chronic pain, persisting beyond three months post-surgery.[1,2,3,4]

Pre-emptive analgesia is a proactive approach to pain management that involves administering analgesic medications before the onset of a painful stimuli.[5] Its goal is to prevent the establishment of central sensitization and reduce the amplification of pain signals, ultimately leading to improved pain control during and after the procedure.

Recognizing the importance to address post-operative pain, this study investigates the potential of intravenous paracetamol as a pre-emptive medication for VATS. Paracetamol, a well-established analgesic, operates by inhibiting the production of prostaglandins, responsible for pain and inflammation.[6,7] Unlike opioid analgesics, paracetamol presents minimal side effects, minimizing concerns such as drowsiness, respiratory depression, nausea and vomiting.[7] Its versatility extends to its compatibility with other analgesics, offering a unique opportunity to enhance pain relief while minimizing the risk of adverse effects.

Significance of the study

This study aims to include pre-emptive intravenous Paracetamol as a potential analgesic agent with the goal of optimizing pain management protocol. Understanding the impact of pre-emptive analgesia on pain scores, opioid requirements and post-operative recovery in the context of VATS is crucial for tailoring patient centered care and enhancing overall surgical experience. This research not only addresses the immediate concerns of post-operative pain but also the potential long-term implications for patients undergoing VATS procedure.

Review of literature

The American Society of Anesthesiologist (ASA) defines acute pain as the presence of pain in a patient following a surgical or medical procedure.[8] This pain may result from trauma caused by the procedure or complications related to the procedure and necessitates effective perioperative pain management. Various studies have explored different analgesic approaches to enhance post-operative pain control and lessen side effects associated with standard pain management strategies.

Paracetamol, a centrally acting drug, inhibiting prostaglandin synthesis and cyclo-oxygenase COX) in the nervous system, presents a promising alternative to other non-steroidal anti-inflammatory drugs (NSAIDS). Its mechanism of action, distinct from NSAIDs, makes it a safer choice, associated with minimal gastrointestinal and central side effects. The study of Mustafa Arslan on pre-emptive intravenous paracetamol in open cholecystectomy reinforces the opioid sparing effects of paracetamol, showcasing decreased 24-hour opioid consumption and increased time to first analgesic use.

Jahangiri et al. compared the use of paracetamol with ketorolac, administered after VATS, observing a significantly lower need for rescue medications in the paracetamol group compared to the ketorolac group.[9] Similarly, Dastan et al. conducted a double-blind, randomized clinical trial comparing continuous intravenous ketorolac, paracetamol and morphine in VATS patients.[6] Their findings revealed the non-inferiority of ketorolac and paracetamol to morphine in controlling post VATS pain, without causing significant side effects.

In the realm of neuraxial and regional anesthesia, Min Kong et al. explored the effectiveness of pre-emptive analgesia for post-operative pain relief after VATS. Their pre-emptive analgesia group, received celecoxib orally, paravertebral nerve block and local infiltration of ropivacaine before surgery. Results showed superior pain relief and reduced analgesic related adverse reactions compared to standard post-operative analgesic regimens.

Objective

The study was conducted to determine the efficacy and safety of pre-emptive paracetamol on post-operative pain control among adult patients undergoing uni-portal video assisted thoracoscopic surgery at the Lung Center of the Philippines. Specific objectives included:

1. To compare the post-operative pain scores between the treatment and control group at:
   a. PACU admission
   b. Every 30 minutes for first 2 hours
   c. Every 2 hours for first 24 hours
   d. Every 4 hours until 48 hours post-operatively
2. To compare the number of rescue doses between the treatment and control group
3. To compare the time to first rescue dose between the treatment and control group
4. To compare development of side effects (atelectasis, fever, tachycardia, tachypnea, splinting) during the 1st 48 hours post-operatively
5. To compare the length of hospital, stay between two groups
6. To determine any adverse event during administration of pre-emptive paracetamol

METHODOLOGY

Study Design

This was a single-center, double-blind, randomized controlled trial with a parallel group design. Participants were assigned to one of the treatment arms at the beginning of the trial and continued in that arm throughout the length of the trial. Participants include patients who underwent uni-portal VATS between July 2023 to November 2023 at the Lung Center of the Philippines. Patients and the primary investigator were blinded. Patients were randomized in a 1:1 ratio to either treatment or control group. Post-operative pain regimen was the same for both groups except with pre-emptive analgesia. Patient participated for 48 hours from the time of completion of the procedure. The primary investigator was the one assesses the outcomes during the entire duration of study.

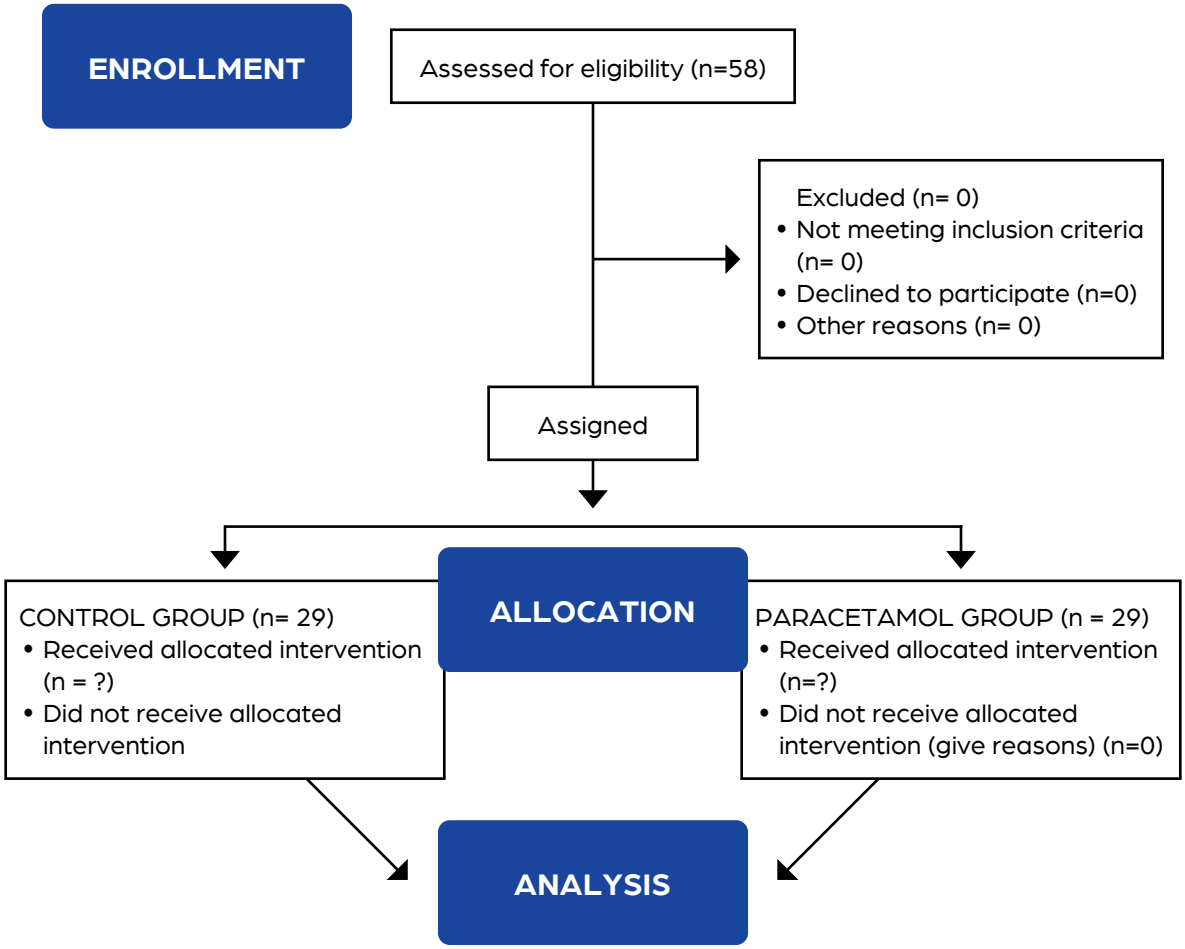

Figure 1. *Process flow of patient selection*

The prospective subjects satisfied the inclusion and exclusion criteria listed below.

Inclusion criteria:

a. Age 18 to 65 years old
b. Pay and service patients
c. Scheduled to undergo elective uni-portal VATS due to any indication.
d. American Society of Anesthesiologist (ASA) Physical Status Classification I to III.

Exclusion criteria:

a. Patients with known allergies to NSAIDS, opioids, and or paracetamol
b. Patients with acute or chronic kidney disease
c. Patients with liver disease
d. Pregnant patient
e. Unable to sign consent and/or mentally unstable
f. Patients with contraindication for paravertebral nerve block like allergic to local anesthesia, infection at puncture site and sepsis.

Withdrawal criteria:

a. Patient refused to continue participation
b. Deferred procedure for any indication
c Table death
d Patient who developed serious adverse reaction during conduct of study: hemodynamic instability, require intubation and/or ICU stay
e Patient showing signs of allergic reaction to paracetamol
f. VATS converted to OPEN thoracotomy

Sampling methodology and sample size computation

Parameters were based on a published study by Min Kong et al.[14] Specifying a mean pain score of 4.7 ± 0.3 for the treatment group and 4.4 ± 0.3 for the control group, alpha set at 0.05, a minimum of 46 patients–23 per group–achieves 90% power to detect a significant difference between the two groups. Sample size was increased to 58 (29 per group) to account for 20% potential dropout. The researcher employed convenience sampling to select study participants.

Description of study procedure

Pre-operative Phase

1. Patient Selection and Consent.
    a. Primary investigator conducted pre-operative evaluation and explained research study to eligible patients.
    b. Informed consent was obtained from each patient.
2. Blinding and Group Assignment.
    a. Both patient and primary investigator were blinded to the treatment details.
    b. Secondary investigator assigned to the case performed pre-operative evaluation and assigned the patients to either Group A (pre-emptive paracetamol) or Group B (control–PNSS).
3. Pre-operative Instructions.
    a. Secondary investigator wrote pre-operative instructions on the patient's chart based on group assignment.
    b. Group A received one gram of Paracetamol in 100 ml via soluset for 15 minutes.
    c. Group B received 100 ml of PNSS via soluset for 15 minutes.

Intra-operative Phase

1. Midazolam 1mg/IV was given prior to anesthesia induction.
2. Fentanyl 1mcg/kg IV was administered upon anesthesia induction followed by Propofol 2mg/kg IV.
3. Endotracheal intubation was facilitated with rocuronium 0.6mg/kg IV.
4. Patients were maintained with sevoflurane and top up doses of rocuronium and fentanyl.

Post-operative Phase

1. Ultrasound guided paravertebral block was done and patient was given 2% lidocaine 10ml plus 0.5% bupivacaine isobaric 20ml.
2. Paracetamol 1gram IV was given 6 hours after the pre-operative dose then every 6 hours thereafter for 4 doses than shifted to oral paracetamol 500mg/tablet 2 tablets every 6 hours for 3 days.
3. Ketorolac 30mg/IV was given at the start of skin closure then every 6 hours thereafter for 4 doses then shifted to celecoxib 200mg/cap, 1 capsule twice a day for 3 days.

Pain Score Assessment/ Rescue Medications

1. Visual Analogue Scale (VAS) was used to assessed post-operative pain (scale 1–10).
2. Assessments were done upon arrival at the Post-Anesthesia Care Unit (PACU) every 30 minutes for the first 2 hours, every 2 hours for the next 24 hours and every 4 hours for the subsequent 48 hours.
3. If VAS score is >4, tramadol 50mg IV was administered every 15 minutes until VAS is <4.
4. Number of rescue doses and time to first rescue dose were recorded.
5. Side effects including the following were recorded:
    a. Fever
    b. Hypertension
    c. Tachycardia
    d. Tachypnea
    e. Splinting
    f. Nausea
    g. Vomiting
    h. Atelectasis

Ethical considerations

This study was done in accordance with the Declaration of Helsinki and the Belmont Report. An informed consent was obtained from each patient who participated in the study. The study procedure, risks and benefits were adequately

explained and accepted by the participant prior to signing the informed consent. The study employed a double blind design, blinding both the patient and the primary investigator to the treatment details ensuring that neither the patient nor the primary investigator were influence by the knowledge of the treatment group assignment. Participants were randomly assigned to either the treatment or the control group in a 1:1 ratio reducing the risk of selection bias and enhancing the validity of the study. This study does not provide any identifying information about individual participants, thus privacy and confidentiality were maintained. Moreover, this study provided procedures to minimize harm to the participants by including provisions for managing breakthrough pain and side effects ensuring patient safety throughout the research process. And lastly this research is self-funded and no financial gains were received by the author related to any of the medications used in this study.

Data analysis plan

Data were encoded in MS Excel by the researcher. Stata MP version 17 software was used for data processing and analysis. Continuous variables were presented as mean (standard deviation/SD) and median (interquartile range/IQR) depending on the data distribution. Shapiro Wilk's test was used to assess normality of data. Categorical variables were presented as frequencies and percentages.

Baseline and outcome data were compared using Mann Whitney U test for continuous variables, and Fisher's Exact test for categorical variables. All randomized patients were included in the intention-to-treat analysis. Median imputation was performed to replace missing values. Patients who were dropped out from the study were excluded in the per-protocol analysis. P values ≤0.05 were considered statistically significant.

RESULTS

A total of 58 patients, 29 for each group were included in the study, 17 dropouts were recorded, 5 in the treatment group, and 12 in the control group. All were randomized and received the allocated treatment. Reasons for dropout included:

- Treatment group: active infection (n=1), converted to open procedure (n=2), no clearance (n=1), unavailability of blood products (n=1).
- Control group: abscess in paravertebral site (n=2), converted to bilateral VATS (n=2), converted to open procedure (n=1), active infection (n=1), anemia (n=1), converted multiple ports (n=1), deranged bleeding parameters (n=1), hypokalemia (n=1), positive TB lamp (n=1), pre-induction SVT (n=1).

Table 1 compares the baseline characteristics of patients. No significant difference between treatment and control group in any of the baseline characteristic.

Table 1. *Baseline demographic and clinical characteristics of patients (n=58)*

CHARACTERISTICS	TREATMENT (n = 29) n (%)	CONTROL (n = 29) n (%)	P VALUE
Age (in years), mean	39.66 ± 14.88	40.48 ± 16.59	0.8422[a]
Sex			
Male	18 (62)	17 (59)	0.788[b]
Female	11 (38)	12 (41)	
Comorbidities, %yes			
Hypertension	14 (48)	8 (28)	0.104[b]
Diabetes mellitus	4 (14)	5 (17)	1.000[c]
PTB	13 (45)	18 (62)	0.188[b]
COPD	1 (3)	2 (7)	1.000[c]
Others	0	3 (10)	0.237[c]
VATS indication, %yes			
Lung decortication	6 (21)	13 (45)	0.092[b]
Lung resection	6 (21)	6 (21)	1.000[b]
Pleural biopsy	10 (34)	8 (28)	0.570[b]
Deloculation	14 (48)	18 (62)	0.291[b]
Anastomosis and closure of fistula	0	0	-
Hernia closure	0	0	-
Pleurodesis	0	0	-
Thymectomy	3 (10)	3 (10)	1.000[c]
Others	1 (3)	2 (7)	1.000[c]

[a] Independent t test; [b] Chi square test; [c] Fisher's Exact test

Intention-to-treat analysis

Table 2 compares the post-operative pain score. Median pain score at 1.5 hours post-op was significantly higher in the control than the treatment group. When categorized, post-operative pain score was significantly different at 2 hours post-op. A higher proportion of patients in the treatment group had no pain than the control group. No significant difference between the two groups in any other time point.

Table 2. *Comparison of post-operative pain score: treatment vs. control (n=58)*

NRS	TREATMENT (n = 29)	CONTROL (n = 29)	P VALUE
PACU arrival, median	0 [IQR: 0-0]	0 [IQR: 0-0]	0.4636[a]
No pain	24 (83)	22 (76)	0.709[b]
Mild	4 (14)	4 (14)	
Moderate	1 (3)	3 (10)	
30 minutes, median	0 [IQR: 0-0]	0 [IQR: 0-2]	0.1577[a]
No pain	23 (79)	19 (66)	0.230[b]
Mild	4 (14)	3 (10)	
Moderate	2 (7)	7 (24)	

NRS	TREATMENT (n = 29)	CONTROL (n = 29)	P VALUE
1 hour, median	0 [IQR: 0–1]	0 [IQR: 0–2]	0.2647[a]
No pain	21 (72)	18 (62)	0.152[b]
Mild	6 (21)	5 (17)	
Moderate	1 (3)	6 (21)	
Severe	1 (3)	0	
1.5 hours, median	0 [IQR: 0–1]	1 [IQR: 1–2]	0.0214*[a]
No pain	14 (48)	6 (21)	0.082[b]
Mild	14 (48)	19 (65)	
Moderate	1 (3)	4 (14)	
2 hours, median	1 [IQR: 0–2]	1 [IQR: 1–3]	0.0629[a]
No pain	11 (38)	2 (7)	0.020*[b]
Mild	15 (52)	22 (76)	
Moderate	3 (10)	5 (17)	
4 hours, median	1 [IQR: 0–1]	1 [IQR: 1–2]	0.3198[a]
No pain	9 (31)	4 (14)	0.285[b]
Mild	18 (62)	22 (76)	
Moderate	2 (7)	3 (10)	
6 hours, median	1 [IQR: 0–1]	1 [IQR: 1–1]	0.9504[a]
No pain	8 (28)	5 (17)	0.640[b]
Mild	20 (69)	22 (76)	
Moderate	1 (3)	2 (7)	
8 hours, median	1 [IQR: 1–2]	1 [IQR: 1–1]	0.5639[a]
No pain	7 (24)	6 (21)	0.760[b]
Mild	21 (72)	23 (79)	
Moderate	1 (3)	0	
10 hours, median	1 [IQR: 1–2]	1 [IQR: 1–1]	0.3404[a]
No pain	5 (17)	4 (14)	0.429[b]
Mild	22 (76)	25 (86)	
Moderate	2 (7)	0	
12 hours, median	1 [IQR: 1–1]	1 [IQR: 1–1]	0.5113[a]
No pain	4 (14)	3 (10)	0.323[b]
Mild	22 (76)	26 (90)	
Moderate	2 (7)	0	
Severe	1 (3)	0	
14 hours, median	1 [IQR: 1–1]	1 [IQR: 1–1]	0.9427[a]
No pain	4 (14)	4 (14)	1.000[b]
Mild	23 (79)	24 (83)	
Moderate	2 (7)	1 (3)	

NRS	TREATMENT (n = 29)	CONTROL (n = 29)	P VALUE
16 hours, median	1 [IQR: 1–1]	1 [IQR: 1–1]	0.5369[a]
No pain	3 (10)	3 (10)	1.000[b]
Mild	25 (86)	26 (90)	
Moderate	1 (4)	0	
18 hours, median	1 [IQR: 1–1]	1 [IQR: 1–1]	0.7948[a]
No pain	2 (7)	3 (10)	1.000[b]
Mild	26 (90)	25 (86)	
Moderate	1 (3)	1 (4)	
20 hours, median	1 [IQR: 1–1]	1 [IQR: 1–1]	0.4128[a]
No pain	3 (10)	2 (7)	0.785[b]
Mild	24 (83)	23 (79)	
Moderate	2 (7)	4 (14)	
22 hours, median	1 [IQR: 1–1]	1 [IQR: 1–1]	0.7452[a]
No pain	4 (14)	3 (10)	1.000[b]
Mild	24 (83)	24 (83)	
Moderate	1 (3)	1 (3)	
Severe	0	1 (3)	
24 hours, median	1 [IQR: 1–1]	1 [IQR: 1–1]	0.5216[a]
No pain	3 (10)	3 (10)	1.000[b]
Mild	24 (83)	25 (86)	
Moderate	2 (7)	1 (4)	
28 hours, median	1 [IQR: 1–1]	1 [IQR: 1–1]	0.4603[a]
No pain	4 (14)	3 (10)	1.000[b]
Mild	23 (79)	23 (79)	
Moderate	2 (7)	2 (7)	
Severe	0	1 (4)	
32 hours, median	1 [IQR: 1–1]	1 [IQR: 1–1]	0.1870[a]
No pain	5 (17)	3 (10)	0.850[b]
Mild	23 (79)	25 (86)	
Moderate	1 (4)	1 (4)	
36 hours, median	1 [IQR: 1–1]	1 [IQR: 1–1]	0.4771[a]
No pain	4 (14)	4 (14)	1.000[b]
Mild	24 (83)	23 (79)	
Moderate	1 (3)	1 (3)	
Severe	0	1 (3)	
40 hours, median	1 [IQR: 1–1]	1 [IQR: 1–1]	0.4378[a]
No pain	4 (14)	4 (14)	0.850[b]
Mild	25 (86)	23 (79)	
Moderate	0	1 (3)	
Severe	0	1 (3)	

NRS	TREATMENT (n = 29)	CONTROL (n = 29)	P VALUE
44 hours, median	1 [IQR: 1–1]	1 [IQR: 1–1]	0.6611[a]
No pain	5 (17)	6 (21)	1.000[b]
Mild	23 (79)	23 (79)	
Moderate	1 (3)	0	
48 hours, median	1 [IQR: 1–1]	1 [IQR: 1–1]	0.2800[a]
No pain	4 (14)	5 (17)	0.564[b]
Mild	23 (79)	24 (83)	
Moderate	2 (7)	0	

[a] Mann Whitney U test; [b] Fisher's Exact test

Table 3. *Comparison of other efficacy measures: treatment vs. control (n=58)*

	TREATMENT (n = 29)	CONTROL (n = 29)	P VALUE
Number of rescue doses, median	1 [IQR: 0–2]	4 [IQR: 3–4]	<0.00001*[a]
Time to first rescue dose (in minutes), median	75 [IQR: 0–480]	60 [IQR: 60–60]	0.5081[a]
LOS (in days), median	10.5 [IQR: 10–14]	12 [IQR: 12–12]	0.3227[a]

[a] Mann Whitney U test

Median number of rescue dose was significantly lower in the treatment than control group. No significant difference in median time to first rescue dose and LOS between the two groups.

Per-protocol analysis

In the per-protocol analysis, 17 patients were excluded. Table 4 compares the post-operative pain score between treatment and control groups. Median pain score at 30 minutes, 1 hour, 1.5 hours, 2 hours post-op was significantly higher in the control than the treatment group. When categorized, post-operative pain score was significantly different at:

- 30 minutes post-op. A higher proportion of patients in the treatment group had no pain than control group. Moreover, a lower proportion of patients in the treatment group had moderate pain than the control group.
- 1 hour post-op. A higher proportion of patients in the treatment group had no pain than control group. Moreover, a lower proportion of patients in the treatment group had moderate pain than the control group.

No significant difference between the two groups in any other time point.

Table 4. *Comparison of post-operative pain score: treatment vs. control (n=41)*

NRS	TREATMENT (n = 24)	CONTROL (n = 17)	P VALUE
PACU arrival, median	0 [IQR: 0–0]	0 [IQR: 0–2]	0.1459[a]
No pain	19 (79)	10 (59)	0.275[b]
Mild	4 (17)	4 (24)	
Moderate	1 (4)	3 (18)	
30 minutes, median	0 [IQR: 0–0.5]	0 [IQR: 0–4]	0.0138*[a]
No pain	18 (75)	7 (41)	0.034*[b]
Mild	4 (17)	3 (18)	
Moderate	2 (8)	7 (41)	
1 hour, median	0 [IQR: 0–1]	2 [IQR: 0–4]	0.0202*[a]
No pain	16 (67)	6 (35)	0.031*[b]
Mild	6 (25)	5 (29)	
Moderate	1 (4)	6 (35)	
Severe	1 (4)	0	
1.5 hours, median	0 [IQR: 0–1]	0 [IQR: 0–3]	0.0431*[a]
No pain	14 (58)	6 (35)	0.161[b]
Mild	9 (38)	7 (41)	
Moderate	1 (4)	4 (24)	
2 hours, median	1 [IQR: 0–2]	2 [IQR: 0–4]	0.0274*[a]
No pain	11 (46)	2 (12)	0.059*[b]
Mild	10 (42)	10 (59)	
Moderate	3 (12)	5 (29)	
4 hours, median	1 [IQR: 0–2]	1 [IQR: 0–2]	0.3106[a]
No pain	9 (38)	4 (23)	0.444[b]
Mild	13 (54)	10 (59)	
Moderate	2 (8)	3 (18)	
6 hours, median	1 [IQR: 0–2]	1 [IQR: 0–1]	1.0000[a]
No pain	8 (33)	5 (29)	0.775[b]
Mild	15 (63)	10 (59)	
Moderate	1 (4)	2 (12)	
8 hours, median	1 [IQR: 0–2]	1 [IQR: 0–1]	0.4692[a]
No pain	7 (29)	6 (35)	1.000[b]
Mild	16 (67)	11 (65)	
Moderate	1 (4)	0	
10 hours, median	1 [IQR: 1–2]	1 [IQR: 1–1]	0.3909[a]
No pain	5 (21)	4 (24)	0.723[b]
Mild	17 (71)	13 (76)	
Moderate	2 (8)	0	

NRS	TREATMENT (n = 24)	CONTROL (n = 17)	P VALUE
12 hours, median	1 [IQR: 1–2]	1 [IQR: 1–1]	0.6201[a]
No pain	4 (17)	3 (18)	0.701[b]
Mild	17 (71)	14 (82)	
Moderate	2 (8)	0	
Severe	1 (4)	0	
14 hours, median	1 [IQR: 1–1]	1 [IQR: 1–1]	0.9272[a]
No pain	4 (17)	4 (23)	0.867[b]
Mild	18 (75)	12 (71)	
Moderate	2 (8)	1 (6)	
16 hours, median	1 [IQR: 1–1]	1 [IQR: 1–1]	0.6275[a]
No pain	3 (13)	3 (18)	1.000[b]
Mild	20 (83)	14 (82)	
Moderate	1 (4)	0	
18 hours, median	1 [IQR: 1–1]	1 [IQR: 1–1]	0.9554[a]
No pain	2 (8)	3 (18)	0.816[b]
Mild	21 (88)	13 (76)	
Moderate	1 (4)	1 (6)	
20 hours, median	1 [IQR: 1–1]	1 [IQR: 1–2]	0.3066[a]
No pain	3 (13)	2 (12)	0.401[b]
Mild	19 (79)	11 (65)	
Moderate	2 (8)	4 (23)	
22 hours, median	1 [IQR: 1–1]	1 [IQR: 1–1]	0.7920[a]
No pain	4 (17)	3 (18)	0.831[b]
Mild	19 (79)	12 (70)	
Moderate	1 (4)	1 (6)	
Severe	0	1 (6)	
24 hours, median	1 [IQR: 1–1.5]	1 [IQR: 1–1]	0.6360[a]
No pain	3 (13)	3 (18)	0.860[b]
Mild	19 (79)	13 (76)	
Moderate	2 (8)	1 (6)	
28 hours, median	1 [IQR: 1–1]	1 [IQR: 1–2]	0.3591[a]
No pain	4 (17)	3 (18)	0.809[b]
Mild	18 (75)	11 (65)	
Moderate	2 (8)	2 (12)	
Severe	0	1 (6)	
32 hours, median	1 [IQR: 1–1]	1 [IQR: 1–2]	0.1782[a]
No pain	5 (21)	3 (18)	1.000[b]
Mild	18 (75)	13 (76)	
Moderate	1 (4)	1 (6)	
36 hours, median	1 [IQR: 1–1]	1 [IQR: 1–2]	0.5081[a]
No pain	4 (17)	4 (23)	0.605[b]
Mild	19 (79)	11 (65)	
Moderate	1 (4)	1 (6)	
Severe	0	1 (6)	
40 hours, median	1 [IQR: 1–1]	1 [IQR: 1–1]	0.5653[a]
No pain	4 (17)	4 (23)	0.266[b]
Mild	20 (83)	11 (65)	
Moderate	0	1 (6)	
Severe	0	1 (6)	
44 hours, median	1 [IQR: 1–1]	1 [IQR: 0–1]	0.3956[a]
No pain	5 (21)	6 (35)	0.581[b]
Mild	18 (75)	11 (65)	
Moderate	1 (4)	0	
48 hours, median	1 [IQR: 1–1]	1 [IQR: 0–1]	0.2233[a]
No pain	4 (17)	5 (29)	0.453[b]
Mild	18 (75)	12 (71)	
Moderate	2 (8)	0	

[a] Mann Whitney U test; [b] Fisher's Exact test

Table 5. *Comparison of other efficacy measures: treatment vs. control (n=41)*

	TREATMENT (n = 24)	CONTROL (n = 17)	P VALUE
Number of rescue doses, median	1 [IQR: 0–2.5]	4 [IQR: 2–4]	0.0033[a]
Time to first rescue dose (in minutes), median	75 [IQR: 0–720]	30 [IQR: 30–120]	0.9838[a]
LOS (in days), median	10.5 [IQR: 9–14.5]	12 [IQR: 9–16.5]	0.7263[a]

[a] Mann Whitney U test

Table 6. *Comparison of other side effects: treatment vs. control (n=41)*

SIDE EFFECTS % YES	TREATMENT (n = 24)	CONTROL (n = 17)	P VALUE
Atelectasis	0	0	
Fever	1 (4)	2 (12)	0.560[a]
Tachycardia	1 (4)	5 (29)	0.066[a]
Tachycardia	0	3 (18)	0.033*
Splinting	1 (4)	6 (35)	0.014*[a]
Nausea	2 (8)	6 (35)	0.049*[a]

[a] Fisher's Exact test

In Table 5, median number of rescue dose was significantly lower in the treatment than control group. No significant difference in median time to first rescue dose and LOS between the two groups. In Table 6, a lower proportion of the treatment group had tachypnea, splinting and nausea than the control group.

DISCUSSION

Acute post-operative pain is a significant problem in patients undergoing thoracic surgeries. It is likely that severe post-operative pain experienced by this patients contributes to post-operative pulmonary complications. Moreover, specific associated pain syndromes may develop during the acute and long term post-operative course because of the surgical or the analgesic techniqes.[10]

VATS has emerged as a preferred approach due to its minimally invasive nature, its potential to reduce surgical stress, reduced pain and reduced morbidity, however a considerable number of patients still experience moderate to severe pain following the procedure.[9]

In the recent years, there has been diverse range of analgesic options utilized in the practice of thoracic anesthesia. While opioids have traditionally been a mainstay to many post-thoracic surgery analgesic protocols, current studies have shifted toward regimens that minimize opioid usage due to their associated side effects such as respiratory depression, nausea and vomiting.[6] One such strategy is pre-emptive analgesia, which aims to prevent the development of central sensitization triggered by surgical incisions and inflammation.[11] This regimen commences prior to incision and extends through both the surgical procedure and the immediate post-operative period.

With the aim of reducing opioid usage, Dastan et al. conducted comparative research into the analgesic efficacy of intravenous Ketorolac, Paracetamol and Morphine among patients undergoing Video-assisted Thoracoscopic Surgery.[6] Their findings revealed that both Paracetamol and Ketorolac were equally effective in managing pain following VATS, with pain scores significantly lower compared to the Morphine group. However, Ketorolac was associated with increased bleeding and heart rate during the 24-hour post-operative period, suggesting that Paracetamol might be a preferrable choice for patients at risk to bleeding and cardiovascular reactions when selecting an analgesic.

Similarly, Jahangiri et al. conducted a comparison between paracetamol and ketorolac administered post-VATS, followed by continuous infusion into the post-operative period.[9] Patients did not receive additional baseline analgesia but were provided with intravenous morphine as a rescue option. The study found no significant distinction between the ketorolac and paracetamol groups regarding pain scores, morphine consumption or patient satisfaction. Although the volume CTT blood drainage was notably higher in the ketorolac group (309 ml vs 273 ml; p=0.001), this difference was not clinically significant. Furthermore, there were no discernible variations in other observed side effects.

Min Kong et al.[10] performed a study aimed to evaluate the clinical application value of pre-emptive analgesia in relieving post-operative pain following video assisted thoracoscopic surgery. Patients undergoing VATS were divided into a trial group or the pre-emptive analgesia (PA) group and a control group or the traditional analgesia group (TA). The PA group were given either celecoxib, paravertebral block, or local infiltration prior to surgical incision. The study compared pain scores, incidence rate of analgesic drug related adverse effects between the two groups. Although the PA group had a slightly lower scores for post-operative resting pain, the difference was not statistically significant as compared to the TA group. However, pain with motion was significantly lower in the PA group as compared to the TA group, with a statistically significant difference at 72 hours post-surgery. Nausea, vomiting and dizziness were common side effects in both groups with no significant difference.

In a study done by Mustafa et al. assessed the efficacy of pre-emptive intravenous Paracetamol in managing post-operative pain following cholecystectomy.[7] Pre-emptive analgesia group exhibited significantly lower pain scores and longer intervals before requiring analgesics compared to the placebo group.

This study investigates the effectiveness of intravenous paracetamol as a pre-emptive analgesic for uniportal video assisted thoracoscopic surgery (VATS). The findings indicate that pre-emptive IV paracetamol results to a significant reduction in post-operative pain thus a notable sparing effect on opioid usage compared to the control group. Baseline post-operative pain scores showed significant results with both groups initially presenting a median pain score of 0 upon arrival at the PACU, but the control group showed a higher incidence of moderate pain (18% vs 4% in the treatment group. Furthermore, at 30 minutes, 1 hour and 1.5 hours post-operatively, the control group consistently reported significantly higher pain scores than the treatment group, indicating a potential analgesic advantage of pre-emptive paracetamol in the immediate post-operative period.

The trends in pain relief were maintained throughout the study duration. At 2 hours post-operatively, 46% of patients in the treatment group reported no pain, contrasting with only 12 % in the control group. The need for rescue doses was significantly higher in the control group, reinforcing the analgesic superiority of pre-emptive paracetamol. The observed side effects, particularly nausea and splinting, were more prevalent in the control group, suggesting a potential role for pre-emptive paracetamol in minimizing adverse events associated with post-operative pain management.

Our findings align with those of the Mustafa's study, albeit with a different surgical procedure. Additionally, when compared to Min Kong's study, despite using different medication exposures, both study support the notion that pre-emptive analgesia serves a promising option in managing post-operative pain in patients undergoing Video Assisted Thoracoscopic surgery.

While this study highlighted the efficacy of pre-emptive paracetamol in uniportal VATS by showcasing superior pain control and reduction in rescue medications, it did not show significant evidence that the intervention affects other crucial post-operative outcomes including length of hospital stay and cost implications.

CONCLUSION

This study provides valuable insights into the efficacy and safety of pre-emptive paracetamol in Uni-portal VATS. The consistent and early pain relief observed in the treatment group, coupled with a favorable side effects profile, suggest that pre-emptive paracetamol merits consideration as a component of multimodal analgesia strategies in uniportal VATS. Future research with larger sample size and extended follow up periods may further elucidate the long-term implications and holistic benefits of incorporating pre-emptive paracetamol in the peri-operative pain management protocols for VATS.

LIMITATIONS

While this study underscores the effectiveness and safety of pre-emptive Paracetamol in Uni-portal VATS, it has several limitations. Firstly, being a single-center study with specific patient population, it restricts the ability to generalize the results to a broader demographic and to patients undergoing diverse surgical procedures. Additionally, the study was limited to pain scores and outcomes within 48 hours post-operatively, potentially overlooking the long term sustainability of the intervention's effect. Moreover, the focus was on pain scores, opioid usage, side effects and hospital stay duration. Including additional outcome measures relating to patient satisfaction, quality of life and functional recovery could offer a more comprehensive understanding of the intervention's impact.

RECOMMENDATIONS

The outcomes of this study underscore the efficacy and safety of pre-emptive paracetamol in managing acute post-operative pain among patients undergoing Uni-portal Video-Assisted Thoracoscopic Surgery. Consequently, the authors advocate for the development of a comprehensive protocol by The Division of Anesthesia. This protocol should define clear guidelines regarding dosage, timing and monitoring procedures to ensure consistent and optimal pain management for all patients. While the study's result indicate the potential superiority of this approach over conventional post-operative pain management strategies, further research is necessary. Subsequent studies could explore larger sample sizes, extended follow-up durations and variations in dosing regimens validate and refine these findings. Moreover, it is recommended that these findings be shared with other medical institutions performing Uni-portal Video-Assisted Thoracoscopic Surgery, encouraging them to contemplate the integration of Pre-emptive intravenous paracetamol into their pain management protocols.

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APPENDICES

Appendix A. Baseline data collection form.

Study number	
Age	_____Years Old
Sex	☐ Male ☐ Female
Comorbidities Check all that applies	☐ Hypertension ☐ DM ☐ Pulmonary tuberculosis ☐ others: _____
Indication for VATS	☐

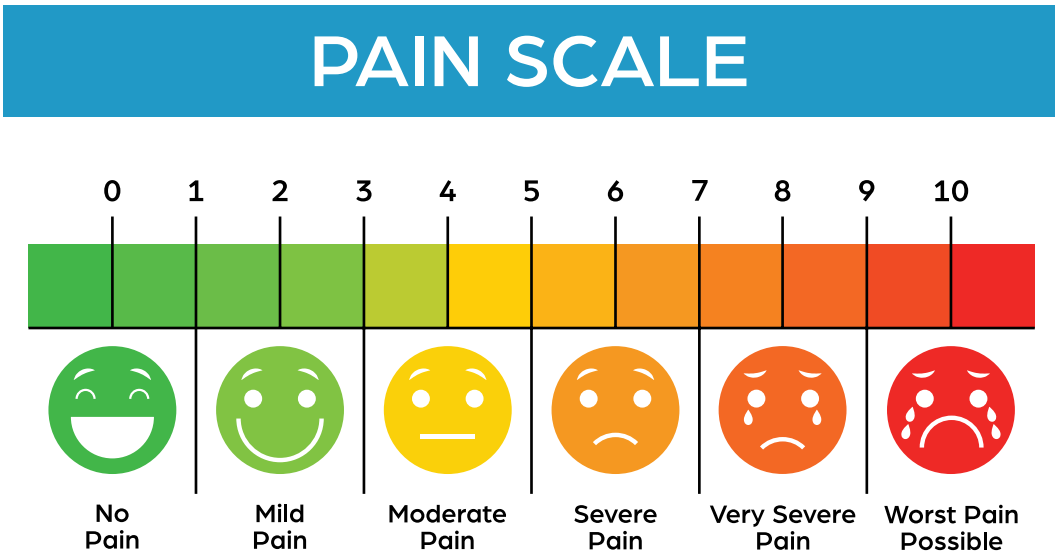
Appendix B. Data collection tool.

Data Number: _____

	ARRIVAL	30 mins	1 min	1.5 hours	2 hours	4 hours	6 hours	8 hours	10 hours	12 hours	14 hours	16 hours	18 hours
Vital Signs													
BP													
HR													
RR													
O2 Sat													
NRS													
0													
1													
2													
3													
4													
5													
6													
7													
8													
9													
10													
Rescue Analgesic (for NRS ≥ 4/10, if given)													
Side effects and other outcomes													
Tramadol50 mg iv													
Length of Hospital Stay							DAYS:						

	20 hours	22 hours	24 hours	28 hours	32 hours	36 hours	40 hours	44 hours	48 hours
Vital Signs									
BP									
HR									
RR									
O2 Sat									
NRS									
0									
1									
2									
3									
4									
5									
6									
7									
8									
9									
10									
Rescue Analgesic (for NRS ≥ 4/10, if given)									
Side effects and other outcomes									
Tramadol50 mg iv									

Appendix C. Pain Scale



Appendix D. Theoretical Definition of Terms

Video-assisted Thoracoscopic Surgery
Video-assisted thoracoscopic surgery (VATS) is a minimally invasive thoracic surgical (MITS) technique in which video camera is inserted thru 4 to 8 cm incisions into the chest to avoid more invasive open thoracotomy.1

Pre-emptive Analgesia
Pre-emptive analgesia is administration of Analgesic in addition to general anesthesia to prevent intra- operative nociception and the formation of painful scars caused by changes in the central nervous system during surgery.

Independent variable
Intervention/Treatment
a) 2 hours prior to procedure, 15-minute administration of either paracetamol 1 gram drip or PNSS 100 ml IV.
b) Experimental Group: Pre-emptive paracetamol.

Dependent variable
1) Efficacy
   a) Ability to control/reduce post-operative pain measured in terms of post-operative pain, number of rescue doses and time to first rescue dose.
2) Post-operative pain
   a) Measured using the Numeric Rating Scale (NRS) at PACU admission, every 30 mins for 2 hours, then every 2 hours for 24 hours then every 4 hours for 48 hours post-op. Mild: 1-3, Moderate: 4-6, Severe 7-10.
3) Number of rescue doses
   a) Total number of rescue dose administered to the patient up to 48 hours post-op.
4) Time to first rescue dose
   a) Number of minutes from the time of arrival at pacu to first rescue dose administration.
5) Side Effects
   a) Adverse events manifested by the patient within 48 hours.
      a1) Atelectasis
      a2) Fever
      a3) Tachycardia
      a4) Tachypnea
      a5) Nausea or vomiting
      a6) splinting

Potential Confounding Variables
1. Age
   a) Patient age (in years) at the time of surgery based on self-report.
2. Sex
   a) Male
   b) Female
3. Comorbidities
   a) Patient self-reported comorbidities
      a1) Hypertension
      a2) Diabetes mellitus
      a3) pulmonary tuberculosis

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ORIGINAL ARTICLE

CENTRAL VENOUS CATHETER–RELATED OUTCOMES OF THE COVID–19 RAPID RESPONSE TEAM (CRRT) VASCULAR ACCESS PROTOCOL OF THE LUNG CENTER OF THE PHILIPPINES

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ABSTRACT

Background. At the onset of the COVID–19 pandemic in March 2020, LCP was designated as a primary referral center for moderate to critical COVID–19 cases. The Covid Rapid Response Team (CRRT) protocol was developed by the different departments of the institution for efficient management of cases.

Objective. This study aimed to describe CVC–related outcomes under the CRRT vascular access protocol in terms of both early and delayed complications that resulted from performing the procedure in a sub–optimal environment. The baseline data analysis from this study may be used to further generate evidence for quality improvement and protocol development in relation to vascular access placement and maintenance in infectious patients in a pandemic setting.

Methodology. Charts of patients referred to the CRRT vascular access team from March 2020 to February 2021 were reviewed by the primary investigator. Catheter utilization for hemodialysis and/or hemoperfusion were presented as frequency, percentage, and 95% confidence intervals. The interval between HD catheter insertion and HD/HP initiation was presented as median days and interquartile range. The cumulative incidence of each of the early–onset complications, and the incidence rate of delayed–onset complications and mortality were presented as number of events per 100 persons and number of events per 1000 person–days, respectively; the frequency are both the point and interval estimates were presented. Measures of central tendency was used to determine the average days from first CVC insertion to development of each complication, as well as the average OR duration in minutes.

Results. The findings of this study showed moderate catheter utilization rates (66%) for hemodialysis and hemoperfusion with 1–2 days interval between insertion and treatment initiation. The only early complication of CVC insertion in this study is pneumothorax, which was observed in 0.4% of patients. Delayed complications such as catheter–related blood stream infection and catheter malfunction were observed 5.51% of patients, while CVC dislodgement occurred in 2.9% of patients and catheter site bleeding was observed in 0.78% of patients.

Conclusion. In terms of early complications, the results showed that despite the less–than–optimal settings in which the CVC insertions was performed, the CRRT vascular access protocol had been efficient and safe in terms of logistics and surgical technique. Though delayed complication rates may partially be due to the inherent pathophysiology of COVID–19 infection, measures to mitigate these events and improve outcomes for this subset of patients are still worth investigating and implementing. Identification of areas necessitating quality improvement to promote patient care and safety and optimize resource allocation are among the clinical benefits of this study. Overall, the LCP experience on the CRRT vascular access protocol provided valuable guidance for future crisis situations to facilitate safe and efficient performance of vascular access procedures on patients requiring urgent HD, HP, or critical hemodynamic monitoring.

Keywords. *COVID–19, central venous catheterization, CVC complications, vascular access, hemodialysis catheter, hemoperfusion catheter*

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INTRODUCTION

Since the beginning of the pandemic in March 2020, the Lung Center of the Philippines (LCP) has seen a sharp increase in the number of COVID-19 admissions, having been designated as a referral center for moderate to severe COVID-19 cases. These patients often require central venous access for several purposes such as hemodynamic monitoring in the intensive care unit, hemodialysis (HD), and hemoperfusion (HP). It is estimated that around 36-46% of hospitalized COVID-19 patients develop acute kidney injury (AKI), and 15-19% would require HD[1,2]. Severe COVID-19 infection has also been documented to induce cytokine storms, the deleterious effects of which may be mitigated by HP.[3]

In response to this healthcare need, the Department of Thoracic Surgery and Anesthesia at LCP developed and implemented the COVID Rapid Response Team (CRRT) Vascular Access Protocol. It is a set of guidelines on the insertion of a French 12 (F12) triple-lumen hemodialysis catheter on both probable and confirmed COVID-19 patients admitted at the LCP requiring intensive care. This protocol also allows for central catheters to be inserted in the emergency room or bedside, instead of the usual sterile environment of the operating room (OR). Details of this protocol may be viewed in Appendix A. Insertion of the catheter at the time of intubation allows the team to maximize the anesthetics and paralytic agent given at this instance. Another projected benefit of this was to avoid repeated peripheral intravenous line insertions aimed at decreasing staff exposure to infected patients. These strategies are expected to result in optimization of patient management, efficacy in healthcare staffing, allocation of resources, and infection control. The guideline includes the timing of catheter placement, the type of catheter to be used, and the logistics to minimize patient transport and handling.

In contrast to LCP practice, routine pre-emptive central line insertion is not performed in other institutions. There is a gap in evidence regarding the indications of early central venous line insertion in patients not yet confirmed to have COVID-19 infection. For instance, data remains to be gathered pertaining to the proportion of patients who will be confirmed positive for COVID-19 infection after the initial referral for central venous catheterization and eventually require hemoperfusion or hemodialysis, and the interval between central venous catheterization and initiation of these treatment modalities.

Performing central venous catheterization in the emergency room or at bedside forgoes optimal patient positioning and sterility provided by the controlled environment of an OR. Inefficient patient positioning may be contributory to immediate catheter-related complications due to technical difficulties during insertion. Another concern is that catheters which are inserted too early may thrombose even before HD or HP is carried out, as COVID-19 is known to induce a hypercoagulable state. Temporary, non-tunneled catheters such as the type specified in the CRRT Protocol only have an intended lifespan of two weeks, hence the higher risk of catheter-related infections and malfunction due to prolonged catheter dwell time.[4,5] Interventions to address both early and delayed CVC-related complications incur additional costs and health risks to the patient.

The envisioned purpose of early central venous access is to balance the benefits of rapid patient resuscitation and reduced staff exposure versus the risk of catheter-related complications that may result from performing the procedure in less-than-optimal settings. However, an evidence base is needed to support this recommendation.

Objective

The study aimed to describe the catheter-related outcomes of COVID-19 patients, both suspected and confirmed, referred to the COVID-19 rapid response team for HD catheter insertion.

Significance

As one of the four designated referral centers for moderate to severe COVID-19 cases in the National Capital Region, this study aimed to document the preliminary experience of LCP on a new institutional protocol in a special patient population requiring vascular access and provide relevant data describing catheter-related outcomes such as pneumothorax, hemothorax, vascular injury, catheter malposition, catheter-related infections and catheter occlusion resulting from the implementation of the CRRT vascular access protocol. As treatment algorithms continue to evolve, an outline to aid in strategies for best practice in severe COVID-19 infection may be adopted to maximize limited healthcare resources and reduce patient morbidity. The data analysis of the study may serve as a supporting scientific tool to enhance quality improvement of institutional vascular access placement and maintenance protocols.

METHODOLOGY

Study Design

This is a descriptive study involving medical records review of COVID-19 confirmed or suspected patients who underwent hemodialysis catheter placement after referral to the COVID-19 Rapid Response Vascular Access Team.

Study Site

The study was conducted at the Lung Center of the Philippines, a premier institution for the diagnosis and management of chest diseases, and one of the four designated COVID-19 referral centers in Metro Manila.

Operator

The operator/surgeons involved in the study have fulfilled the required period of training in general surgery in board-accredited training programs and have basic vascular competency skills for central venous catheter insertion.

Study Population

The study population is comprised of severe and critically ill COVID-19 confirmed or highly suspected patients, who underwent central venous catheter placement under the CRRT protocol from March 1, 2020 to February 28, 2021. Patients were identified by reviewing the Division of Thoracic Surgery's census of vascular surgical procedures during the indicated time frame. Chart review for patients with COVID-19 indicated as part of the pre-operative diagnosis or post-operative diagnosis was carried out by the primary investigator. The sample size was determined by the number of patients whose medical records were available for review.

Inclusion/ Exclusion Criteria

Inclusion

COVID-19 confirmed or suspected patients who underwent CVC insertion under the CRRT vascular access team protocol at LCP from March 1, 2020 to February 28, 2021. The CRRT protocol for central venous catheterization is specific for COVID-19 suspected and confirmed patients. This also covers patients that were referred for central venous catheterization upon intubation due to high clinical suspicion of COVID-19 infection even before confirmatory RT-PCR results were available.

Exclusion

Patients who had central venous catheters inserted prior to admission to LCP were excluded. Patients with a recent diagnosis of pleural effusion and/or pneumothorax documented by chest x-ray at least 48 hours prior to central venous catheterization were excluded. Charts with missing pertinent pages such as operative techniques, records of operation, progress notes, and nurses' notes were also excluded.

Conduct of the COVID-19 Rapid Response Team (CRRT) Protocol

Patients who are either COVID-19 suspects or COVID-19 positive in respiratory distress are referred to the CRRT for intubation and/ or CVC insertion. The team is comprised of the thoracic surgeon and anesthesiologist on deck, thoracic surgery, and thoracic anesthesia fellows-in-training on duty, one operating room nurse, and a nursing aide. The indications for urgent central line insertion are: absence of a stab le peripheral line, immediate hemoperfusion or hemodialysis, and critical hemodynamic monitoring. Urgent central line insertion is done immediately following intubation at the ER or bedside. Indications for elective central line insertion are: presence of a stable peripheral line, planned hemoperfusion or hemodialysis, and planned hemodynamic monitoring. Elective central line insertion is done within twenty-four (24) hours of referral in the ER at bedside. All catheters used are temporary F12 triple-lumen, non-tunneled hemodialysis catheters.

Study Procedure

After the approval of the LCP Technical Review Board and Institutional Ethics Review Board, the monthly census of the Division of Thoracic Surgery was reviewed. All patients referred for central venous catheterization following the CRRT protocol from March 1, 2020-February 28, 2021 were included in this study. Charts of these patients were retrieved from both the Central Medical Records and Electronic Medical Records of the hospital and reviewed within the hospital premises by the primary investigator. Central venous catheter-related complications, as defined above, were identified by reviewing both physicians' and nurses' progress notes, as well as hemodialysis treatment records of patients who underwent HD and/or HP, for pertinent indications for referral to the Thoracic Surgery service and subsequent interventions carried out to address the specific concern.

Data analysis

The clinical and demographic profile of the study participants were summarized by descriptive statistics. Continuous numerical variables were assessed for normality of distribution by Shapiro-Wilk test of normality and were found non-normally distributed. These were described as median and interquartile range. Categorical variables were described as frequency and percentage.

The catheter utilization for hemodialysis and/or hemoperfusion were presented as frequency, percentage, and 95% confidence intervals. The interval between HD catheter insertion and HD/HP initiation were presented as median days and interquartile range. The cumulative incidence of each of the early-onset complication, and the incidence rate of delayed- onset complication and mortality were presented as number of events per 100 persons and number of events per 1000 person-days, respectively; the frequency and both the point and interval estimates were presented.

Measures of central tendency were used to determine the average days from first CVC insertion to development of each complication, as well as the average OR duration in minutes.

RESULTS

Five-hundred eight (508) patients who underwent central venous catheter (CVC) insertion after referral to the CRRT vascular team were included in this study. Twenty-one (21) patients who had pre-CVC insertion diagnoses of pneumothorax and/or pleural effusion ipsilateral to the CVC site, as well as three (3) patients who had their first CVC inserted prior to admission to LCP were excluded from this study. One (1) patient who had the CVC converted to ECMO access and four (4) patients without post-operative chest x-rays were also excluded.

In accordance with the CRRT protocol, 318 (62.5%) patients underwent CVC insertion within 24 hours of intubation. Seven (7) intubated patients had their CVCs inserted after 24 hours of intubation mostly due to a delay by the families in giving consent for the procedure. One-hundred eighty-three (183) non-intubated patients were also referred to the vascular access team after the need for hemoperfusion and/or hemodialysis was established, with central venous catheterization being performed within 24 hours.

Of the 508 cases that were reviewed, 498 (98.03%) had their first CVC inserted into the internal jugular veins (IJV) in accordance with the PATACSI and PSVES guidelines for vascular access in COVID-19 patients. Nine patients (1.77%) had CVCs inserted into the femoral vein (FV) instead of the IJV due to the following reasons: small IJV (3), inability to pass a guidewire into the IJV (2), previous pacemaker implantation (1), presence of a mediastinal mass with SVC syndrome (1), multiple neck lymphadenopathy (1), and inability of the patient to tolerate a supine position (1). One CVC (0.20%) was inserted into the subclavian vein (SCV) due to resistance during guidewire introduction into bilateral IJ veins. Three-hundred seventeen (62.4%) of CRRT referrals comprised of COVID suspects/COVID-probable cases, and 191 (37.6%) were confirmed cases.

Out of the 317 suspected/probable COVID referrals, 195 (61%) were eventually confirmed to be COVID positive, 86 (16.93%) were confirmed to be non-COVID cases, and 36 (7.09%) were diagnosed as COVID probable.

Of all central venous catheters that were inserted, 338 (66.5%) were utilized for hemodialysis and/or hemoperfusion, with two (2) median days from CVC insertion to first HD/HP use. One-hundred seventy (170, 33.5%) were used as infusion lines.

Mean operative time for first CVC insertions was 18.5 minutes.

The only documented early complication was pneumothorax, occurring twice (0.4%). Closed tube thoracostomy was done for both cases. No catheter malposition, hemothorax, nor inadvertent arterial puncture/ cannulation were observed.

Among the delayed complications observed in this study, the most frequent were CRBSI (5.51%, 3.71/1000 person-days), and catheter malfunction (5.51%, 3.54/1000 person-days). Catheter dislodgement was observed in 15 patients (2.9%, 1.92/1000 person-days), mainly due to removal by the patient during episodes of agitation and accidental removal during patient transport. Catheter site bleeding requiring intervention such as suturing was observed in 0.78% (0.5/1000 person-days). The least frequently occurring delayed complication was exit-site infection, at 0.4% (0.25/1000 person-days).

Measures employed to address CRBSI were as follows: catheter removal (46%), catheter replacement (36%), and antibiotic therapy (18%). The most frequent intervention for catheter malfunction was catheter flushing (61%), followed by catheter replacement (32%) and catheter removal (3.6%). Of the 15 CVCs that were dislodged, nine (9) were replaced and two (2) were re-anchored.

Presented in the tables below are the summaries of patient demographics, catheter-related outcomes, and average times to complication onset.

Table 1. *Clinico-demographic profile of CRRT vascular access patients.*

	Median (IQR); Frequency (%)
Age, years	61 (20.5%)
Sex	
Male	329 (64.76%)
Female	179 (35.24%)
Comorbidities	
Hypertension	314 (61.81%)
Diabetes mellitus	197 (38.78%)
Stroke	20 (4.26%)
Cardiac disease	114 (22.44%)
Cancer	32 (6.30%)
Kidney disease	69 (13.58%)
Pulmonary tuberculosis	126 (24.85%)
Bronchial asthma	25 (4.92%)
Chronic Obstructive Pulmonary Disease	39 (7.68%)
Others	59 (11.61%)
COVID status pre-CVC	
Confirmed	191 (37.60%)
Suspected	317 (62.40%)
COVID status post-CVC	
Confirmed positive	386 (75.98%)
Confirmed negative	86 (16.93%)
Probable	36 (7.09%)
CVC insertion site	
Subclavian vein	1 (0.20%)
Internal jugular vein	498 (98.03%)
Femoral vein	9 (1.77%)

Table 2. *Outcomes of CRRT vascular access patients.*

	Frequency	Estimate	95% Confidence Interval
CVC utilization, per 100 persons	338	66.54	62.25, 70.63
1st CVC to HD/HP, median days [n=337]		2	1, 2
Early complications, per 100 persons			
Malposition	0	-	-
Pneumothorax [n=501]	2	0.4	0.04, 1.43
Hemothorax [n=501]	0	-	-
Inadvertent arterial puncture/cannulation	0	-	-
Delayed complications, per 100 person-days			
Catheter-related bloodstream infections	28	3.71	2.56, 5.37
Exit site/wound infection	2	0.25	0.06, 1.00
Catheter malfunction	28	3.54	2.42, 5.16
Catheter site bleeding	4	0.5	0.19, 1.33
Catheter dislodgement	15	1.92	1.16, 3.18
Mortality, per 1000 person-days	278	36.13	32.12, 40.63

Table 3. *Time from 1st CVC insertion to development of delayed complications*

Delayed complications	Median days
Catheter-related blood stream infection	14.5 (+/- 10.7)
Exit site infection	12 (+/- 6)
Catheter malfunction	6.5 (+/- 11.7)
Bleeding	2 (+/- 3.03)
Catheter dislodgment	9 (+/- 11.09)

Table 4. *Intubation status on CVC complications*

Catheter-related complications	CVC insertion done w/in 24h intubation	Non-intubated on CVC insertion
Pneumothorax	2	0
Catheter infection	22	6
Catheter malfunction	12	14
Catheter dislodgement	11	4
Catheter site bleedings	4	0

Table 5. *Final COVID-19 status of patients with CVC complications*

Catheter-related complications	COVID-19 positive	Non-COVID-19	COVID-19 probable
Pneumothorax	1	1	0
Catheter infection	23	5	0
Catheter malfunction	25	2	1
Catheter dislodgement	11	5	0
Catheter site bleedings	2	1	1

DISCUSSION

The onset of the COVID-19 pandemic presented unique challenges to hospitals all over the world. Institutional protocols were developed and adopted to streamline patient care amidst the healthcare crisis. Since the CRRT vascular access team protocol is relatively new and was developed part of an initiative to manage the influx of pandemic patients, documentation of outcomes may aid in further development of crisis response measures. Immediate complications such as pneumothorax, malposition, arterial puncture, and other vascular injuries may be attributed to catheter insertion, while delayed complications, such as CRBSI, exit site infections, catheter malfunction, and catheter dislodgement or bleeding, can occur during catheter use. Extensive published data on vascular access

team outcomes during the COVID-19 pandemic is still limited. To the best of our knowledge, this is the first study in the country. This study aimed to provide a summary of central venous catheter outcomes of patients referred to the CRRT vascular access team over a one-year period.

Central venous catheters inserted by the CRRT vascular access team were all short-term non-tunneled dialysis catheters. Actual utilization for HD/HP in this study was 66% (338/508); the median time from CVC insertion to first use for HD/HP was two (2) days, with the 95% confidence interval (CI) ranging from 1-2 days. This suggests that in terms of catheter usage, the CRRT protocol for vascular access is effective in facilitating timely initiation of HD/HP, as the median time from insertion to treatment was relatively short.

In this study, we also noted that 9% of patients expired within the first 48 hours of central venous catheterization. Twenty-two (22) of these patients expired within the first 24 hours, and 24 expired the next day. Eighty-six patients (16.93%) of all CRRT vascular access team referrals were also found to be non-COVID cases, as indicated in their final diagnoses. As severe to critical COVID-19 infection during this period was shown to have high mortality rates, this suggests the need for prognostication and further assessment prior to referral to the CRRT vascular access team to avoid futile procedures and facilitate resource and manpower allocation during a crisis response, as recommended by Ilonzo et al.

Early complications

The rates of immediate complications documented in this study are relatively comparable to previously cited literature. For instance, the rate of pneumothorax in our institution was observed to be 0.4% (CI 0.04, 1.43), while pre-pandemic studies show rates at 0.8-6.6%7,8 Arterial puncture, catheter malposition, and vascular injury manifesting as hemothorax, all had an incidence of zero (0) in this study. Data from studies of Kornbau et al. (2015) and Dixon et al. (2017) showed arterial puncture rates at 4.2-10%. Despite having to perform these procedures in conditions limiting surgeon mobility and preventing optimal patient positioning, the CRRT vascular access team managed to maintain relatively low technical complication rates, with an average time of 18.5 minutes per procedure.

Delayed complications

Catheter-related bloodstream infection rate in this study was found to be 5.51% (3.71/1000 person-days; CI 2.56, 5.37), and exit site infection was at 0.4% (IR 0.25/1000 person-days). The incidence of catheter-related bloodstream infection varies across studies performed before and during the pandemic. For instance, the studies by LeRose et al. (2020) and Antonio et al. (2020) showed the CRBSI rate in COVID-19 patients in their respective institutions are higher (1.4-1.7%) than their non-COVID counterparts (median days to development: 17.2). On the other hand, pre-pandemic studies by Lok et al. (2020) and Bell et al. (2018) documented an incidence rate of 1.0-3.6, approximating the results of this study.

In this study, the mean days to CRBSI development was 14.5. Considering the findings of Weber et al. (2011) which suggests that infections developing within five days post-CVC insertion were likely due to an intraoperative break in sterility, this study's findings suggest that the CRRT vascular access protocol implemented in the Lung Center of the Philippines was effective in maintaining aseptic techniques, even when CVC insertion was performed outside the regular OR setting.

Studies performed during the pandemic suggest higher CRBSI rates than the pre-pandemic period. Possible causes are extended non-tunneled catheter dwell times beyond the recommended two-week period, the inherent immune dysregulation present in COVID-19 patients and breaks in sterility during central line handling.[12,4,5] This data suggests the need for further investigation and interventions, such as the use of chlorhexidine dressings, to reduce CVC-related infections.[14]

Catheter malfunction rate observed in this study is 5.51% (3.54/1000 person-days; CI 2.42, 5.16), with a median time of 6.5 days from insertion to malfunction. Based on previously reviewed publications, the pre-pandemic prevalence of catheter occlusion in the United States is notably higher at around 25%.15 The Lombardy group of hospitals in Italy recorded a catheter malfunction rate of 2.9% for all types of catheters inserted, with a median time of 8.7 days. Shanmugasundaram et al. (2022) reported a median time of 8 days for IJ catheters and 3 days for femoral catheters, and 23.4% percent of CVCs necessitated replacement due to dysfunction. In our institution, 32% of malfunctioning CVCs were reinserted, and 3.6% were removed without replacement. Findings on catheter malfunction in this study are presumably congruent with available data from international studies in the COVID-19 population. This may be attributed to the pathophysiology of COVID-19 that renders patients at higher risk for development of systemic thrombosis due to hypercoagulability.[17] In line with this, the previous recommendation of Vailati et al. to prevent malfunction caused by thrombosis by prophylactic or therapeutic LMWH administration may be considered for these patients.

Catheter malfunction and infection rates were also observed to occur more frequently in COVID confirmed patients compared to non-COVID patients. This may be supported by findings in previously mentioned studies citing the pathophysiology of COVID-19 in predisposing the patient to immunodepression and hypercoagulability. In addition to immune dysregulation, agents used to mitigate the deleterious effects of this disease, such as Tocilizumab and steroids, also contribute to immunosuppression in this specific population.[12]

Other complications documented in this study were CVC dislodgement and CVC site bleeding. The dislodgement rate for CRRT vascular access team procedures was 2.9% (1.92/1000 person-days, CI 1.16, 3.18), occurring around 9 days post-operatively. This is relatively low compared to the findings of Antonio et al. (2020) with a reported rate of 7.7%, and a median time of 7 days to occurrence. Similar to the findings of the previously mentioned study, the CVCs in our study's population were pulled out either by the patient during episodes of agitation or accidentally by members of the staff during the transport process. Placement of deeper subcutaneous anchoring sutures, as recommended by Vailati et al. may be considered in this patient population. Other methods such as placing a more secure dressing over the catheter or placement of additional sutures may also be further investigated in follow-up studies.

Catheter site bleeding, although rarely fatal, is certainly bothersome and may occur due to inadvertent trauma to the surgical site even in the absence of suture disruption or CVC dislodgement. It may be a result of prolonged dwell time and maceration of the insertion site, or as a result of anticoagulation therapy for DVT prophylaxis in severely ill COVID-19 patients. In a 2013 study by Kander et al. the rates of CVC site bleeding ranged from 0.5-1.6%. Loosely comparing these pre-pandemic rates, our reported rate of 0.78% (0.5/1000 person-days; CI 0.19, 1.33) is comparable. Despite the acceptable values, inadvertent catheter dislodgement and bleeding are preventable complications, and measures such as placing additional or deeper subcutaneous anchoring sutures, reinforcing central line dressings, and careful patient handling to minimize these occurrences to further improve outcomes.

LIMITATIONS

Although the findings of this study provided important descriptive information on CVC-related outcomes in the COVID-19 population, this study has several limitations. First, the study design is retrospective, and the findings are based on chart review. Medical records review is dependent on the quality of documentation by the healthcare team. As such, relevant information required to make accurate and complete conclusions may be lacking. Second, this study focused on a specific patient population in a single institution. As such, the findings of this study have limited generalizability to other healthcare settings. The outcomes and experiences observed in LCP may not be representative of other healthcare centers where practices and patient populations may vary. This study also included a relatively small sample size as selected by the availability of medical records for review, hence the probability of selection bias and lack of representation for the entire COVID-19 population. This study also primarily focused on immediate and short-term CVC outcomes; long-term follow up may provide a more comprehensive evaluation of the risks and benefits associated with central venous catheterization in COVID-19 patients. Lastly, pre-pandemic institutional CVC outcomes as well as a control group with which the COVID-19 population might be compared to were also not present in this study, making it difficult to discern any difference in catheter utilization and catheter outcomes between CRRT vascular access team patients and non-CRRT patients.

CONCLUSION

This study provided valuable information on LCP's CVC-related outcomes on the vascular access protocol implemented during the height of the COVID-19 pandemic. The information obtained on both early and delayed CVC-related complications offered clearer understanding of the risks and potential challenges in vascular access placement in a unique patient population during a healthcare crisis.

The findings showed moderate catheter utilization rates for hemodialysis and hemoperfusion with an interval of 1-2 days among patients who underwent CVC insertion following CRRT vascular access team protocol. Considering the short period between catheterization and HD/HP initiation, application of this protocol was shown to be efficient in facilitating timely hemofiltration treatments. However, moderate HD/HP utilization rates suggested the need for improvement in patient selection, warranting further studies.

The only early complication of CVC insertion is pneumothorax, which was observed in 0.4% of patients. This showed that despite the suboptimal settings in which the CVC insertions were performed, the CRRT vascular access protocol had been efficient and safe in terms of logistics and surgical technique.

Delayed complications included catheter-related blood stream infection, catheter malfunction, CVC dislodgement and CVC site bleeding. Catheter-related blood stream infection and catheter malfunction were observed 5.51% of patients, while CVC dislodgement occurred in 2.9% of patients, and catheter site bleeding was observed in 0.78% of patients. Though these rates may partially be due to the inherent pathophysiology of COVID-19 infection, measures to mitigate these events and improve outcomes for this subset of patients are still worth investigating and implementing.

Identification of areas necessitating quality improvement to promote patient care and safety and optimize resource allocation are among the clinical benefits of this study. Overall, the LCP experience on the CRRT vascular access protocol provided valuable evidence guidance for future crisis situations to facilitate safe and efficient performance of vascular access procedures on patients requiring urgent HD, HP, or critical hemodynamic monitoring.

RECOMMENDATIONS

The results of the study have an important impart in guiding the implementation of the CRRT vascular access team protocol. For instance, the findings of a catheter utilization rate for hemodialysis and hemoperfusion of 66%. Comprised, a third of patients who underwent CVC insertion did not benefit from its intended use. In this regard, future studies should be performed to guide appropriate patient selection with consideration of the benefits and risks of CVC insertion among patients with suspected or confirmed COVID infection as well as optimal utilization of limited healthcare resources.

Furthermore, the research contributed information on specific areas where management intervention may be given to improve patient outcomes. For instance, considerable delayed catheter-related complications such as CRBSI and catheter malfunction were observed in this study. Future evidence-based quality improvement strategies may be implemented to reduce the incidence of such complications and enhance patient safety in our setting, such as conducting staff workshops on the proper care and handling of central lines and incorporating CVC care monitoring sheets into the charts. Subsequent research related to this topic should include a larger sample size, prospective research design, multi-center collaborations, and inclusion of a control group to improve the generalizability of the study's findings. Further research is also needed to explore the optimal catheter size during CVC insertion, patient prognostication prior to referral to the CRRT vascular access team, and cost-benefit analysis.

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CONFLICT OF INTEREST

None declared.

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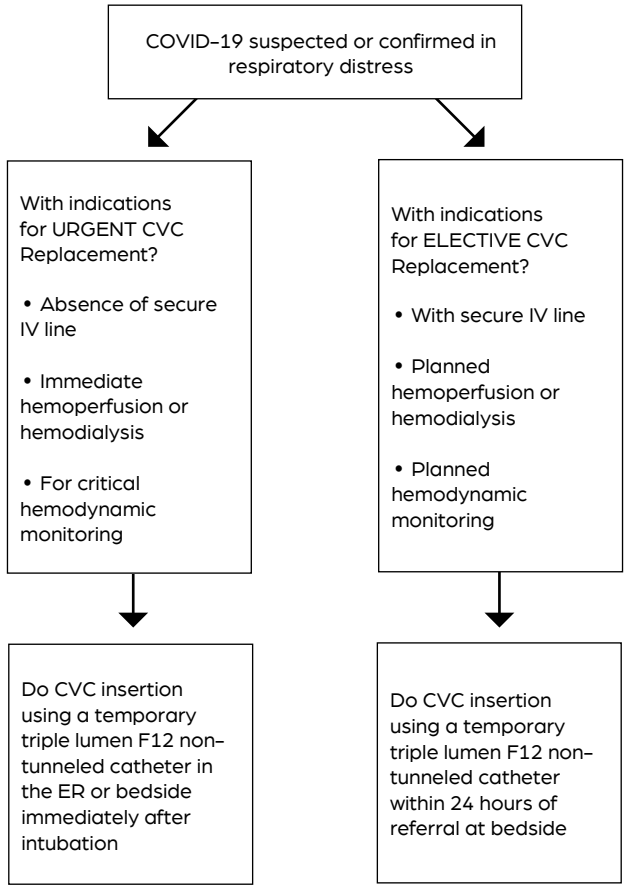
APPENDICES

Appendix A. COVID–19 Rapid Response Team Vascular Access Protocol

CRRT Vascular Access Team
Thoracic surgeon on deck Thoracic anesthesiologist on deck Thoracic surgery fellow on duty Thoracic anesthesia fellow on duty OR nurse Nursing aide
Personal Protective Equipment
Coverall protective suit Face shield and/or goggles N95 mask Sterile gloves (double) Shoe covers/ boots *Centers for Disease Control (CDC) guidelines on donning and doffing are followed



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The Lung Center of the Philippines Section of Pulmonary Rehabilitation offers structured and monitored exercise training that improves muscle function to decrease shortness of breath; education on maintaining and improving body function; emotional and psychological support, and instructions on breathing techniques to lessen breathing problems. **Duration of program is 4 weeks, every Tuesday and Thursday 9AM - 11AM via virtual platform.**

Materials for Virtual Sessions

Digital Platforms Requirements
- -Zoom Account
- -Viber Account

For the Virtual Session
- -Pedometer
- -Pulse Oximeter
- -Digital Blood Pressure Apparatus
- -Cycle Pedometer
- -Incentive Spirometer (*optional)
- -Cycle Ergometer (*optional)

CONDITIONS RECOMMENDED FOR THE PROGRAM

- CHRONIC OBRSTRUCTIVE PULMONARY DISEASE
- BRONCHIECTASIS
- POST COVID-19
- INTERSTITIAL LUNG DISEASE
- PERIOPERATIVE REHAB
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ORIGINAL ARTICLE

A SYSTEMATIC REVIEW AND META-ANALYSIS ON THE EFFECTIVENESS OF GUIDED SELF-MANAGEMENT UTILIZING A CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) ACTION PLAN AMONG STABLE COPD PATIENTS IN A PRIMARY CARE SETTING

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ABSTRACT

Background. Stable COPD patients managed in the primary care setting can be given guidance to manage their disease using an Action Plan. This study was done to determine the effectiveness of guided self-management utilizing COPD action plan among stable COPD patients managed in the primary care setting.

Methodology. A systematic search of electronic medical databases, such as MEDLINE, Google Scholar, and Cochrane, was done for randomized controlled trials (RCTs) enrolling stable COPD patients to participate in self-management interventions utilizing the COPD action plan versus usual care in the primary care setting, as of August 31, 2023. Risk of bias assessment was done using the revised Cochrane risk of bias tool for randomized trials version 1. Data synthesis was done using Review Manager version 5.4.1. Certainty of evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.

Results. Ten RCTs were included in the quantitative analyses (n = 2436). There was a trend toward benefit in all-cause mortality with a relative risk (RR) of 0.52 (95% CI 0.27, 0.99). Self-management intervention also proved to be beneficial in the pooled result of exacerbation rate leading to hospitalization with RR 0.63 (95% CI 0.54, 0.74) and in one RCT with Odds Ratio (OR) 0.33, 95% CI 0.13, 0.84 in exacerbation rate leading to ER visit. Other outcomes of interest such as exacerbations leading to ER visit showed pooled result (RR 1.03, 95% CI 0.89, 1.19) crossing the line of no effect. Pooled and un-pooled results of COPD related QoL using the CAT and SGRQ score as well as lung function also showed no significant difference. Only one RCT reported on exercise capacity showing inconclusive result (Adjusted difference 8.53, 95% CI -9.18 to 25.28). There were no data available for adverse events.

Conclusion. Self-management intervention utilizing a COPD action plan decreases all-cause mortality and exacerbations leading to hospitalization. It does not cause an additional harm, may benefit patients in the management of their symptoms and encourages them to develop skills and behaviors they need to successfully manage their disease.

Keywords. *COPD, primary care, self-management, quality of life, action plan*

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is the third leading cause of death worldwide, causing 3.23 million deaths in 2019.[1] In the Philippines, chronic lower respiratory diseases, including COPD, continue to be part of the top 10 causes of mortality.[2] Aside from its impact on mortality, COPD causes compromised quality of life among its survivors. COPD patients experience persistent and progressive respiratory symptoms, including difficulty in breathing, cough and phlegm production making them at risk for exacerbations and hospitalizations. The COPD burden is projected to increase in the coming decades because of continued exposure to COPD risk factors and aging of the population.[3] In the latest local study on the burden of COPD in a rural setting in the Philippines in 2011, the prevalence of COPD in a rural setting was 20.8%, which was higher than that determined previously for an urban area. This may be attributed to smoking, exposure to wood fuels and a high prevalence of tuberculosis in the community.[4]

Primary care management of COPD is important for early diagnosis, initial management, and prompt referral to specialists to slow the progression of symptoms, reduce exacerbations, and improve survival of these patients. Patient education through guided self-management has been an effective strategy in obstructive lung diseases such as bronchial asthma and may be employed in the primary care setting.

Self-management intervention is a "structured but personalized and often multi-component, with goals of motivating, engaging, and supporting patients to positively adapt their health behaviors and develop skills to better manage their disease".[5] It is usually accompanied by a COPD action plan, a written document that outlines specific steps and instructions for managing symptoms of COPD. Self-management interventions are associated with improvement in health-related quality of life (HRQoL), lower probability of respiratory-related hospital admissions and unlikely to cause harm.[6] However, there are variations in terms of the components of self-management intervention among stable COPD patients due to heterogeneity among interventions, study populations, follow-up time and outcome measures presented in the included studies.[7] These variations as mentioned are at the patient level and at the intervention provided itself. Despite these variations, self-management with a written action plan has been recommended by international and local guidelines (Global Initiative for Chronic Obstructive Lung Disease,[8] Philippine College of Chest Physicians,[9] National Institute for Health and Care Excellence).[10]

This systematic review and meta-analysis shall provide the latest evidence on the effectiveness of guided self-management utilizing a COPD action plan among stable COPD patients in the primary care setting and see if aforementioned variations have been addressed and the interventions provided were uniformly provided to the subjects enrolled by looking at the available updated studies.

Self-management is incorporated in the education component of the LCP COPD Support Group, but no written Action Plan is specifically implemented and provided to the patients. The results of this review shall contribute to the evidence base of the LCP COPD support group advocacy in crafting their primary care provider training module for managing COPD in the primary care setting. This study shall follow the Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) guidelines in reporting the findings of systematic review and meta-analysis.[11]

Objectives

This study was done to determine the effectiveness of guided self-management utilizing COPD action plan among stable COPD patients managed in the primary care setting. The outcome measures the researchers pursued in this analysis are: 1) Number of exacerbations 2) COPD related Quality of Life (QoL) 3) Symptom improvement 4) Exercise Capacity 5) Mortality 6) Lung function and 7) Adverse Events

METHODOLOGY

Eligibility Criteria

The authors looked at randomized controlled trials (RCTs) published in the English language that compared self-guided management versus usual care among stable COPD managed in primary care from 2015 up to August 31, 2023. There were no restrictions as to the components of the "self-management interventions" and "usual care" as described in the studies. Time restriction to start in the year 2015 until the date of last search was done in the attempt to limit variations and capture the more recent interventions being done in the primary care setting. Outcomes of interest included symptom improvement, COPD-related QoL, reduction of exacerbations, COPD-related hospitalization, Mortality (all-cause and COPD-related) or ER visits. A study is deemed eligible or excluded as guided by the following inclusion and exclusion criteria:

Inclusion Criteria

a. Population of interest are stable COPD patients in the primary care setting. Stable COPD patients are those not in exacerbation at the time of study recruitment as defined by each study. Primary care setting is any first responder facility such as rural health clinics or outpatient clinics that is not inside a hospital facility
b. Intervention of interest is guided self-management including the use of COPD Action Plan. Guided self-

management is a self-management plan that is made by the healthcare provider tailor fitted to the patient's current status.

c. Comparator may be any usual standard of care which may include unstructured patient education as described in the studies not utilizing a COPD action plan.
d. Outcomes of interest. Include studies with any the following outcome (at least one): symptom improvement, COPD related quality of life, number of exacerbations, exercise capacity, Safety/Adverse events, death, and lung function, regardless of how the results are reported (different units, scores, scales). See Operational definition of variables Appendix 2.
e. Only randomized controlled trials and systematic reviews and meta-analysis (RCTs) with complete results available were included.

Exclusion Criteria

Studies without available full text articles (such as conference abstracts, study protocol) after all means (sending email request to authors) were exhausted to retrieve these data and those without complete data tables with outcome measures were excluded.

Information Sources

A systematic search was done using PubMed, Cochrane Library and Google Scholar. The latest database search was August 31, 2023. The authors also looked at reference list of the latest meta-analysis [6] done on the topic of guided self-management and stable COPD patients in primary care for any possible records that were not included in the database search.

Search Strategy

The search was done independently by the authors with a combined MeSH and free text search using the following terms as keywords in different combinations using the operational term "OR": COPD, stable COPD, chronic obstructive pulmonary disease, self-guided management, guided management, self-management, symptom diary, COPD action plan, action plan (Table 1).

Selection Process and Data Collection

Study selection was done independently by the authors. After combining results and de-duplication, all records were screened on title and abstract by the authors using Covidence software. All records coded as "maybe" or "include" were retrieved in full text and assessed for eligibility by the principal authors. An evidence table was produced which included all the study characteristics including the expected outcomes. The two authors also independently assessed trial quality and synthesized relevant findings from included studies. Disagreements were resolved by involving the research adviser. When necessary, researchers contacted authors of potentially eligible studies to ask for further information and availability of the full text and data results. Detailed information of this process can be found in the PRSIMA flow diagram (Figure 1).

Data Items

The following outcomes that were sought were defined and listed as follows:

1. Number of exacerbation episodes – the number of exacerbation episodes recorded per study. Time to exacerbation will be dependent on the study's definition.
   Exacerbation is worsening of the patient's respiratory symptoms that is beyond the normal day by day variation and leads to a change in medication; or any of the following: Change in sputum character or purulence, increase in sputum production, Increase in dyspnea.
2. COPD-related Quality of Life (QoL) – is a concept which aims to capture well-being of an individual with COPD regarding both positive and negative elements within the entirety of their existence at a specific point of time as measured by any of the commonly used scales such as the St. George Respiratory questionnaire (SGRQ), COPD assessment test (CAT), etc. (Appendix 2)
3. Symptom improvement – this is when a patient returns to a baseline condition or when current exacerbation manifestations abate such as coughing or breathlessness. Time to symptom improvement will be dependent on the study's definition. This can be measured using a dyspnea scale e.g., the modified medical research council (mMRC) scale for breathlessness, Borg Scale etc. (Appendix 2)
4. Exercise Capacity – is the amount of physical exertion that a patient can sustain. It may be measured using the 6-minute walk distance
   6-minute walk test (6MWT) is a submaximal exercise text used to assess aerobic capacity and endurance. The distance covered over a time of 6 minutes (reported as 6-minute walk distance or 6MWD) is used as outcome by which to compare changes in performance capacity
5. Mortality – cessation of life that is due to COPD or other cause reported during the period stipulated in the study protocol.
6. Lung function – measure of the capacity of the lungs during respiration and may be measured using FEV1, FEV1/FVC etc.
7. Adverse Events – undesirable experience reported during the study period which may or may not be associated with the use of a COPD action plan or self-management intervention (other than exacerbation, hospitalization, and mortality) such as trauma during exercise training, delay in ER consultation, etc.

Study Risk of Bias Assessment

The Revised Cochrane Risk of Bias Tool for Randomized trials version 1 was used to assess the quality of the studies included. The following domains were used to assess risk of bias: 1) Random sequence generation and 2) allocation concealment for selection bias 3) blinding of participants and personnel for performance bias 4) blinding of outcome assessment for detection bias 5) incomplete outcome data for attrition bias and 6) selective reporting for reporting bias. The assessment was done independently by the two primary authors and any disagreement was resolved through the research adviser. Each included study was rated for each domain to have "low risk," "high risk," or "unclear risk" of bias.

Effect Measures

For each of the outcome specified, the following effect measures with the corresponding 95% confidence interval were used for the synthesis and data presentation: Adjusted mean difference, odds ratio, and relative risk for exacerbations, mean, change in score and mean difference for COPD-related QoL, mean score, change from baseline and median for symptom improvement, adjusted difference for exercise capacity, relative risk for mortality and standardized mean difference for lung function. The authors were not able to find any study which reported adverse events

Synthesis Methods

Statistical analysis was done using Review Manager version 5.4.1. When appropriate, the authors pooled study results using random effects modelling meta-analyses. For studies that cannot be pooled, a narrative description of the result was extracted from the study. The authors assessed for heterogeneity of data across the included studies using frank heterogeneity looking at the direction of the result and I2 value.

Certainty Assessment

Using the criteria outlined in the Cochrane Handbook, the authors created a summary of findings including key information concerning quality of evidence, the magnitude of effect of the self-management intervention and the sum of available data for the outcomes of interest. This study used the five Grading of Recommendations Assessment, Development and Evaluation (GRADE) consideration which uses the following domains: risk of bias, inconsistency, indirectness, and imprecision to assess the quality of the body of evidence as it related to studies that contributed data to the meta-analyses for prespecified outcomes by using the GRADE pro GDT software. In the summary of findings table footnotes and comments, the authors included justifications for decisions to downgrade the quality of evidence to aid in the understanding of the review.

RESULTS

We found 10 RCTs12–21 that included a total of 2,436 subjects. Two (2) RCTs from the Netherlands and Canada recruited patients with at least 1 (Netherlands) and at least 2 (Canada) comorbidities. All subjects recruited were those with established COPD diagnosis based on GOLD or through local COPD registries. Three (3) RCTs from Spain, Canada and Australia included patients who had previous severe respiratory infection/exacerbation leading to clinic or emergency department visit or hospitalization in the past 1–2 years. Three (3) RCTs (UK, Canada, Spain) did not specify the COPD classification recruited in the subjects.

Interventions for self-guided management in the 10 RCTs included education, exercise training, stress management, skills management, and case management (which included steroid/antibiotic prescription, provision of vaccination, referral to health professionals as needed, smoking cessation, travel planning, use of medications and inhalers, exacerbation awareness, breathing techniques, advanced care/end-of-life planning, and counseling). Nine (9) RCTs delivered the intervention via a mixed approach of group and one-on-one sessions. Individualized approach involved either a respiratory nurse, a certified respiratory educator, or a trained case manager. Two (2) RCTs delivered the intervention via telephone coaching (England, USA) while 1 RCT from Iceland involved a family member in the self-management action plan.

Usual care across these studies varied depending on the standard of practice of the respective country. One study from England provided a 13-page leaflet to the control group which describes the basic information, symptoms and management of COPD and its exacerbation using the British Lung Foundation and NHS Smoke free resources while another study from Canada provided an individualized action plan and educational materials, and a referral to an 8-week in-hospital rehabilitation program based on the discretion of the treating specialist and a referral to a smoking cessation program. Usual checkups were scheduled at a range of 3-6-month periods.

Outcomes measures included exacerbations leading to ER visit or hospitalization, COPD-related QoL, symptom improvement, exercise capacity, all-cause mortality, and lung function. No additional data on safety or adverse events were extracted. The characteristics of the included studies is available on Table 2.

Of the 10 included RCTs, the study by Hernandez and Jolly had high risk of bias due to selection, performance, detection and reporting bias (Figure 2). Due to the nature of COPD self-management intervention, it is not possible to blind participants and personnel during RCTs. Detection bias was seen in the studies conducted by Ferrone and Jolly as well as attrition bias in 2 studies (Hernandez and Jonsdottir). There was no sufficient information to permit judgment in the studies of Jolly and Lenferink in terms of

the possibility of selective outcome reporting. There was also insufficient reporting of outcome data in the study of Lenferink causing unclear reporting bias.

Efficacy Outcomes

Exacerbations leading to ER visits or hospitalization

This study included data from 2 RCTs in the meta-analysis of exacerbation rate leading to ER visits showing no significant change (RR 1.03, 95% CI –0.33 to –0.22) and in 1 study (Adjusted Mean Difference –0.05, 95% CI 0.13 to 0.84. However, one RCT showed benefit with an Odds Ratio of 0.33 (95% CI 0.13, 0.84). There was a trend toward benefit in the use of self-management in terms of exacerbation leading to hospitalization with 856 subjects from 3 RCTs (RR 0.63, 95% CI 0.54 to 0.74) (Figures 3 and 4).

Symptom Improvement and Quality of Life

Quality of Life using the CAT Score was inconclusive when comparing self-management intervention and usual care after 9 months from 2 RCTs (MD –5.04, 95% CI –15.75 to 5.67). One study which reported CAT score could not be pooled because reporting of CAT score was done at 12 months which showed no difference between the 2 groups (Mean CAT score at 9 mos of 15.5 to 15.8 at intervention group versus 14 to 14.7 usual care) (Figure 5). Unpooled result for the SGRQ score (Change in score at 12 months 3.35 vs 4.69 with between group change of 2.21, 95% CI –2.86 to 7.28; Mean score in 12 mos with MD –1.3, 95% CI –3.6 to 0.9;) showed no difference to inconclusive results comparing the self-management and the usual care group. In terms of breathless using the mMRC, 3 RCTs were included however, there was a difference in the manner of reporting of results (mean mMRC score at 9 months, change from baseline at 12 months and median % improved at 12 months), hence these studies cannot be pooled. All 3 RCTs showed no difference in the intervention group versus the control group (mMRC score at 9 mos of 2.4 to 2.7 intervention group, 2.5 to 2.4 in usual care; Change in baseline score at 12 months of 0.28 vs 0.08 and a change in between group difference of 0.21, 95% CI of –0.09 to 0.5; Median, % improved at 12 months of 1, 21.2% for intervention and 1, 18.2% for control).

Exercise Capacity

One (1) RCT reported the 6-minute walk distance result among its 192 subjects which shows inconclusive result (Adjusted Difference of 8.53, 95% CI –9.18 to 25.28).

Mortality (All-cause)

This study included 5 RCTs which reported on all cause – mortality with a total of 1459 subjects with noted significant difference favoring self-management (RR 0.52 95% CI, 0.27 to 0.99) over usual care. One study showed a trend favoring usual care due to the 5 deaths that occurred in the intervention group however this study emphasized that the cause of death was not considered related to the intervention (Figure 4).

Lung Function

There was inconclusive result from the pooled studies from 3 RCTs reporting FEV1 score (SMD 0.05, 95% CI –0.13, 0.23) and 2 RCTs reporting FEV1/FVC score (SMD 0.19, 95% CI –0.03, 0.42) (Figures 7 and 8).

Safety Outcomes

No data on the adverse events were reported other than exacerbations leading to ER visits and/or hospitalization and mortality, which were included as efficacy outcomes.

Of the 10 included RCTs, two 14–15 had high risk of bias due to selection, performance, detection and reporting bias (Table 3). There was also note of heterogeneity in reporting (i.e., exacerbation) and measurement (i.e., quality of life, healthcare utilization) of most of the outcomes causing inconsistency, imprecision, and indirectness. This directly affected the GRADE score resulting to an overall certainty of evidence being downgraded from Moderate to Low (Table 4).

DISCUSSION

This study systematically evaluated 10 RCTs on the effectiveness of utilizing a guided self-management utilizing a COPD action plan compared to usual care among stable COPD patients seen in the primary care setting. Though the latest review was done only in 2022,[6] this study had a more updated pool of RCTs since the authors limited study inclusion to 2015 and disregarded older studies. Positive effects of COPD self-management intervention on the number of exacerbations were seen in 1 RCT reporting on the outcome of exacerbation leading to ER visit and pooled result for exacerbation leading to hospitalization. In addition, a trend toward benefit in the use of a self-management intervention utilizing a COPD action plan was seen in the all-cause mortality.

This study observed no difference in the health-related quality of life using the COPD and SGRQ scores and symptom improvement by using the mMRC breathlessness score. The authors determined that this could be possibly due to studies which measured this only included results in the short- to medium-term length (≤ 6 months up to 12 months). There were no studies included which evaluated patients more than 12 months later. Despite the wide confidence interval, a visual representation in the forest plot showed a trend favoring self-management intervention compared to usual care. COPD related QoL may further improve when patients develop their self-management skills over time. Symptom improvement also did not show any beneficial effect and the authors owe this to the same deduction as with health related QoL. Also, since the data cannot be pooled because of the difference in the manner

of reporting of the results (one study recorded a change in baseline mMRC compared to 9 months, another compared a change in mMRC compared to 12 months and the other study reported a median score and a percent change from baseline), individual assessment of each study result was done. All the 3 studies did not meet the MCID of 1 to show a significant effect. It is possible that despite no significant effect in symptom improvement, patients were able to do more activity at the same level of breathlessness.

This study observed inconclusive effect between self-management interventions and usual care for exercise capacity and lung function. While some studies suggest that self-management programs, which typically encompass education, symptom monitoring and personalized action plans, can lead to modest improvements in exercise capacity and lung function, others have failed to establish a consistent and significant advantage over usual care. This lack of definitive findings could be attributed to variations in intervention designs, patient populations and the duration of follow up. It highlights the complexity of managing COPD, which involves multifaceted factors beyond self-management alone. Consequently, more robust, and long-term studies are needed to elucidate the true impact of self-management interventions, helping healthcare practitioners and policymakers make informed decisions on the incorporation of these programs into routine COPD care.

A trend toward benefit can be seen in the pooled results for all-cause mortality using self-management intervention compared to usual care. Although there was 1 out of the 5 included studies which favored usual care, the authors concluded that the cause of death of these 5 subjects in their study is considered not probably related to COPD.

There are several limitations in the evidence included in this review. The studies included exhibits heterogeneity in intervention components and outcome measures making it challenging to synthesize the data cohesively. Moreover, the quality of included studies varies with some lacking rigorous methodology and reporting as seen in the studies of Bourne and Hernandez showing reporting bias. The limited long-term follow-up data also restricts the assessment of the sustained impact of self-management interventions.

Although the findings did not show positive or benefit effects across all outcomes, the intervention of interest may still be recommended based on benefits on all-cause mortality. The implementation of guided self-management, particularly through the utilization of COPD action plan in primary care setting has profound implications across various facets of healthcare. In healthcare practice, it empowers patients with COPD to take an active role in managing their condition, leading to improved adherence to treatment plans, reduced exacerbations leading to hospitalization and decrease in all-cause mortality. Patients may also develop confidence in their activities of daily living and become more independent. It may probably improve quality of life in the long run if action plan adherence is good. This approach fosters a patient-centered care model, promoting shared decision-making and better communication between patients and primary care physicians. In terms of policy, the integration of COPD action plan into primary care can result in cost savings by reducing hospital admission and emergency room visits if patients can self-manage their symptoms as long as it is reiterated in their action plan specifically when to call their doctor or go to the emergency department. It also aligns with the growing emphasis on preventive and community-based care within healthcare policies. With the growing and updated beneficial evidence of self-management among stable COPD patients with the use of a COPD action plan, a training for primary care physicians and other healthcare support system is justified.

A randomized controlled trial utilizing the COPD action plan designed for Filipino COPD patients in the primary care setting may be done to refine and optimize its effectiveness and tailor fit it to our local setting. Researchers may explore the most effective means of patient education, technology-based solutions, and the impact on long term outcomes, ultimately contributing to evidence-based guidelines that can further enhance COPD management in primary care settings.

CONCLUSION

While there are positive effects on reducing exacerbations and potential trend towards decreased all-cause mortality, the evidence is inconclusive regarding improvements in health-related quality of life, symptom improvement, exercise capacity and lung function. The complexity of COPD management and variations in study designs contribute to this emphasizing the need for more robust, long-term studies to clarify the true impact of self-management interventions utilizing a COPD action plan. Nevertheless, implementation of guided self-management has significant implications for healthcare, cost savings and a patient-centered care model. It also underscores the necessity for further research to optimize self-management strategies, refine patient education and leverage technology to enhance COPD management in primary care setting. Since an action plan has been feasible among asthma patients, its role in COPD is expected to be beneficial as well. Overall, the findings support the integration of COPD action plan into primary care, calling for training and support healthcare providers in implementing and promoting self-management among stable COPD patients.

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CONFLICT OF INTEREST

This evidence review is included in the DOH-initiated and LCP-led COPD CPG Development where three authors served as technical working group members and one author as consensus panelist.

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Table 1. *Search Strategy*

DATABASE	SEARCH STRATEGY / SEARCH TERMS	DATE AND TIME OF SEARCH	RESULTS	
			Yield	Eligible
PubMed	(Chronic Obstructive Pulmonary Disease OR COPD OR Obstructive Airways Disease) AND ((guided self-management OR self-management OR guided management) AND (COPD action plan OR action plan OR chronic obstructive pulmonary disease action plan OR symptom diary)) Filters: Free full text, Meta-Analysis, Randomized Controlled Trial, Systematic Review	Aug 31, 2023	16	8
Cochrane	'*Population* "Chronic Obstructive Pulmonary Disease" AND *Intervention* ("Self-management" OR "COPD Action Plan") Filters: Filters: Free full text, Meta-Analysis, Randomized Controlled Trial, Systematic Review	Aug 31, 2023	4	2
Google Scholar	"COPD" OR "Chronic Obstructive Pulmonary Disease" AND "self-management"; FILTER 2020-2023, reviews	Aug 31, 2023	67	9

Table 2. *Characteristics of Included Studies*

Title/Author	Study design	Country	Number of patients	Population	Intervention Group(s)	Control	Outcomes
Self-management programme of activity coping and education – SPACE for COPD (C) – in primary care: a pragmatic randomised trial Bourne et.al. 2022	prospective, single-blinded randomized controlled trial	United Kingdom	193	Established COPD diagnosis as defined by the GOLD from seven general practices and hospitals	Self-management Programme of Activity, Coping and Education (SPACE) for COPD group-based program 1. Education 2. Exercise training 3. Stress management 4. COPD action plan	Usual Care 1. Checkup/reviews 2. No additional care provided or removed from current access 3. if pulmonary rehabilitation will be offered, they will not be denied access, but they will not be included in the final analysis 4. no additional advice, information or recommendations will be provided	Primary outcome: CAT score Secondary outcome: 1. Bristol COPD Knowledge Questionnaire (BCKQ) 2. EuroQoL 5 dimension 3. Chronic Respiratory Questionnaire (CRQ) 4. Hospital Anxiety and Depression Scale (HADS) 5. Patient Activation Measure (PAM) 6. ISWT 7. ESWT
The impact of integrated disease management in high-risk COPD patients in primary care Ferrone et. al. 2019	multicenter randomized controlled trial	Canada	180	Confirmed COPD from 8 primary care centers	Integrated disease management program by a certified respiratory educator 1. Case management (general patient support, education and skills management training, prednisone/antibiotic prescription for exacerbation management, provision of vaccination, referral to health professionals as needed, smoking cessation counseling) 2. Education (COPD, energy conservation, regular exercise, nutrition, role and correct use of medications and adherence, travel planning, advanced care/ end-of-life planning) 3. Skills training (self-management education including exacerbation awareness management, action plan, inhaler device technique, coping skills, breathing techniques)	Usual care Delivered according to normal practice patterns in the Family Health Teams delivered on as needed basis or "needs to be assessed" basis Study visits (no defined clinical intervention) for the purpose of measuring study outcomes only were scheduled at the same intervals as the IDM visits (baseline, 3, 6, and 9 months with the close-out visit at one year	Primary outcome: CAT score Secondary outcome: 1. Clinical COPD Questionnaire (CCQ) 2. COPD specific knowledge questionnaire (Bristol knowledge questionnaire) 3. Airflow limitation (FEV1 and FEV1/FVC) 4. proportion of patients with COPD exacerbation 5. proportion and rate of COPD-related health service utilization
Effectiveness of community-based integrated care in frail COPD patients Hernandez et.al. 2015	Randomized controlled trial	Spain	155	Clinically stable COPD age 45 and above with history of at least 2 hospital admission due to severe respiratory exacerbations the past 2	Integrated Care which includes 1. patient's empowerment for self-management (2-h educational program – knowledge of the disease, pharmacological and non-pharmacological treatment, techniques for self-management of the disease and comorbid conditions, strategies to adopt	Usual care Conventional treatment being managed by their physician without any support from specialized nurses Visits were usually scheduled every 6 months in the outpatient clinic	Primary outcome: Number of hospitalizations and ED visit Secondary outcome: 1. Smoking status 2. SGRQ Score 3. mMRC dyspnea scale 4. Hospital Anxiety and Depression Scale 5. COPD knowledge and self-

Title/Author	Study design	Country	Number of patients	Population	Intervention Group(s)	Control	Outcomes
				consecutive years	with future exacerbations-- administered by a respiratory nurse followed by patient-specific support material 2. individualized care plan (done through one joint visit of the specialized nurse and the primary care team at the patient home) including reinforcement of the logistics for treatment of comorbidities and social support 3. access to a call center 4. coordination between the levels of care		management score 6. Lawton index for performance of ADL 7. COPD treatment (LTOT, vaccination, medications)
Self-management of patients with mild COPD in primary care Jolly et.al. 2018	randomized con-trolled trial	England	577	Primary care COPD registers with mMRC score of 1 or 2	1. telephone health coaching intervention by a nurse which includes medication management, smoking cessation, increasing physical activities, action planning, setting of new goals and discussion of barriers to achieving goals 2. use of pedometer 3. self-monitoring diary	Usual care Received a 13-page leaflet which includes the definition of COPD, a detailed description of associated symptoms, how the illness can be managed with the use of inhalers, how to treat exacerbations, and details of other resources (e.g., British Lung Foundation and NHS Smoke free)	primary outcome: SGRQ-C at 12 months secondary outcomes: 1. mMRC 2. self-reported physical activity (International physical activity questionnaire) 3. psychological morbidity (Hospital anxiety and depression scale) 4. Stanford self-efficacy scale 5. EuroQoL 5 dimensions 6. SQRQ-C at 6 months 7. smoking cessation rate 8. physical activity measurement using GENEactiv accelerometer
Randomized Controlled Trial of Health Coaching for Vulnerable Patients with Chronic Obstructive Pulmonary Disease Thom 2018	Randomized Control Trial	USA	192	seen at least once in the past 12 months, were age 40 years or older spoke Spanish or English, and had at least moderate COPD	health coaching for 9 months phone check-in call at least every 3 weeks, including within 2 weeks after each medical visit	Routine visits with primary care provider	overall COPD-related quality of life minimal clinically important difference [MCID], 1.0) Chronic Respiratory Disease Questionnaire 6MWD Number of exacerbations
Efficacy of a self-management plan in exacerbations for patients with advanced COPD Sanchez Nieto 2016	Controlled, randomized, parallel-group, single-blind study with follow-up of 1 year	Spain	96	Stable COPD patients	SMP-COPD, group education session on the main characteristics of the disease, an individual training session, on inhalation techniques according to the devices indicated for each patient, and an action plan with written material consisting of color-coded sheets with treatment instructions for	Routine care and usual visits	CAT mMRC dyspnea scale no of exacerbations, glucocorticoid, and antibiotic use

Title/Author	Study design	Country	Number of patients	Population	Intervention Group(s)	Control	Outcomes
					physical exercise (green) and exacerbations (orange)		
Program of Integrated Care for Patients with Chronic Obstructive Pulmonary Disease and Multiple Comorbidities (PIC COPD+): a randomised controlled trial Rose 2018	Parallel group, RCT	Canada	470	Chronic Obstructive Lung Disease (GOLD) criteria [3] and published Canadian reference values [9] confirmed by a respirologist or internist, ≥50 years of age, ≥1 emergency department visit or hospital admission for COPD exacerbation in previous 12 months, and ≥2 prognostically-important COPD associated comorbidities (as defined by GOLD and Canadian Thoracic Society Guidelines) identified via medical record screening	1) case-manager delivered 40-min standardized education session based on Living Well with COPD [10] on study enrolment. 2) individualized care and action plans for COPD exacerbation recognition, self-management, and management of comorbidities 3) case manager-initiated telephone consultations (12 weekly, and monthly for the subsequent 9 months; 21 sessions) comprising standardized reinforcement/motivational interviewing focusing on health behaviours; action plan teach-back sessions; assessment of symptoms/ symptom monitoring, problems and problem-solving strategies; 4) ongoing case manager communication with family physicians and with hospital specialists including respirologists; 5) priority access to ambulatory outpatient clinics. Exacerbation management prescriptions were provided with the action plan either directly to the participant or to their pharmacy. Case managers received standardized training focused on the Living Well with COPD Programme	1) 3-monthly outpatient clinic visits with dictated patient summary sent to family physician; 2) referral to an 8-week in-hospital rehabilitation programme for clinically stable patients experiencing recent exacerbation at the discretion of the treating specialist 3) an individualized action plan and referral to educational materials again at the discretion of the treating specialist. Smokers were referred to smoking cessation resource	1. ER visits one year after randomization 2. Mortality 3. Change in BODE index 4. HADS 5. SGRQ Client Satisfaction Questionnaire (CSQ8)

Title/Author	Study design	Country	Number of patients	Population	Intervention Group(s)	Control	Outcomes
Interdisciplinary COPD intervention in primary care: a cluster randomized controlled trial Liang 2019	Two arm, cluster randomized RCT	Australia	272	Patients were eligible if they were aged ≥40 years, had at least two clinic visits during the previous year and self-reported being a current/ ex-smoker (≥10 pack-year smoking history) or those who had a documented diagnosis of COPD on clinic records or were being treated with COPD-specific medications	RADICALS model of care was underpinned by Australian COPD-X guidelines Individualized smoking cessation support was provided to smokers using QUIT resources and guided by a treatment algorithm Home medicines review conducted by pharmacist The 8-week home-based pulmonary rehabilitation (HomeBase) programme	GPs in usual care practices continued to provide routine care to their patients.	1. SGRQ score 2. CAT score 3. mMRC grade 4. FEV1 5. HADS
Exacerbation action plans for patients with COPD and comorbid-ities: a randomised controlled trial Lenferink 2019	RCT	Netherlands	201	COPD patients (Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification II-IV) with ≥1 comorbidity (ischemic heart disease, heart failure, diabetes, anxiety, depression)	Group sessions and individual sessions on COPD and comorbidities as well as symptom recognition and monitoring, breathing and relaxation exercises, exacerbation plan training, mastery of inhaler technique	Usual care, symptom monitoring through diary	COPD exacerbation days per patient per year Duration of COPD exacerbation per patient per year
Effectiveness of a partnership-based self-management programme for patients with mild and moderate chronic obstructive pulmonary disease: a pragmatic randomized controlled trial Jonsdottir 2015	Pragmatic randomized control trial	Iceland	100	45-65 years old, with mild and moderate chronic obstructive pulmonary disease were invited with a family member	6-month, partnership-based self-management programme consisting of: (a) three to four conversations between nurse and patient-family member; (b) 6 months of smoking cessation; and (c) interdisciplinary team-patient-family member group meeting	Usual care, self-generated or routine appointments	SGRQ Illness Intrusiveness Rating Scale (IIRS) HADS International Physical Activity Questionnaire (IPAQ)

Table 3. *Summary of Findings*

Outcomes	Measure	Basis	Effect Size	95% Ci	Interpretation	Certainty Of Evidence
EXACERBATIONS	ALL	1 RCT (n =146)	AMD –48.9	–62.5, –35.3	Benefit	Moderate
	ER visits	1 RCT (n = 155)	OR 0.33	0.13,0.84	Benefit	Low
		2 RCTs (n = 555)	RR 1.03	0.89, 1.19	Inconclusive	
		1 RCT (n = 158)	AMD –0.05	–0.33, –0.22	No difference	
	Hospitalization	3 RCTs (n = 856)	RR 0.63	0.54,0.74	Benefit	Moderate
COPD related QoL	CAT (*MCID 2 units)	1 RCT (n = 193)	Intervention – Mean CAT score from 15.5 to 15.8 at 9 months Usual care – Mean CAT score from 14 – 14.7 at 9 months		No difference	Low
		2 RCT (n=418)	MD of –5.04	–15.75 – 5.67	Inconclusive	
	SGRQ (MCID 4units)	1 RCT (n = 272)	Change in score at 12mos Intervention 3.35 (0.57–6.14) Usual Care 4.69 (1.96–7.41) Between group 2.21 (–2.86 –7.28)		Inconclusive	Low
		1 RCT (n = 528)	Mean score in 12 mos Intervention 30.9 from 29.8 Usual care 30.9 from 29.5 Mean Difference –1.3 (–3.6 to 0.9)		No difference	
Symptom Improvement	Level of breathlessness (mMRC) (MCID 1)	1 RCT (n = 155)	Mean mMRC score, at 9mos Intervention decreased from 2.7 to 2.4 Usual care decreased from 2.5 to 2.4		No difference	Low
		1 RCT (n = 211)	Change from baseline, 12 mos Intervention 0.28 Usual care 0.08 change in between group difference 0.21 (–0.09; 0.50)			
		1 RCT (n = 272)	Median, % improved, at 12mos Intervention 1, 21.2% Control median 1, 18.2%			
Exercise Capacity	6MWD in meters	1 RCT (n = 192)	Adjusted Difference 8.53	–9.18 to 25.28	Inconclusive	Moderate
Death	All–cause	5 RCTs (n = 1459)	RR 0.52	0.27, 0.99	Benefit	Low
Lung Function	FEV1	3 RCT (n = 574)	SMD 0.05	–0.13, 0.23	Inconclusive	Moderate
	FEV1/FVC	2 RCT (n= 302)	SMD 0.19	–0.03, 0.42	Inconclusive	

AMD-Adjusted Mean Difference, MD-Mean Difference, SMD-Standardized Mean Difference, OR-Odds Ratio, RR-Relative Risk, MCID -Minimal Clinically Important Difference

Table 4. *GRADE Table*

Certainty Assessment							No. of Patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Guided self-management	Usual care	Relative (95% CI)	Absolute (95% CI)		
Hospitalization (follow-up: mean 12 months; assessed with: evaluator)												
3	randomised trials	not serious	not serious	not serious	serious[a]	none	Pooled data from 3 RCTs showed a RR of 0.63 (95% CI 0.54, 0.74) indicating benefit of guided self-management in reducing hospitalizations from exacerbation				⊕⊕⊕◯ Moderate	CRITICAL
SGRQ (follow-up: range 6 months to 12 months; assessed with: questionnaire)												
3	randomised trials	serious[b]	not serious	not serious	not serious	none	Three RCTs all reported no significant differences in SGRQ scores after 12-month follow – up for the Usual Care and Self-Management group (Hernandez Mean 43 (20) in self-management vs 49 (22) for usual care, Jolly MD -1.3 (95% CI -3.6, 0.9), Liang MD 2.21 p=0.38 (95% CI -2.86, 7.28).				⊕⊕⊕◯ Moderate	CRITICAL
mMRC dyspnea score (follow-up: mean 12 months; assessed with: evaluator)												
3	randomised trials	not serious	serious[c]	not serious	serious[a]	none	All three RCTs found no significant difference in mean mMRC between self-management and usual care after 12-month follow-up (Hernandez mean mMRC dyspnea score 2.4 (SD 1.3) in usual care vs 2.4(SD 1.2) in integrated care after 12 months (p value 0.96) , Lenferink OR 0.21 (95% CI -0.09-0.5) , Liang Median mMRC dyspnea score 1 (IQR 0-2) (18.2% proportion with significant improvement) in usual care vs mMRC dyspnea score 1 (IQR 1-2)(21.2% proportion with significant improvement) in intervention after 12 month follow-up (p value 0.74)				⊕⊕◯◯ Low	CRITICAL
FEV1 (follow-up: mean 6 months; assessed with: spirometry)												
3	randomised trials	not serious	serious[c]	not serious	not serious	none	One out of three RCTs found significant change in FEV1 after integrated disease management compared to control (Ferrone et al 100ml (95% CI 20-180) mean difference (p = 0.016) in preBD FEV1 after guided self-management) while two RCTs found no significant change in pre and post BD FEV1 in self-management vs usual care (Lenferink: -1.09 (95% CI -3.52 – 1.33) mean difference in FEV1 % predicted between SM vs UC after 12 months, Liang: Post BD FEV1 1.09 (95% CI -1.59-3.76) mean difference between UC vs SM after 6 months).				⊕⊕⊕◯ Moderate	IMPORTANT
FEV1/FVC (follow-up: mean 6 months; assessed with: spirometry)												
2	randomised trials	not serious	serious[c]	not serious	not serious	none	One RCT found significant improvement in mean difference of FEV1/FVC between guided self-management versus usual care (Ferrone: 2.2 (95% CI 0.1-4.5) MD (p = 0.044) while another RCT found no significant change in FEV1/FVC after 12 months (Lenferink: 0.69 (95% CI -1.43-2.81) MD in FEV1/FVC).				⊕⊕⊕◯ Moderate	IMPORTANT

Certainty Assessment							No. of Patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Guided self-management	Usual care	Relative (95% CI)	Absolute (95% CI)		
Mortality (follow-up: mean 12 months; assessed with: evaluator)												
2	randomised trials	not serious	not serious	serious[e]	serious[d]	none	21/283 (7.4%)	38/272 (14.0%)	OR 0.52 (0.29 to 0.90)	62 fewer per 1,000 (from 95 fewer to 12 fewer)	⊕⊕◯◯ Low	CRITICAL
COPD related Quality of Life (follow-up: mean 9 months; assessed with: change in CAT score)												
2	randomised trials	not serious[f]	serious[g]	not serious	serious[d]	none	326	285	-	MD 5.04 SD lower (15.75 lower to 5.67 higher)	⊕⊕◯◯ Low	CRITICAL
All-Cause Mortality (follow-up: mean 12 months)												
4	randomised trials	serious[h]	not serious[c]	not serious	not serious	none	Two out of four RCTs found significant differences in incidence of all-cause mortality between the self-management group and usual care (Rose 2018 HR 0.56 (95% CI 0.32–0.95) p=0.03 Hernandez 2015 OR 0.36 (95% CI 0.14–0.93) p=0.034) while the other two studies found no significant reduction of deaths in the self-management group.				⊕⊕⊕◯ Moderate	CRITICAL
6-minute walk distance (follow-up: mean 9 months; assessed with: physical therapist)												
1	randomised trials	not serious	not serious	not serious	seriousd	none	100	92	-	SMD 8.53 SD higher (8.18 lower to 25.28 higher)	⊕⊕⊕◯ Moderate	CRITICAL

CI: confidence interval; **MD**: mean difference; **OR**: odds ratio; **RR**: risk ratio; **SMD**: standardized mean difference

Explanations

a. difference in measuring outcomes
b. high risk of selection bias in Jolly 2018 and Hernandez 2015
c. heterogeneity in reporting of outcomes
d. imprecise due to small number of events and confidence intervals included potential for important benefits or harm
e. differing population included (presence of comorbidities is a major factor for the inclusion and exclusion in the subjects)
f. multiple imputations were generated for missing data based on the assumption that data were from a multivariate normal distribution and were missing at random
g. significant heterogeneity
h. high risk of selection bias for Hernandez 2015 and performance bias for Sanchez Nieto 2016 and Rose 2018

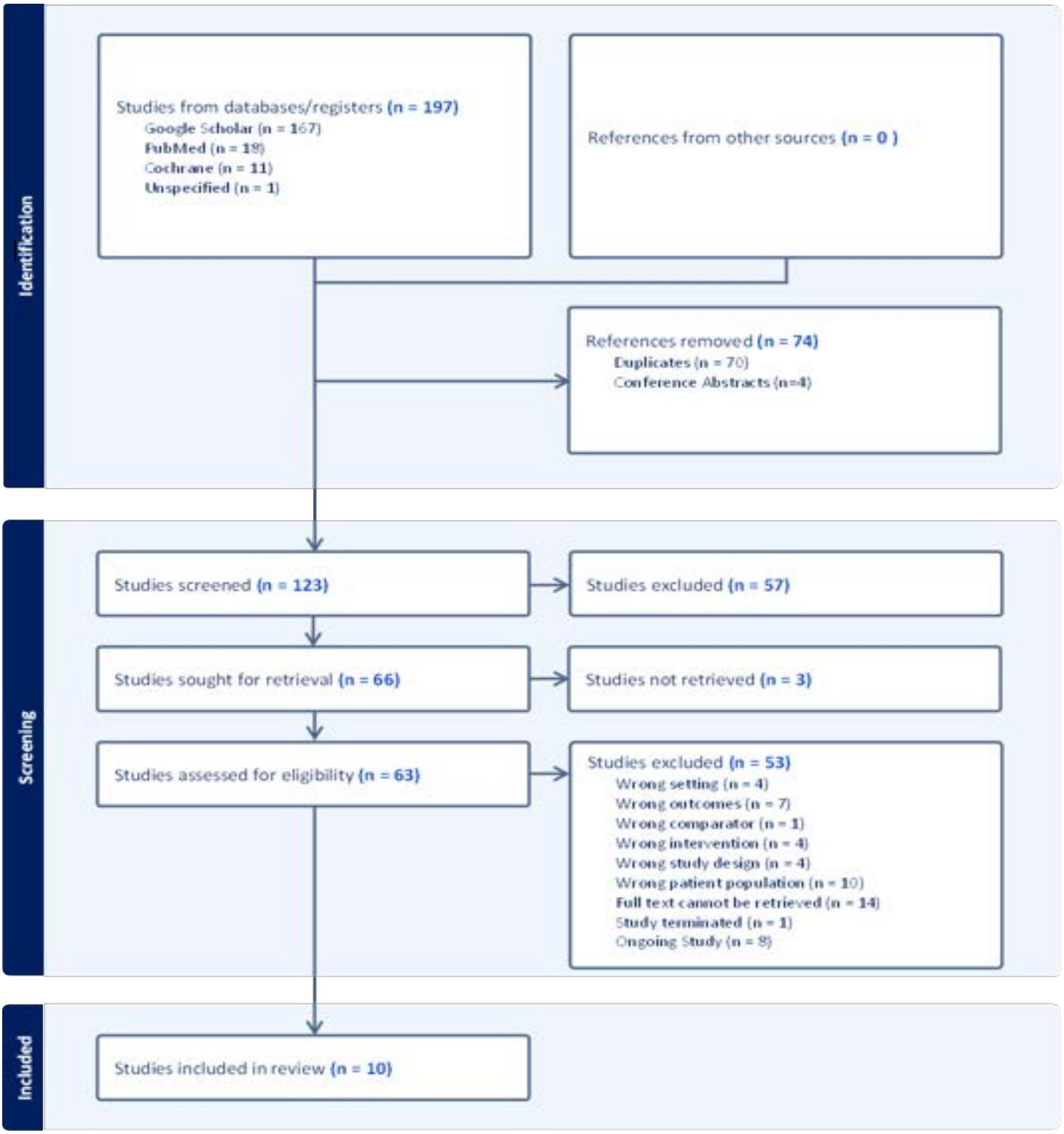

Figure 1. *PRISMA Flow diagram*

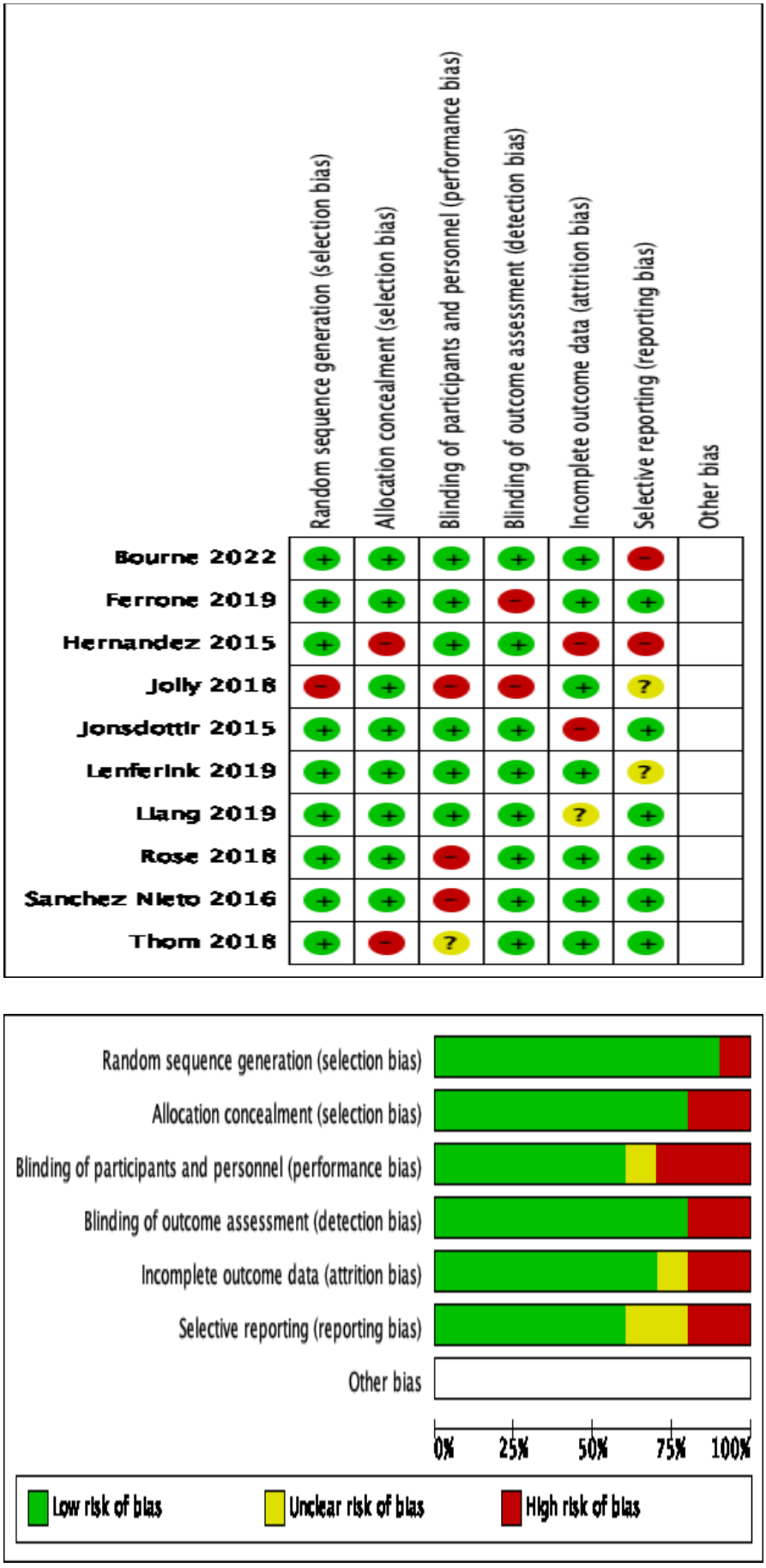

Figure 2. *Risk of Bias*

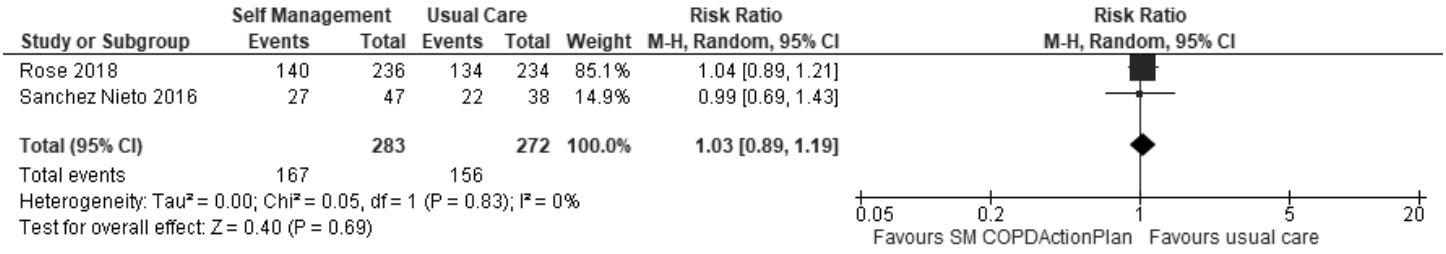

Figure 3. *Exacerbation leading to ER Visit*

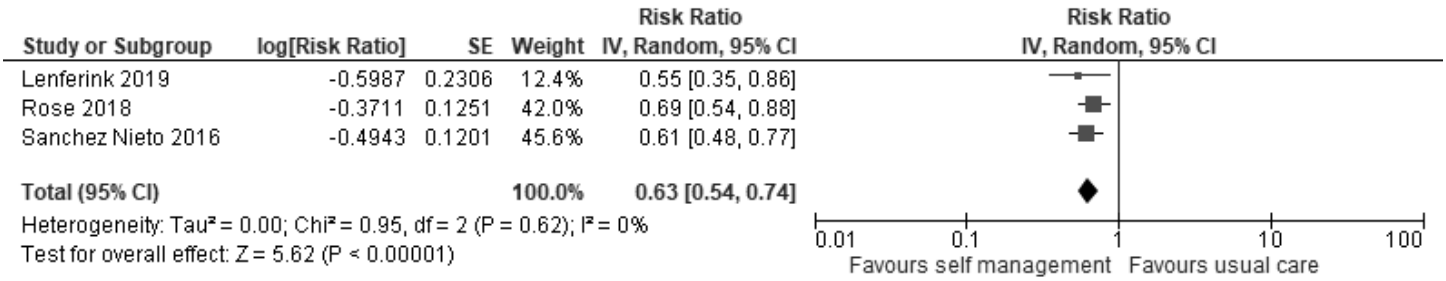

Figure 4. *Exacerbation leading to hospitalization*

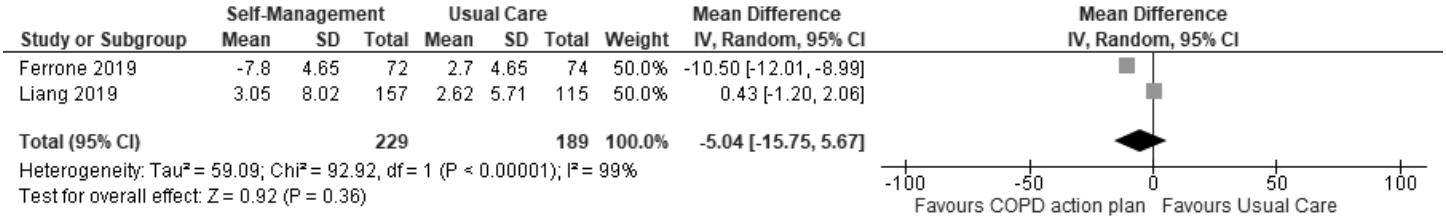

Figure 5. *Change in CAT score after >9 mos*

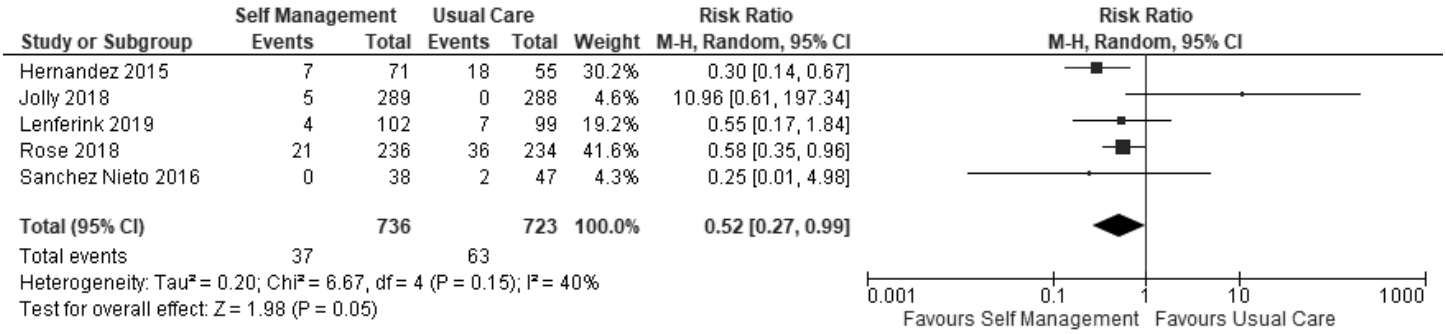

Figure 6. *All-cause Mortality*

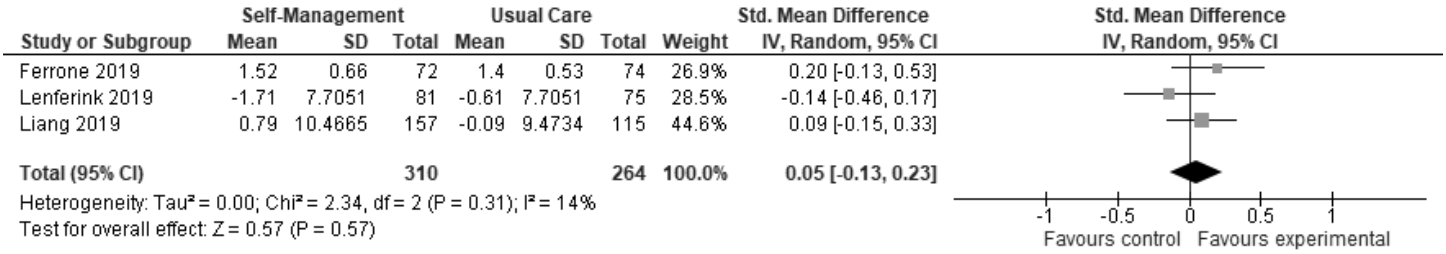

Figure 7. *Lung Function: FEV1*

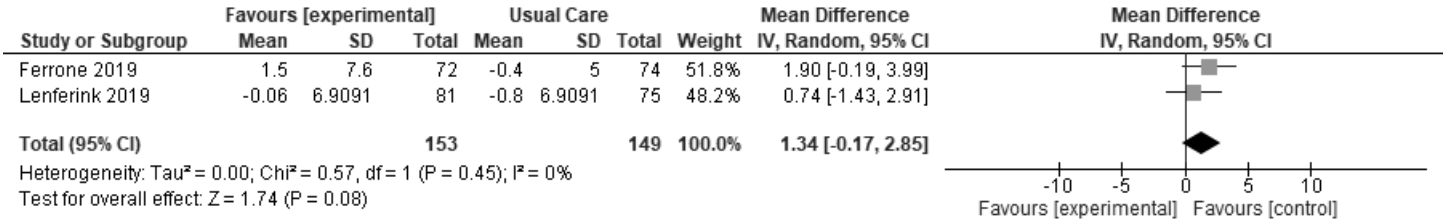

Figure 8. *Lung Function: FEV1/FVC*

Appendix 1 – Operational Definition of Variables

Intervention: Guided self-management with COPD Action Plan vs. usual standard of care

Guided self-management – is a structured, but personalized, and often multicomponent management, with goals of motivating, engaging, and supporting the patients to positively adapt their health behavior and develop skills to better manage their disease. It comes with a COPD action plan which is a patient-tailored worksheet that lists the steps to take to manage COPD depending on current symptoms. It includes instructions when to take medications, when to call a healthcare provider and when to proceed to the emergency department.

Usual standard of care – Treatment that is accepted by medical experts as a proper treatment for COPD which may include unstructured patient education as described in the studies not utilizing a COPD action plan

Difference in comprehensiveness – differences in the self-management intervention whereby some intervention utilizes telemedicine, mobile application, handouts/pamphlets etc.

Co-intervention – supplemental intervention provided to the recruited subjects such as pulmonary rehabilitation, home visit from a case manager etc.

Disease Severity – severity of enrolled subject which may be based on GOLD Classification, symptom severity score (breathlessness scale, quality of life questionnaire) or presence of comorbidities

Outcomes:

8. COPD related Quality of Life (QoL) – is a concept which aims to capture well-being of an individual with COPD regarding both positive and negative elements within the entirety of their existence at a specific point of time as measured by any of the commonly used scales such as the St George Respiratory questionnaire (SGRQ), COPD assessment test (CAT), etc. (Appendix 3)

9. Number of exacerbation episodes:
   The number of exacerbation episodes recorded per study. Time to exacerbation will be dependent on the study's definition.
   Exacerbation is worsening of the patient's respiratory symptoms that is beyond the normal day by day variation and leads to a change in medication; or any of the following: Change in sputum character or purulence, increase in sputum production, Increase in dyspnea.

10. Symptom improvement – This is when a patient returns to a baseline condition or when current exacerbation manifestations abate such as coughing or breathlessness. Time to symptom improvement will be dependent on the study's definition. This can be measured using a dyspnea scale e.g., the modified medical research council (mMRC) scale for breathlessness, Borg Scale etc.

11. Exercise Capacity – is the amount of physical exertion that a patient can sustain. It may be measured using the 6-minute walk distance

    6-minute walk test (6MWT) is a submaximal exercise text used to assess aerobic capacity and endurance. The distance covered over a time of 6 minutes (reported as 6-minute walk distance or 6MWD) is used as outcome by which to compare changes in performance capacity

12. Lung function – measure of the capacity of the lungs during respiration and may be measured using FEV1, FEV1/FVC etc.

13. Mortality – cessation of life that is due to COPD or other cause reported during the period stipulated in the study protocol.

14. Adverse Events – undesirable experience reported during the study period which may or may not be associated with the use of a COPD action plan or self-management intervention (other than exacerbation, hospitalization, and mortality) such as trauma during exercise training, delay in ER consultation etc.

Appendix 2

Quality of Life Questionnaires and Breathlessness Scales

ST. GEORGE'S RESPIRATORY QUESTIONNAIRE

ID NUMBER: ☐☐☐☐☐☐☐☐

FORM CODE: **SGR**
VERSION: 3.0 10/24/2017

Event: _____

0a) Date of Collection ☐☐/☐☐/☐☐☐☐ 0b) Staff Code ☐☐☐

Instructions: *This form should be completed during the participant's clinic visit. Please read the script exactly as written.*

This questionnaire is designed to help us learn much more about how your breathing is troubling you and how it affects your life. We are using it to find out which aspects of your illness cause you most problems, rather than what the doctors and nurses think your problems are.

Please ask if you have difficulty understanding the questions. Do not spend too long deciding about your answers.

0c) Please pick one response to show how you describe your current health:

Very good$_1$	Good$_2$	Fair$_3$	Poor$_4$	Very Poor$_5$
☐	☐	☐	☐	☐

The following questions ask about your chest trouble. Please answer as it applies to you.

PART 1

1) I cough:
- ☐ Most days a week$_1$
- ☐ Several days a week$_2$
- ☐ Only with respiratory infections$_4$
- ☐ Not at all$_5$

2) I bring up phlegm (sputum):
- ☐ Most days a week$_1$
- ☐ Several days a week$_2$
- ☐ Only with respiratory infections$_4$
- ☐ Not at all$_5$

3) I have shortness of breath:
- ☐ Most days a week 1
- ☐ Several days a week 2
- ☐ Not at all 5

4) I have attacks of wheezing:
- ☐ Most days a week 1
- ☐ Several days a week 2
- ☐ A few days a month 3
- ☐ Only with respiratory infections 4
- ☐ Not at all 5

5) How many attacks of chest trouble did you have during the last year?
- ☐ 3 or more attacks 1
- ☐ 1 or 2 attacks 2
- ☐ None 3

6) How often do you have good days (with few respiratory problems)?
- ☐ No good days 1
- ☐ A few good days 2
- ☐ Most days are good 3
- ☐ Every day is good 4

7) If you have a wheeze, is it worse when you get up in the morning?
- ☐ No 0
- ☐ Yes 1

PART 2

8) How would you describe your respiratory problems?
- ☐ Cause me a lot of problems or are the most important physical problem I have 1
- ☐ Cause me a few problems 2
- ☐ Cause no problems 3

ID NUMBER:								

FORM CODE: **SGR**
VERSION: 3.0 10/24/2017

Event: _____

9) Questions about what activities usually make you feel breathless. For each statement, please tell me which applies to you these days.

	False0	True1
9a) Washing or dressing yourself	☐	☐
9b) Walking around the house	☐	☐
9c) Walking outside on the level ground	☐	☐
9d) Walking up a flight of stairs	☐	☐
9e) Walking up hills	☐	☐

10) Some more questions about your cough and breathlessness. For each statement, please tell me which applies to you these days.

	False0	True1
10a) Coughing hurts	☐	☐
10b) Coughing makes me tired	☐	☐
10c) I am short of breath when I talk	☐	☐
10d) I am short of breath when I bend over	☐	☐
10e) My cough or breathing disturbs my sleep	☐	☐
10f) I get exhausted easily	☐	☐

11) Questions about other effects that your chest trouble may have on you. For each statement, please tell me which applies to you these days.

	False0	True1
11a) My cough or breathing is embarrassing in public	☐	☐
11b) My respiratory problems are a nuisance to my family, friends, or neighbors	☐	☐
11c) I get afraid or panic when I cannot catch my breath	☐	☐
11d) I feel that I am not in control of my respiratory problems	☐	☐
11e) I have become frail or an invalid because of my respiratory problems	☐	☐
11f) Exercise is not safe for me	☐	☐
11g) Everything seems too much of an effort	☐	☐

12) These are questions about how your activities might be affected by your respiratory problems. For each statement, please tell me which applies to you because of your breathing.

	False0	True1
12a) I take a long time to get washed or dressed	☐	☐
12b) I cannot take a bath or shower, or I take a long time to do it	☐	☐

ID NUMBER:								

FORM CODE: **SGR**
VERSION: 3.0 10/24/2017

Event: _____

	False$_0$	True$_1$
12c) I walk slower than other people, or I stop to rest	☐	☐
12d) Jobs such as house chores take a long time, or I have to stop to rest	☐	☐
12e) If I walk up one flight of stairs, I have to go slowly or stop	☐	☐
12f) If I hurry or walk fast, I have to stop or slow down	☐	☐
12g) My breathing makes it difficult to do things such as walk up hills, carry things up stairs, do light gardening such as weeding, dance, bowl, or play golf	☐	☐
12h) My breathing makes it difficult to do things such as carry heavy loads, dig the garden or shovel snow, jog or walk briskly (5 miles per hour), play tennis, or swim	☐	☐

13) We would like to know how your chest usually affects your daily life. For each statement, please tell me which applies to you because of your breathing.

	False$_0$	True$_1$
13a) I cannot play sports or do other physical activities	☐	☐
13b) I cannot go out for entertainment or recreation	☐	☐
13c) I cannot go out of the house to do the shopping	☐	☐
13d) I cannot do household chores	☐	☐
13e) I cannot move far from my bed or chair	☐	☐

14) How do your respiratory problems affect you? Please pick one response.

- ☐ They do not stop me from doing anything I would like to do$_1$
- ☐ They stop me from doing one or two things I would like to do$_2$
- ☐ They stop me from doing most of the things I would like to do$_3$
- ☐ They stop me from doing everything I would like to do$_4$

COPD Assessment Test (CAT)

Your name:_____

Today's date:_____

How is your COPD? Take the COPD Assessment Test™ (CAT)

This questionnaire will help you and your healthcare professional to measure the impact that COPD (Chronic Obstructive Pulmonary Disease) is having on your wellbeing and daily life. Your answers and test score can be used by you and your healthcare professional to help improve the management of your COPD and gain the greatest benefit from the treatment.

For each item below, place a mark (X) in the box that best describes your current situation. Please ensure that you only select one response for each question.

Example: I am very happy [0] [X] [2] [3] [4] [5] I am very sad

			SCORE
I never cough	[0] [1] [2] [3] [4] [5]	I cough all the time	☐
I have no phlegm (mucus) on my chest at all	[0] [1] [2] [3] [4] [5]	My chest is full of phlegm (mucus)	☐
My chest does not feel tight at all	[0] [1] [2] [3] [4] [5]	My chest feels very tight	☐
When I walk up a hill or a flight of stairs I am not out of breath	[0] [1] [2] [3] [4] [5]	When I walk up a hill or a flight of stairs I am completely out of breath	☐
I am not limited to doing any activities at home	[0] [1] [2] [3] [4] [5]	I am completely limited to doing all activities at home	☐
I am confident leaving my home despite my lung condition	[0] [1] [2] [3] [4] [5]	I am not confident leaving my home at all because of my lung condition	☐
I sleep soundly	[0] [1] [2] [3] [4] [5]	I do not sleep soundly because of my lung condition	☐
I have lots of energy	[0] [1] [2] [3] [4] [5]	I have no energy at all	☐
		TOTAL SCORE	☐☐

A COPD assessment test was developed by an interdisciplinary group of international COPD experts with support from GSK. GSK's activities in connection with the COPD assessment test are monitored by a supervisory council that includes external, independent experts, one of which is chair of the council.

Modified Medical Research Council (mMRC) Dyspnea Scale

MODIFIED MRC DYSPNEA SCALE[a]

PLEASE TICK IN THE BOX THAT APPLIES TO YOU | ONE BOX ONLY | Grades 0 - 4

mMRC Grade 0.	I only get breathless with strenuous exercise.	☐
mMRC Grade 1.	I get short of breath when hurrying on the level or walking up a slight hill.	☐
mMRC Grade 2.	I walk slower than people of the same age on the level because of breathlessness, or I have to stop for breath when walking on my own pace on the level.	☐
mMRC Grade 3.	I stop for breath after walking about 100 meters or after a few minutes on the level.	☐
mMRC Grade 4.	I am too breathless to leave the house or I am breathless when dressing or undressing.	☐

* Fletcher CM. BMJ 1960; 2: 1662.

PUBLIC HEALTH AND DOMICILIARY DIVISION

This is a program that caters to adult afflicted with TB since early 2000 and children with TB in 2007. The Lung Center of the Philippines DOTS clinic is the first public health facility engaged implementing Programmatic Management for Drug resistant TB in 2005 as a satellite treatment center under the Green Light Committee. In 2008, it became one of the ten (10) treatment centers implementing the DOH guidelines on PMDT as issued by DOH Administrative Order 2008-0018.

SERVICES OFFERED

- CONTACT TRACING
- DSTB/DRTB SCREENING (GENEXPERT)
- HIV COUNSELING AND TESTING FOR ENROLLED TB PATIENTS (15 YEARS OLD AND ABOVE)
- PROVISION OF ANTI TB MEDICATIONS (DSTB/DRTB) FOR ADULT AND CHILDREN FOR FREE
- DIRECT SPUTUM SMEAR MICROSCOPY TEST FOR ENROLLED PATIENTS

OTHER SERVICES PROVIDED

- CONDUCTS TB EDUCATION
- REFERRING AND PROVIDING CENTER FOR PRESUMPTIVE DSTB/DRTB PATIENTS
- ACT AS TREATMENT PARTNER
- FOLLOW UP CASES WHO FAILED TO REPORT FOR TREATMENT
- SUBMITS ACCOMPLISHMENT REPORTS TO LCP/NTP/QCHD

OUR OBJECTIVES

TB-FREE PHILIPPINES

ENSURE THAT TB DOTS SERVICES ARE AVAILABLE, ACCESSIBLE, AND AFFORDABLE IN COLLABORATION WITH THE LGUS AND OTHER PARTNERS.

TO REDUCE PREVALENCE AND MORTALITY FROM TB.

CONTACT INFORMATION AND SCHEDULE

SCHEDULE:
MONDAY TO FRIDAY, 8AM-5PM

CONTACT US AT:
8924-6101 LOC 1856-57

EMAIL US AT:
PHDD@lcp.gov.ph

LUNG CENTER OF THE PHILIPPINES
NATIONAL REFERENCE LABORATORY FOR CLINICAL CHEMISTRY

ADENOSINE DEAMINASE (ADA)

Is a protein that is produced by cells throughout the body and is associated with the activation of lymphocytes, a type of white blood cell that plays a role in the immune response to infections. Conditions that trigger the immune system, such as an infection by Mycobacterium tuberculosis, the bacteria that causes tuberculosis (TB), may cause increased amounts of ADA to be produced in the areas where the bacteria are present. This test measures the amount of adenosine deaminase present in pleural fluid in order to help diagnose a tuberculosis infection of the pleurae.

1 WHY GET TESTED?

ADA tests helps to detect or rule out Mycobacterium Tuberculosis infection in Pleural Fluid. This may also be detected in other body fluids such as Cerebrospinal Fluid (CSF).

2 WHEN TO GET TESTED?

- Upon doctor's request
- Consult your Attending Physician before the tests. Your doctor may guide you for further instructions specifically if a particular medication might need to stop.

3 SAMPLE COLLECTION

Required sample: **PLEURAL FLUID**
A volume of Pleural Fluid is collected by a Physician using a procedure called THORACENTESIS and placed on a sterile container. This shall be sent to the laboratory as soon as possible without delay.

Volume: At least 5-10 mL in sterile container
Sample Handling: Room temperature
Sample Processing: Freshly collected or frozen sample (4 or -20°C)

LABORATORY GUIDELINES

Sample Preparation / Receiving of Samples:
1. Freshly collected samples: must be sent to the laboratory within 2 hours at room temperature
2. For send in referrals: call the LCP Patient Laboratory Service (02-89246101 loc. 1196) for more details
   : specimen preferably frozen or kept at controlled temperature 4 or -20°C

Time of collection is indicated on the request form

Processing Day: Mondays, Wednesdays and Fridays
Cut off Time: 10:00AM
Releasing of result: Same day, 4:00PM

Price: Php 2,700.00

For more information, please contact us:
NATIONAL REFERENCE LABORATORY FOR CLINICAL CHEMISTRY
Quezon Avenue, Quezon City
89246101 local 4041-4043 nrl@lcp.gov.ph

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All manuscript submissions to the **Scientific Proceedings** shall be online. The manuscript and other documentary requirements shall be e-mailed to scientificproceedings @lcp.gov.ph. A manuscript submission checklist (Form SPLCP-2021-ASC-001) is provided to guide the submission as to the journal's requirements.

Cover Letter

A cover letter addressed to the Editor-in-Chief of the **Scientific Proceedings** should be prepared, stating the complete title of the work, list of all authors, and the intention to submit to the **Scientific Proceedings**. The corresponding author with complete contact information (institutional mailing address, work telephone, fax number [if any], and work e-mail address) should be clearly indicated. Presentation of the study findings as an abstract or poster in previous conferences should be mentioned in the letter, to include information on the title and dates of the conference, as well as awards won, if any.

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For all original articles, the authors shall submit a scanned copy of the ethical review board approval of the study performed on which the manuscript is based.

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For case reports/case series, the authors shall submit a scanned copy of the written/informed consent for publication from the involved patient/subject. The **Scientific Proceedings** requires the use of its standard Informed Consent Form (SPLCP-2021-CF-001), duly accomplished and submitted with the other requirements. In case the involved subject/s and/or relative/guardian can no longer be contacted after all means have been undertaken by the author, the author should state so in the cover letter with a description on the efforts made to secure consent.

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The title page should include:

- Complete title of the article which should be informative, concise, meaningful, and as brief as possible (no more than 20 words)
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- Listing of any meeting(s)/conference(s) where the material is under consideration for presentation, has been previously presented, and/or has been awarded. Indicate title, place month and year of the meeting/conference.
- Corresponding author's name, mailing address, telephone, fax, and e-mail address. The corresponding author will be responsible for all questions about the manuscript. Only one author is to be designated as corresponding author and he/she does not need to be the first author on the manuscript.
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- Financial support, if any. Provide the agency name and city, company name and city, fellowship name and/or grant number.

Abstract

- Original Articles, Review Articles require a structured abstract of not more than 500 words, with the following four headings:
  - Objective/s: Briefly state the purpose/s or aim/s of the study.
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- At least 5 keywords listed in the Medical Subject Headings database ([MeSH] of the National Center for Biotechnology Information [NCBI] [https://www.ncbi.nlm.nih.gov/mesh/]) should be provided.

Body of the Text

- The manuscript should be written in IMRAD format (Introduction, Methodology, Results and Discussion, Conclusion).
- Organize and prepare the manuscript to include the following sections:
  - *Introduction:* The Introduction, without a heading, should refer only to the most pertinent past publications and should not be an extensive review of the literature. Include a brief background, the research question and/or rationale, objectives/purposes of the study, and major hypothesis to be tested if any.
  - *Methodology:* Methods should be written with sufficient detail to permit others to duplicate the work.
    Study Design: State the study design using a phrase such as randomized or nonrandomized clinical trial, case-control study, cross-sectional study, cohort study, case series, case report, systematic review, meta-analysis, review, experimental study, or historical manuscript; Setting: (e.g., multicenter, institutional, clinical practice); Participants, Patients, or Study Population: Number of patients, selection procedures, inclusion/exclusion criteria, randomization procedure and masking; Intervention or observation procedure(s); Main and secondary outcome measure(s); Data and statistical analyses, to include what software was used for the computations. For original articles, statements regarding adherence to the Declaration of Helsinki, approval by the Institutional Review Board (IRB)/Ethics Committee, and description of the informed consent process should be included.
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- All measurements and weights should be expressed in SI units.

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- Use generic names only in the text body. State the trade name of a particular drug cited in parentheses including manufac-turer's name, city, state and/or country when first mentioned in the text. With regard to instruments or equipment utilized in the study, enclose in parentheses the specific model, manufacturer's name, city, state and/or country.

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Funding Sources

- Funding source/s for the study on which the manuscript is based, to include the writing of the manuscript, should be stated.

Acknowledgments

- Contributors to the work who do not fulfill the authorship criteria should be acknowledged.

Tables, Figures, Illustrations and Photographs

Tables

- Tables should follow references. Each table must be titled and numbered consecutively using Arabic numbers as mentioned in the text. The title should be brief and fully understandable without reference to the text. Each table column and row must have a heading. Tables that indicate the mean should have the corresponding standard deviation. Legends must identify all symbols that appear on the tables and graphs. A maximum of five tables may be included in the manuscript.

Figures (Graphs, Illustrations, and Photographs)

- Each final figure should be submitted as individual Joint Photographic Experts Group (JPEG), Portable Network Graphics (PNG), or Tag Image File Format (TIFF) files with appropriate labels (figure number, title).
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- Each figure must be numbered consecutively in Arabic numerals by order of citation in the text. Each should have a brief explanatory legend. Legends must identify all symbols or letters that appear on the prints. Histologic figures, stains, and magnifications should be noted in the legend. Graphs that indicate the mean should include the standard deviation. Clinical photographs should be masked when possible to prevent identification of the patient. Photographs may be in black and white, or submitted in full color.
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- Appendices should be used very sparingly. However, it is appropriate to provide survey forms, to list the members of a study group, or explain complex formulas or information. In studies involving a study group, the writing group authors should be listed along with the group name on the title page. Other group members should be listed in an appendix.

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- Website references must include author (or website owner), title of article, date article was posted, publication (if applicable), complete website address and date accessed.
- Examples:

  Journal Article (if four or fewer authors, list all)

  Miller WT, Macgregor RR. Tuberculosis: Frequency of unusual radiographic findings. Am I of Roentgenology 1978; 130: 867-75.

  Journal Article (if five or more authors, list only the first three and add et al.

  Libshitz HI, Mckenna RJ, Haynie TP, et al. Mediastinal evaluation in lung cancer. Radiology 1984; 151:295-99.

  Chapter in Book

  Meltzer PS, Kallioniemi A, Trent JM, Chromosome alterations in human solid tumors. In: Vogelstein B, Kinzler KW, editors. The genetic basis of human cancer. New York: McGraw-Hill; 2002. p. 93-113.

  Book

  Murray, PR, Rosenthal KS, Kobayashi GS, Pfaller MA. Medical microbiology. 4th ed. St. Louis: Mosby; 2002.

  Gilstrap LC 3rd, Cunningham FG, VanDorsten JP, editors. Operative obstetrics. 2nd ed. New York: McGraw-Hill; 2002.

  Website

  World Health Organization. Hospital infection control guidelines for severe acute respiratory syndrome. April 16, 2003: http://who.int/csr/sars/infectioncontrol/en (accessed April 24, 2003).

- For a complete sample of references, please refer to http://www.nilm.gov/bsd/uniform_requirements.html

LUNG CENTER OF THE PHILIPPINES

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- Oxygen requiring

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- Histolopathologic / radiographic diagnosis of ILD
- Abnormal lung function (FVC <80% or DLCO <40%)
- Oxygen requiring
- Progressive disease

BRONCHIECTASIS

- Progressive disease despite maximal treatment
- FEV1 <40%
- Refractory or recurrent pneumothorax or hemoptysis

Referral is not equivalent to automatic enlistment to the program, but a screening of whether lung transplant may benefit your patient.

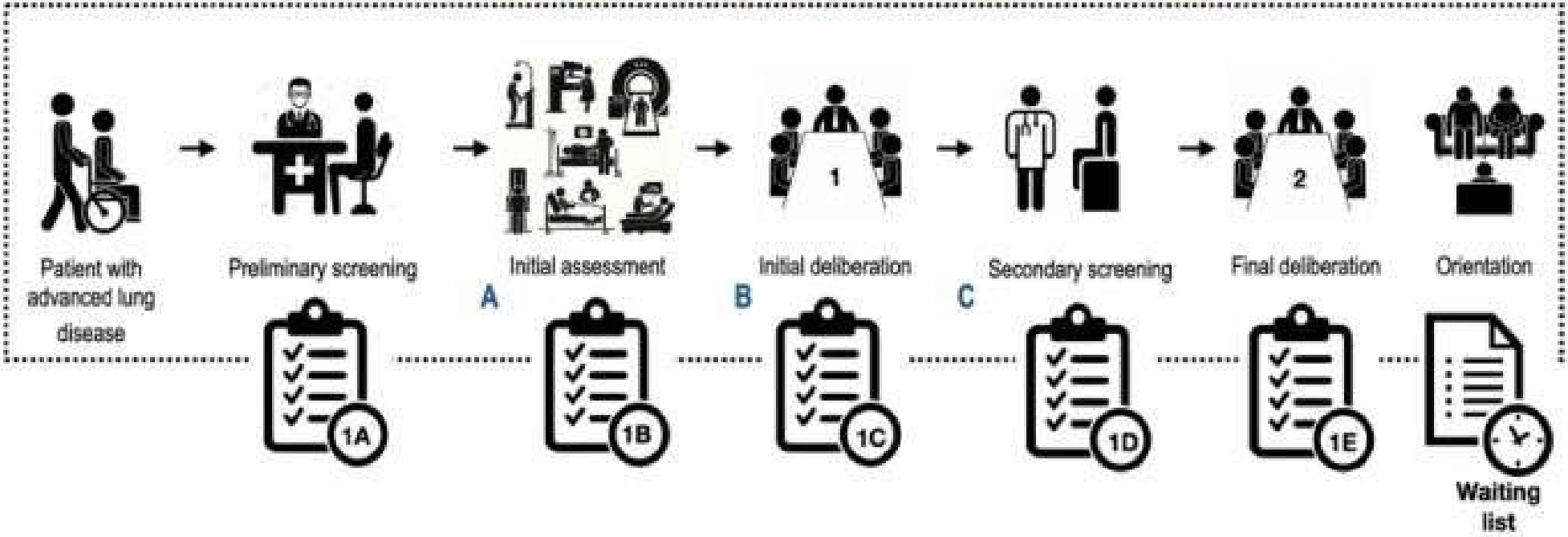
FOR MORE INFORMATION:

+639673812440

(02) 8924-6101 loc 2033

/Lung-Transplant-Program

I. Pre-transplant: Lung recipient evaluation & listing



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LCP Form No. 61-006

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MISSION

We provide high quality health services and state of the art facilities for the diagnosis and management of respiratory and chest diseases, and promotion of lung health for the Filipino people with excellence and compassion, regardless of creed, color, sex, socio-economic status, and political affiliation.

CORE VALUES

Customer-focused
Commitment
Compassion
Creativity
Collaboration

SHARED VALUES

Concern and care for patients, employees and the institution
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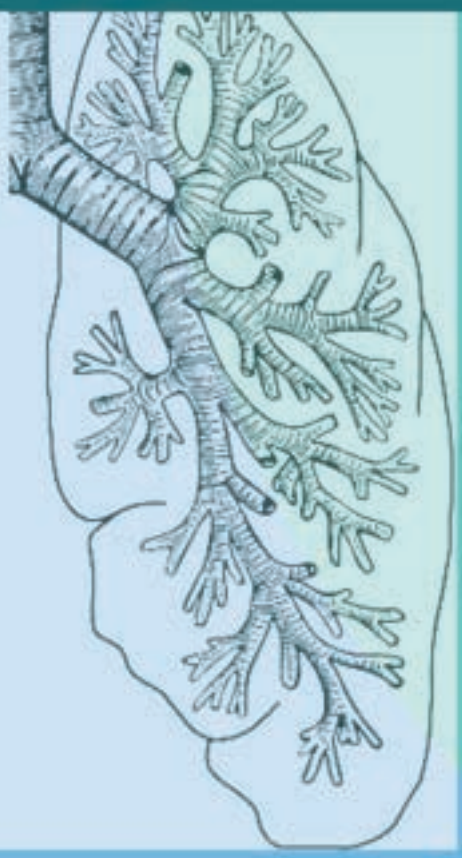

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