# PHILIPPINE JOURNAL OF CHEST DISEASES

Volume 21 Number 1
January-April 2023

## IN THIS ISSUE



AN OFFICIAL PUBLICATION OF PHILIPPINE COLLEGE OF CHEST PHYSICIANS

PHILIPPINE JOURNAL OF CHEST DISEASES
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# INSTRUCTIONS TO AUTHORS

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- After the names, state if the paper has been presented in any convention and whether any awards have been conferred.
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B. Figures are acceptable as Word, PowerPoint or Excel files. All files supplied must be "live: figures that can be opened and formatted. PDFs and JPGs are not accepted. Figures should be two dimensional; black and white or grayscale and without gridlines or background shading. X and Y axes, if present, must be labeled.

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   A. Supporting material that cannot be included in the publication of the manuscript for reasons of space but is complementary and directly relevant to the manuscript content, can be made available online as supplementary material. These may include additional figures or tables, data sets or detailed methods.
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# EDITORIAL

**Benilda B. Galvez, MD, FPCCP**
Editor-in-Chief

## *Why Publish Your Research in Journals*

Conducting research is a key part of academic and clinical careers of physicians. Post-graduate residency training programs and specialty fellowship training programs require producing research papers as requirement for completion of training and graduation. Submission of a research paper conducted during Pulmonary Medicine Fellowship training is also a requirement in applying for the specialty diplomate examination. But beyond doing research for training requirements, many of our pulmonary colleagues continue to conduct and write researches with passion and dedication.

After writing your research paper, the next crucial question is – "Should I have it published?" Researcher Chris A. Mack stated that publication in a peer-reviewed journal is the obvious goal of most research projects. It is through publication that researchers have an opportunity to share their thoughts and ideas with the rest of the scientific community which may prove invaluable in improving the existing and prospective knowledge base in a particular field.[1]

Duncan Nicholas (*Vice President of the European Association of Science Editors)* in his article "Guide to Getting Published in Journals" cited several key benefits to publishing research in journals, to wit: [2]

1. Discoverability - Publishing in journals can give your work visibility among other researchers in your field, outside of your immediate circle of contacts and colleagues. Journals can make your work more discoverable, as they are already being read by circles of interested readers.
2. Contributing to the Records of Research in the Field - Journal publication helps to preserve your work in the permanent records of research in the field. Publishing your work through visible sources helps others to learn. By adding your experiences to the literature of the field, it helps to build the corpus of knowledge in your subject area.
3. The Benefits of Peer Review - The peer review process helps improve the presentation and communication of research. The feedback can help you to frame your arguments in the most effective ways, and may even present valuable new insights into your own work. In addition, the peer review process can also help you reach peers and senior members of the research community by having journal editors, editorial boards and

reviewers read your work.

4. **Dissemination and Impact -** Selecting the appropriate journals can help add information to the public discussion of contemporary topics, beyond academic circles.
5. **Career Advancement -** Publishing in particular journals can be an essential component to advance your career, by meeting necessary assessment criteria and output performance targets. The number of quality publications you have produced can prop you up the ladder of success. Publishing your work will also give you a better chance of getting a promotion.[3]
6. **Preventing Duplication of Effort -** And last but by no means least, publishing your work ca prevent waste and increase efficiencies, by enabling others to build on your achievements or avoid unnecessary duplication of efforts.

Patrick A. Regoniel, PhD[3] stated that the greatest benefit for publishing your research findings will be sharing your knowledge to make this world a better place for everyone. Of what use are your findings if you are the only one who knows it? If you are able to publish your research findings in a reputable scientific journal, that gives you an inner confidence that indeed you have been a good researcher.[3]

Added benefit is the feeling of inner satisfaction and achievement when your published research paper is cited as reference in other research papers or scientific lectures of speakers. With the above benefits of publishing your research, I hope that pulmonary fellows-in training, pulmonary consultants and other researchers will be inspired and motivated to submit their researches for publication in our own peer-reviewed Philippine Journal of Chest Diseases.

REFERENCES:

1. Chris A. Mack. *How to Write a Good Scientific Paper?* https://rsi.or.id/why-is-it-imporant-to-publish-your-research/
2. Duncan Nicholas. Guide to Getting Published in Journals. https://ifis.libguides.com/journal-publishing-guide/why-publish-in-journals
3. Patrick A. Regoniel, PhD. Why Publish Research Findings? https: simplyeducate.me/2013/07/20/why-publish-research-findings/

Philippine Journal of Chest Diseases

Original Research

# Association of Demographic and Clinical Characteristics with Disease Severity in COVID-19 Cases Admitted at the Lung Center of the Philippines

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## ABSTRACT

**BACKGROUND:** COVID-19 is a new emerging disease which caused global hysteria when it spread sporadically and became a pandemic. We have limited health care resources including widespread testing, treatment and healthcare providers across the world and the overwhelming influx of COVID19-infected patients to many hospitals continues to strain healthcare systems. Hence, identifying clinical factors that may be of use to clinicians to predict COVID-19 severity and mortality will help them to immediately recognize and predict severe-to-critical COVID-19 for timely personalized management and prevent fatal outcomes and to save resources.

**OBJECTIVES:** To determine the association of demographics and clinical characteristics with disease severity in COVID-19 confirmed cases admitted at Lung Center of the Philippines (LCP). Specifically, we aim to compare socio-demographic and clinical profiles according to disease severity of COVID-19 confirmed cases admitted in LCP and to determine which clinical characteristics can be associated with COVID-19 disease severity.

**METHODS:** We utilized a cross-sectional study design which involved a retrospective chart review of 366 confirmed COVID-19 patients admitted at LCP from March 7 to August 31, 2020.

**RESULTS:** Majority of the patients were males (n= 233, 63.44%) and the median age was 58.5 years (IQR 54 - 70). Multivariable regression analysis showed increasing odds of having severe or critical COVID-19 infection associated with patients aged 40 to 59 years old (OR=7.79, 95% CI=1.28 to 47.2, p=0.026) and ≥60 years old (OR=8.17, 95% CI=1.4 to 47.6, p=0.020). Results also showed that patients who presented with dyspnea (OR=4.16, 95% CI=1.60 to 10.8, p=0.003), tachypnea (OR=1.17, 95% CI=1.08 to 1.28, p=<0.001) and increased oxygen support (OR=1.03, 95% CI=1.01 to 1.05, p=0.010) increased the odds of having severe to critical COVID-19 infection. There was decreased odds of having severe or critical COVID-19 infection with increasing PF ratio (OR=0.9938, 95% CI=0.98 to 0.998, p=0.001) and increasing oxygen saturations (OR=0.9361, 95% CI=0.90 to 0.97, p=0.001).

**CONCLUSION:** Advanced age, dyspnea, tachypnea and increase in oxygen support requirement were significantly associated with disease severity of COVID-19. Higher oxygen saturations and PF ratios were significantly associated with decreased odds of having severe or critical COVID-19 infection. Hence, clinicians should always be mindful of these contributing factors to recognize the disease severity of COVID-19 during initial evaluation and to enable them to give immediate appropriate measures and avoid poor outcomes with these patients.

**KEYWORDS:** *COVID-19, demographic characteristics, clinical characteristics, disease severity*

## INTRODUCTION

COVID-19 was declared as a pandemic by the World Health Organization on March 11, 2020 due to considerable countries affected by the disease.[2] In the Philippines, the first reported case of COVID-19 infection was on January 30, 2020 and sustained community transmission on March 7, 2020 was detected. The numbers of confirmed COVID-19 cases worldwide had grown to 629 million cases and counting as of October 2022.[3] In the Philippines, the confirmed cases of COVID-19 was already at 3,997,941 as of October 2022.[3] COVID-19 affected both the health system and economic aspect of the country, and the government imposed strict lockdown on the affected areas as early as March 2020.

In a study conducted in China, nearly half of patients with COVID-19 infection have comorbidities such as hypertension, diabetes, and coronary artery diseases.[4] Most of the patients with COVID-19 infection reported in the literature were males.[4-8] Previous studies revealed that male patients and older patients infected with COVID-19 had an increased risk of death.[4,8,9] Patients with coexisting illnesses were also noted to develop severe COVID-19 infection than those without comorbid conditions.[10,11] COVID-19 is an emerging disease and poses continuous threat to the health system.

There is a lack of local data regarding COVID-19, hence, studies should be conducted to identify the clinical characteristics of the patients that can be associated with the disease severity of COVID-19. This information is vital to help clinicians readily recognize severe and critical patients and provide the appropriate management.

The LCP is a specialty center for lung diseases that was designated as one of the COVID-19 referral centers to accommodate mild-to-critical cases of COVID-19 infection and a good ground for studies regarding this disease. As to our knowledge, there were limited local studies that describe the demographic and clinical characteristics of the patients with COVID-19 and associate it with the disease severity. Thus, this study aims to present clinical data of COVID-19 cases here in the Philippines to understand the novel disease and to associate the demographic and clinical characteristics on presentation and disease severity of COVID-19 infection during admission.

## OBJECTIVES

To determine the association of demographics and clinical characteristics of admitted COVID-19 confirmed cases with disease severity of COVID-19 at the Lung Center of the Philippines. Specifically, to (1) compare the socio-demographic and clinical profile of admitted COVID confirmed cases according to disease severity of COVID-19 in terms of socio-demographic profile (i.e., age, sex, occupation, smoking status) and clinical characteristics (i.e., comorbidity, symptoms, time from illness onset to hospital admission, blood pressure, pulse rate, respiratory rate, temperature, and pO2/FiO2 ratio) and (2) determine which clinical characteristics can be associated with COVID-19 disease severity.

## METHODS

### Research Design

We utilized a cross-sectional study design which involved a retrospective chart review of 366 confirmed COVID-19 patients admitted at LCP from March 7 to August 31, 2020. The study site, LCP, was designated as one of the COVID-19 referral centers by the Department of Health on March 20, 2020 and has allotted 80 to 120 beds to accommodate mild to critical cases of COVID-19 infection.

### Inclusion and Exclusion Criteria

Adult patients (>19 years old) with confirmed COVID-19 according to World Health Organization (WHO) interim guideline who were admitted in LCP between March 7, 2020 to August 31, 2020 were included in this study. Missing or incomplete data in the chart was excluded in our study.

### Sample Size and Sampling Design

A minimum of 221 confirmed COVID-19 patients satisfying the inclusion/exclusion criteria were required to have a 90% chance of determining, as significant at the 5% level, the relationship of clinical characteristics with disease severity based on anticipated medium effect size of 0.3 of duration of symptoms versus disease severity. A total of 526 cases were identified. There were 160 cases that were excluded, wherein six cases were aged 18 and below, 11 cases had incomplete data, and 143 charts were unavailable during data collection. A total of 366 cases were finally randomly retrieved in the medical records based on availability of the charts and were included in the final data analysis.

### Study Procedure

The principal investigators (PI) submitted a letter of request to the Medical Records Section of LCP to retrieve the medical charts of the admitted patients diagnosed with confirmed COVID-19 infection. The PI did a chart review of the discharged patients' medical charts with confirmed COVID-19 infection admitted in LCP from March 7, 2020 to August 31, 2020. Their demographic profile, comorbidities and clinical profile of the patient ,including the symptoms and initial physical examination, were obtained from the medical records of the patient and were classified accordingly. The disease severity classification of each case was based on the admitting diagnosis. It was classified as mild, moderate, severe, and critical according to the classification and definition of the WHO Clinical Management of COVID-19 Interim Guidance as of May 2020. The investigators did the review of the medical records of the patients included in this study. To ensure that all important information was gathered, the researchers used a pre-specified Microsoft-Excel file data collection form to record the said data. All the necessary data was encoded in the excel file.

### Statistical analysis

Descriptive statistics was used to summarize the demographic and clinical characteristics of the patients. Frequency and proportion were used for categorical variables and median and interquartile range (IQR) for non-normally distributed continuous variables. Kruskal-Wallis test and Fisher's Exact test were used to determine the difference of median and frequency, respectively, within different disease severity. Odds ratio and corresponding 95% confidence intervals from binary logistic regression were computed to determine significant factors of severe and critical COVID-19 disease severity. The disease severity was categorized into 2 groups to facilitate statistical analysis: (1) mild to moderate and (2) severe to critical. Stepwise method was utilized to determine the final multivariate model. Shapiro-Wilk test was used to test the normality of the continuous variables. Missing values were neither replaced nor estimated. Null hypotheses were rejected at 0.05α-level of significance. STATA 13.1 was used for data analysis.

### Ethical Considerations

This research underwent ethics review, and was approved with approval number LCP-PF-017-2020. It followed the National Ethical Guidelines for Health Research (NEGHR) and the Data Privacy Act of 2012.

## RESULTS

A total of 366 patients were enrolled in the study. Most of the admitted patients were classified as moderate COVID-19 that comprised 58% (n=211) of cases. The rest were classified as mild (5%, n=18), severe (16%, n=60) and critical (21%, n=77). Forty-eight percent (n=174) of patients with confirmed COVID-19 were aged 60 years old and above, while 39% (n=142) of the population belong to the age group of 40 to 59 years old. The median age of patients with severe (60 (IQR:53-67)) and critical (64 (IQR:54-70)) COVID-19 infection were older in comparison with mild and moderate cases (37 and 57, respectively). As shown in Table 1, there was a predominating age group population for each disease severity. More than half (61.11%) of the mild cases were in the younger age group of 19 to

39 years old. Moderate cases of COVID-19 were mostly in the age group of 40 to 59 (41.7%) and more than 60 years old (43.13%). On the other hand, more than half of the severe and critical cases were 60 years and older.

Table 1. Age Distribution of COVID-19 Patients According to Disease Severity

| Age | Total (n=366) | Disease severity | | | | P-value (<0.05) |
|---|---|---|---|---|---|---|
| | | Mild (n=18, 5%) | Moderate (n=211, 58%) | Severe (n=60, 16%) | Critical (n=77, 21%) | |
| [Median ( IQR)] | 58.5 (48 to 67) | 37 (28 to 59) | 57 (46 to 67) | 60 (53 to 67) | 64 (54 to 70) | **<0.001** |
| 19 to 39 years old (%) | 50 (13.66) | 11 (61.11) | 32 (15.17) | 2 (3.33) | 5 (6.49) | **<0.001** |
| 40 to 59 years old (%) | 142 (38.8) | 3 (16.67) | 88 (41.71) | 25 (41.67) | 26 (33.77) | |
| > 60 years(%) | 174 (47.54) | 4 (22.22) | 91 (43.13) | 33 (55) | 46 (59.74) | |

Table 2 shows that the majority of the patients were males although there was almost similar distribution of gender among the different disease severity classification. Most patients with confirmed COVID-19 cases were non-cigarette smokers. Overall, 266(72.68%) patients were non smokers, however it was noted that there was an increase in the number of smoker patients among severe and critical disease severity as shown in the table below. Majority of the patients were non-healthcare workers while only 7% (n=27) of the included population were health care workers. A larger proportion of healthcare workers were classified as mild COVID.

Figure 1 and Table 3 below shows that about 79% of patients infected with COVID-19 had comorbidities. As depicted in the chart, a larger proportion of severe and critical COVID-19 patients have more than one comorbidities. There were 138 COVID-19 confirmed cases (37.7%) that were noted to have one comorbid condition while 154 (42.08%) cases had more than one co-morbid condition. Most of the severe and critical cases have at least 1 comorbid condition while the majority of moderate cases have two or more comorbid conditions. Conversely, the majority of mild cases have no comorbid condition.

Table 2. Demographic characteristics of COVID-19 patients according to disease severity

| | Total (n=366) | Disease severity | | | | P-value (<0.05) |
|---|---|---|---|---|---|---|
| | | Mild (n=18, 5%) | Moderate (n=211, 58%) | Severe (n=60, 16%) | Critical (n=77, 21%) | |
| Sex Male | 233 (63.66) | 11 (61.11) | 129 (61.14) | 43 (71.67) | 50 (64.94) | 0.503 |
| Smoking Status: (current/ previous) | 100 (27.32) | 3 (16.67) | 48 (22.75) | 24 (40) | 25 (32.47) | **0.028** |
| Occupation (%) | | | | | | |
| *Healthcare worker* | 27 (7.38) | 6 (33.33) | 19 (9) | 1 (1.67) | 1 (1.3) | <0.001 |
| *Non-healthcare worker* | 339 (92.62) | 12 (66.67) | 192 (91) | 59 (98.33) | 76 (98.7) | |

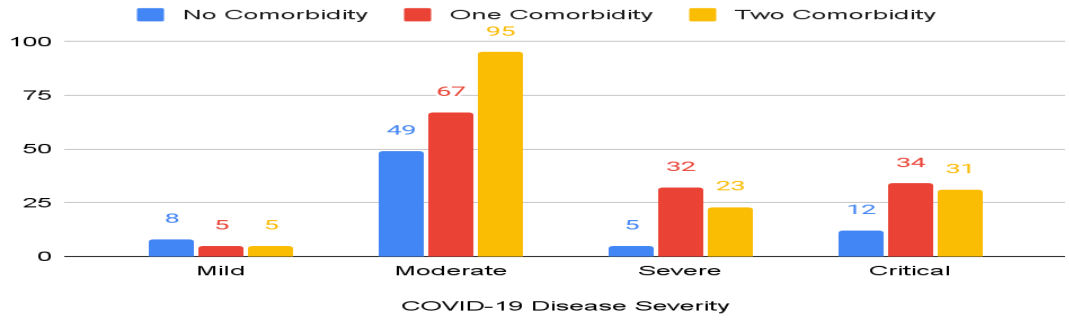


**Figure 1.** Comorbid Conditions of COVID-19 Patients According to Disease Severity

**Table 3.** Comorbid Conditions of COVID-19 Patients According to Disease Severity

| Number of comorbidity n(%) | Total (n=366) | Disease Severity (n,%) | | | | P-value (<0.05) |
|---|---|---|---|---|---|---|
| | | Mild (n=18, 5%) | Moderate (n=211, 58%) | Severe (n=60, 16%) | Critical (n=77, 21%) | |
| Two comorbidities | 154 (42.08) | 5 (27.78) | 95 (45.02) | 23 (38.33) | 31 (40.26) | 0.003 |
| One comorbidity | 138 (37.7) | 5 (27.78) | 67 (31.75) | 32 (53.33) | 34 (44.16) | |
| No comorbidity | 74 (20.22) | 8 (44.44) | 49 (23.22) | 5 (8.33) | 12 (15.58) | |

As seen in Table 4, hypertension (53.83%), DM (35.25%) and BA (9.29%) were the most self-reported comorbid conditions. Remarkably, there was a significant increase in the number of hypertensive patients among severe (70%) and critical cases (62.34%). Diabetes, the second leading co-morbid condition, was reported in 40.28% of moderate, 25% of severe and 33.77% critical cases. Interestingly, 80 cases (21.86%) had respiratory conditions which included PTB, BA, COPD and bronchiectasis. Of the 38 patients who self-reported with PTB, 13 were active and 25 cases had previous PTB.

The median time from symptom onset to hospital admission for mild cases of COVID-19 were shorter (2 days (IQR 0-4 days)) in comparison to the moderate, severe and critical cases with a mean length of 7 days. In Table 5, the most prominent symptoms were

**Table 4.** Number of Comorbid Condition of COVID-19 Patients According to Disease Severity

| Number of comorbidity n(%) | Total (n=366) | Disease Severity (n,%) | | | | P-value (<0.05) |
|---|---|---|---|---|---|---|
| | | Mild (n=18, 5%) | Moderate (n=211, 58%) | Severe (n=60, 16%) | Critical (n=77, 21%) | |
| **Comorbidities** n(%) | | | | | | |
| Hypertension | 197 (53.83) | 5 (27.78) | 102 (48.34) | 42 (70) | 48 (62.34) | **0.001** |
| Diabetes mellitus | 129 (35.25) | 3 (16.67) | 85 (40.28) | 15 (25) | 26 (33.77) | **0.048** |
| Bronchial Asthma | 34 (9.29) | 3 (16.67) | 21 (9.95) | 5 (8.33) | 5 (6.49) | 0.562 |
| Cardiovascular | 26 (7.1) | 0 | 17 (8.06) | 2 (3.33) | 7 (9.09) | 0.311 |
| Chronic Kidney | 23 (6.28) | 1 (5.56) | 12 (5.69) | 5 (8.33) | 5 (6.49) | 0.902 |
| Disease | 12 (3.28) | 1 (5.56) | 4 (1.9) | 2 (3.33) | 5 (6.49) | 0.253 |
| Cerebrovascular | 14 (3.83) | 1 (5.56) | 9 (4.27) | 3 (5) | 1 (1.3) | 0.611 |
| disease | 7 (1.91) | 0 | 4 (1.9) | 1 (1.67) | 2 (2.6) | 0.905 |
| Malignancy | | | | | | |
| COPD | 13 (3.55) | 0 | 11 (5.21) | 0 | 2 (2.6) | **0.005** |
| PTB | 25 (6.83) | 1 (5.56) | 6 (2.84) | 7 (11.67) | 11 (14.29) | |
| Active | | | | | | |
| Previous | | | | | | |

non-productive cough (64%), dyspnea (72%) and fever (67%). These three symptoms were prevalent among patients with moderate to critical cases (p= <0.001) while it was less likely reported among patients with mild COVID-19 infection. Notably, dyspnea was present in more than 90% of patients who were classified under severe and critical cases. In contrast, mild COVID-19 patients were mostly asymptomatic. Other symptoms reported were body weakness, sore throat, diarrhea and myalgia, anosmia, anorexia, dysgeusia and headache.

values of less than 100 per minute.

The respiratory rate was also noted to be significantly increased in critical patients with a median value of 30 (IQR 26-35). There was no significant difference in the temperature in all the severity classification and majority of the participants were afebrile during admission.

Lowest oxygen saturation was seen in critical patients with a median value of 80%. The oxygen saturation for mild, moderate and severe cases were 98%, 95%, and 89%, respectively. Higher oxygen supports were given to critical (100%) and severe (47%) cases with median

**Table 5.** Clinical Signs and Symptoms on Admission of COVID-19 Patients According to Disease Severity

| Clinical Signs and Symptoms (on admission) | Total (n=366) | Disease severity | | | | P-value (<0.05) |
|---|---|---|---|---|---|---|
| | | Mild (n=18, 5%) | Moderate (n=211, 58%) | Severe (n=60, 16%) | Critical (n=77, 21%) | |
| Cough | | | | | | |
| Non productive | 235 (64.21) | 3 (16.67) | 139 (65.88) | 43 (71.67) | 50 (64.94) | **<0.001** |
| Productive | 59 (16.12) | 1 (5.56) | 29 (13.74) | 10 (16.67) | 19 (24.68) | |
| Dyspnea | 266 (72.68) | 4 (22.22) | 135 (63.98) | 57 (95) | 70 (90.91) | **<0.001** |
| Fever | 246 (67.21) | 4 (22.22) | 153 (72.51) | 39 (65) | 50 (64.94) | **<0.001** |
| Body Weakness | 43 (11.75) | 0 | 25 (11.85) | 8 (13.33) | 10 (12.99) | 0.447 |
| Sore throat | 31 (8.47) | 2 (11.11) | 24 (11.37) | 3 (5) | 2 (2.6) | 0.078 |
| Diarrhea | 19 (5.19) | 1 (5.56) | 16 (7.58) | 2 (3.33) | 0 | 0.069 |
| Myalgia | 19 (5.19) | 1 (5.56) | 12 (5.69) | 3 (5) | 3 (3.9) | 0.945 |
| Colds | 18 (4.92) | 4 (22.22) | 10 (4.74) | 1 (1.67) | 3 (3.9) | **0.004** |
| Anosmia | 15 (4.1) | 0 | 7 (3.32) | 6 (10) | 2 (2.6) | 0.077 |
| Fatigue | 9 (2.46) | 0 | 6 (2.84) | 0 | 3 (3.90) | 0.430 |
| Asymptomatic | 10 (2.73) | 7 (38.89) | 3 (1.42) | 0 | 0 | **<0.001** |

Table 6 shows the findings of the initial physical examination COVID-19 patients admitted in LCP. The median systolic blood pressure (SBP) measurement was significantly different among the severity classification with p value of 0.007. The median systolic BP in critical COVID-19 patients was elevated at 140mmHg as compared to mild, moderate, and severe cases with median SBP values of 129mmHg, 130mmhHg, 121mmHg respectively.

The median pulse rate was also significantly higher in critical patients, with a median value of 109 as compared to mild, moderate, and severe cases with pulse rate median values as compared to moderate and mild cases wherein most of them were stable at room air (FiO2 21%).

All of the patients enrolled in the study with the exception of the mild cases had a respiratory alkalosis with mild to moderate hypoxemia on arterial blood gas (ABG), with median values of pH 7.4 for critical and 7.46 for both severe and moderate cases. There was a decrease in the pCO2 (<36) median values for critical, severe, and moderate cases. The PF ratio was also seen significantly low among critical and severe patients with median value of 107 and 165.

**Table 6.** Vital Signs and ABG Findings of COVID-19 Patients During Admission According to Disease Severity

| | Total (n=366) | Disease Severity | | | | P-value (<0.05) |
|---|---|---|---|---|---|---|
| | | Mild (n=18, 5%) | Moderate (n=211, 58%) | Severe (n=60, 16%) | Critical (n=77, 21%) | |
| | Median (IQR) | | | | | |
| SBP | 130 (120 to 140) | 121 (120 to 137) | 130 (120 to 140) | 129 (120 to 137) | 140 (120 to 158) | **0.007** |
| DBP | 80 (70 to 88) | 80 (78 to 85) | 80 (70 to 88) | 78 (68.5 to 84.5) | 80 (70 to 90) | 0.447 |
| Pulse rate | 98 (87 to 110) | 95 (84 to 110) | 95 (86 to 105) | 99 (84.5 to 110) | 109 (98 to 119) | **<0.001** |
| Respiratory rate | 24 (21 to 28) | 20 (20 to 22) | 22 (21 to 25) | 25 (23 to 28) | 30 (26 to 35) | **<0.001** |
| Temperature | 36.5 (36.1 to 37) | 36.3 (36 to 37) | 36.5 (36.3 to 37) | 36.5 (36 to 36.7) | 36.7 (36 to 37) | 0.099 |
| O2 Saturation | 94 (87 to 97) | 98 (97 to 99) | 95 (92 to 97) | 89 (83 to 94) | 80 (60 to 89) | **<0.001** |
| *ABG on admission* | | | | | | |
| O2 support | 29 (21 to 53) | 21 (21 to 21) | 21 (21 to 32) | 47 (32 to 72) | 100 (52 to 100) | **<0.001** |
| pH | 7.46 (7.4 to 7.49) | 7.44 (7.42 to 7.5) | 7.46 (7.44 to 7.5) | 7.46 (7.43 to 7.5) | 7.4 (7.3 to 7.46) | **<0.001** |
| pCO2 | 34.7 (31 to 39.6) | 37.6 (32 to 43.6) | 34.3 (31 to 38.8) | 32 (28.5 to 37.7) | 35.9 (31.7 to 46) | **0.008** |
| HCO3 | 23.9 (22 to 26.3) | 23.85 (23 to 29) | 24.5 (22.5 to 27) | 23.6 (20.3 to 26) | 22.3 (18.6 to 25) | **<0.001** |
| pO2 | 74.3 (62.4 to 92) | 94.85 (86 to 98) | 73.2 (64 to 88.9) | 67 (56 to 83.6) | 75 (56.3 to 102) | **<0.001** |
| PF ratio | 251 (140 to 336) | 452 (408 to 465) | 303 (244 to 363) | 165 (88 to 216) | 107 (88 to 160) | **<0.001** |

Table 7 shows the association of clinical characteristics with disease severity in COVID-19 patients. The proponents of this study obtained the highest sensitivity and specificity for each significant variable including pulse rate, respiratory rate, oxygen saturation, pH and bicarbonate levels, and PF ratio. It was used as the significant cut-off value to associate with the disease severity of COVID-19.

Results of the univariate analysis showed that among the socio-demographic variables of the patients with COVID-19, older age, healthcare workers and smokers were significantly associated with the disease severity of COVID-19. Notably, the patients under 40 to 59 years old and 60 and above were have 3-fold risk and 5-fold risk, respectively, of having severe or critical COVID-19 infection. Smokers were 94.34% more likely to have severe or critical COVID-19 infection as compared to non-smoker patients.

Patients with a single comorbidity were three times more likely to have severe or

critical COVID-19 infection as compared to patients without comorbidity. Among the comorbidities present, it was shown that only hypertension and previous history of PTB were noted to have increased risk of having severe or critical COVID-19 infection.

Among the symptoms self-reported by the patients, cough and dyspnea were noted to be significantly associated with severe to critical COVID-19 infection. Those with productive cough were three to four times more likely to have severe or critical COVID-19 infection as compared to patients with dry cough and without cough. Expectedly, dyspneic patients were 8 times more likely to have severe or critical disease. In contrast, those with sore throat (70.43%) and diarrhea (81.53%) were less likely to have severe or critical COVID-19 infection.

Physical exam findings that were identified as high risk for developing severe to critical COVID-19 infection were increased in systolic blood pressure (SBP), pulse rate and respiratory rate. In relation to dyspnea, those patients who presented with tachypnea with respiratory rate of more than 25 cpm, had also higher odds of having severe or critical COVID-19 infection by 7 fold. Furthermore, it was also noted that there was a six-fold increased risk of having severe or critical COVID -19 infection for oxygen saturations below or equal to 93%. Remarkably, those patients with oxygen support of greater than 37% FiO2 were 23 times more likely to have severe to critical COVID-19 infection. A PF ratio of less than 215.3 was also significantly associated with disease severity with as much as 24 times chance to develop severe to critical COVID-19 infection.

Multivariate analysis showed that advanced age, patients with dyspnea, tachypnea with lower oxygen saturations, patients requiring higher oxygen support and those who have lower PF ratios were significantly associated with severe to critical COVID-19 infection.

The values for each parameter (i.e., dyspnea, respiratory rate, oxygen saturation, oxygen support and age) were all adjusted to determine the likelihood of having severe or critical COVID-19 infection. Dyspneic patients have a fourfold likelihood of having severe or critical COVID-19 infection after adjusting for age, respiratory rate, oxygen saturation, oxygen support and PF ratio. For every 1 cpm increase in respiratory rate above 25cpm, the odds of having severe or critical COVID-19 infection also increased by 17.47%. For every percentage increase in oxygen saturation of more than 93%, the odds of having severe or critical COVID-19 infection decreased by 6.39%. There was also an increased risk of 2.85% for every percent increase in oxygen support more than 37% FiO2. Lastly, for every unit increased in PF ratio of more than 215.3, the odds of having severe or critical COVID-19 infection decreased by 0.62%.

## DISCUSSION

COVID-19 is a new disease and there is limited information on risk factors for disease severity across different populations. This study aimed to associate the demographic and clinical characteristics of patients with disease severity of COVID-19 infection. A total of 366 patients admitted at the LCP from March 7 to August 31, 2020 were included in the study. Overall, 58% of the population were moderate cases, 21% were critical cases and 19% were severe cases. Only 5% of the mild cases were included because most of the mild cases were advised for home quarantine or were referred to other quarantine facilities.

Majority of the patients were males (n= 233, 63.44%) and the median age was 58.5 years (IQR= 54-70) which was similar in the profile of patients in the previous literatures published in Wuhan China, Lombardy Italy and New York City, USA [4,5,8,9,11]. The Center for Disease Control (CDC) identified that advanced age was shown to be associated with disease severity of COVID-19 infection [38]. In many studies, advancing age was a major independ-

**Table 7.** Association with disease severity in COVID-19 patient

| | Univariate | | | Multivariate | | |
|---|---|---|---|---|---|---|
| **Parameters** | **Crude OR** | **95% CI** | **P-value** | **Adjusted OR** | **95% CI** | **p-value** |
| **Age** | 1.0364 | 1.02 to 1.05 | **<0.001** | - | - | - |
| 19 to 39 years old | (reference) | - | - | (reference) | - | - |
| 40 to 59 years old | 3.4427 | 1.44 to 8.21 | **0.005** | 7.7895 | 1.28 to 47.2 | **0.026** |
| > 60 years | 5.1083 | 2.18 to 12 | **<0.001** | 8.1663 | 1.4 to 47.6 | **0.02** |
| **Healthcare worker** | 0.1209 | 0.03 to 0.52 | **0.004** | | | |
| **Hypertensive** | 2.1833 | 1.41 to 3.38 | **<0.001** | - | - | - |
| **PTB** | | | | | | |
| None | (reference) | - | - | - | - | - |
| Active | 0.3279 | 0.07 to 1.150 | 0.151 | - | - | - |
| Previous | 4.6374 | 1.88 to 11.4 | **0.001** | - | - | - |
| **Number of comorbidity** | | | | | | |
| Two comorbidities | 1.8105 | 0.96 to 3.42 | 0.067 | - | - | - |
| One comorbidity | 3.0735 | 1.63 to 5.81 | **0.001** | - | - | - |
| None | (reference) | - | - | - | - | - |
| **Smoking Status** | | | | | | |
| Smoker (current/ previous) | 1.9434 | 1.22 to 3.10 | **0.005** | - | - | - |
| **Cough** | | | | | | |
| Non productive | 2.4888 | 1.33 to 4.65 | **0.004** | | | |
| Productive | 3.6733 | 1.71 to 7.89 | **0.001** | | | |
| **Clinical Signs and Symptoms on Admission** | | | | | | |
| Dyspnea | 8.223 | 4.10 to 16.5 | **<0.001** | 4.1606 | 1.60 to 10.8 | **0.003** |
| Sore throat | 0.2957 | 0.11 to 0.79 | **0.015** | | | |
| Diarrhea | 0.1847 | 0.04 to 0.81 | **0.025** | | | |
| ***Physical exam during admission*** | | | | | | |
| SBP > 131 | 1.2536 | 0.82 to 1.92 | 0.301 | | | |
| Pulse rate > 101 | 2.7241 | 1.76 to 4.21 | **<0.001** | | | |
| Respiratory rate > 25 | 7.1558 | 4.46 to 11.5 | **<0.001** | 1.1747 | 1.08 to 1.28 | **<0.001** |
| O2 Saturation < 93 | 6.7347 | 4.17 to 10.9 | **<0.001** | 0.9361 | 0.90 to 0.97 | **0.001** |
| ***ABG on admission*** | | | | | | |
| O2 support > 37 | 23.246 | 13.3 to 40.6 | **<0.001** | 1.0285 | 1.01 to 1.05 | 0.01 |
| pH < 7.453 | 2.0283 | 1.32 to 3.12 | **0.001** | | | |
| HCO3 < 23.8 | 1.9683 | 1.28 to 3.03 | **0.002** | | | |
| PF ratio < 215.3 | 24.305 | 13.8 to 42.7 | **<0.001** | 0.9938 | 0.98 to 0.998 | **0.01** |

ent predictor of severity and mortality for COVID-19 [4,5,8,9,10,39]. Similarly, the result of our study using the multivariate analysis showed that advancing age was significantly associated with severe and critical COVID-19 infection. There was a 7-fold (CI 1.28,47.2, p=0.026) and an 8-fold (CI 1.4, 47.6, p=0.020) increase of having severe to critical COVID-19 infection among patients aged 40 to 59 year-old and patients aged 60 and above, respectively. This may be due to increasing medical conditions associated with advancing age, and factors like the differences in the immune system, glycation, epigenome, inflammasome activity, and biological age. The ability to control viral load was one of the prognostics of whether a patient will develop mild or severe COVID-19 symptoms. The immune system performs four main tasks like recognizing, alerting, destroying and clearing the pathogen to effectively suppress and eliminate SARS-CoV-2. In elderly, these mechanisms were known to be dysfunctional and increasingly heterogeneous and there is a gradual decline in the immune function called immunosenescence, which hampers pathogen recognition, alert signaling and clearance. Other immune system changes include chronic increase in systemic inflammation called inflammaging [40].

Majority of the population included in this study were non-smokers. Although smokers were significantly associated with the disease severity of COVID-19 infection. Using the univariate analysis, smoker patients were 94.34% more likely to have severe or critical COVID-19 infection as compared to non-smoker patients. Mild cases of COVID-19 were mostly non-smokers (83.33%). This was comparable to the findings of Constantine et. al. in his systematic review of 5 studies regarding the relationship of smoking and COVID-19. The largest study showed that current and former smokers required more ICU support and mechanical ventilation and had died. A higher percentage of smokers were also in severe cases [29]. However, this study showed that multivariate analysis did not prove that smokers had significant association with severe and critical COVID-19.

Seven percent (n=27) of the admitted patients were healthcare workers, and among them, only two were classified as severe and critical COVID cases. The low percentage of healthcare workers infected with COVID-19 may be due to the better knowledge of healthcare workers in responding to the threat of COVID-19 infection as demonstrated by the study of Limbu D. et. al. on knowledge, attitude and practices of healthcare workers in which 81.5% answered correctly the knowledge questionnaire [41].

The patients who were reported with one comorbid condition in this study were shown to have an increased chance of having severe or critical COVID-19 infection, while patients who were reported with more than one co-morbid condition did not show significant additional risk for disease severity. A nationwide analysis on the impact of comorbid condition in the outcome of COVID-19 patients was done in China and it involved 1,590 subjects [18]. Results showed that those who presented with one co-morbid condition had an increased risk for ICU admission, invasive ventilation, and death. However, their findings also reported an increase in risk for poor clinical outcome among patients who have two or more comorbid conditions which was not reflected in our study. This may be explained by the increased number of patients who self-reported with only one comorbidity during admission among those with severe and critical cases.

The presence of comorbid conditions had been identified as one of the predictors of poor outcome, severity, and mortality for COVID-19. Similarly in other reports, hypertension and DM were also identified in this study as the most common comorbid conditions among patients with COVID-19 [4,5,8,10,18,39]. The strength of association between the different comorbidities and disease severity, however, was less consistent when compared with the literature reports. For

instance, comorbid conditions including DM and COPD were identified as strong predictors for severity in other studies, however, it was not reflected in this study [4,5,10,18,38,39]. Only hypertension and previous history of PTB were shown to have increased odds of having severe or critical COVID-19 infection. Hypertensive patients were two times (p=<0.001) more likely to have severe or critical disease. This was congruent with four studies done in China (Zhou F et.al.[4], Guan WJ et.al.[10], Huang C. et.al.[17] and Liang W.H. et.al.[18)] and a study done in Italy by Grasselli G. et.al.[5] showing hypertension as the most common comorbidity seen in COVID-19. However, multivariate analysis revealed that it was not an independent predictor for disease severity. This was because the majority of the population in each disease severity had hypertension as the predominating comorbid condition across among the four severity classifications.

The prevalence of PTB was at 10.38% which was almost similar to previous reports of J.M. Leung et. al. but was twice more than the recent reports in a large meta-analysis done by Yao Gao at 0.37 to 4.47% [21,22]. Most of the patients with active TB (n=11) had moderate COVID-19 infection while majority of patients with previous PTB (n=11) had critical COVID-19. The Association of Pulmonary Tuberculosis with COVID-19 disease severity had limited data and with conflicting results. In one meta-analysis conducted by Y. Gao, et. al., PTB was associated with 2-fold risk of severe COVID-19, however it was not proven to be statistically significant [22], while a local study done by K.T.L. Sy, et. al. showed that previous and active tuberculosis was significantly associated with an increased risk of death and prolongs the recovery of patients with COVID-19 infection[23]. Another study noted that COVID-19 patients with both active or previous history of PTB had a 2.5 times higher risk and 50% risk of death respectively [24]. Similar results were also noted in the study of Sy et. al. wherein patients with previous pulmonary tuberculosis were 4 times (95% CI 1.88, 11.4, p= 0.001) more likely to have severe or critical COVID-19 infection as compared to patients without PTB. Although univariate analysis showed significant correlation of PTB with disease severity, the results of the multivariate analysis did not exhibit any significant association, probably because of the small number of patients reported in the study (n=13) which may have underestimated the actual result. Obesity was also identified as one of the predictors for severity in previous literature, however, this was not included in our parameters since the majority of the charts did not report the body mass index of the patients [38,39].

Mild cases have a short time of illness onset to hospital admission which may indicate that they sought early consultation as compared to moderate to critical cases. The patients who reported longer time from illness onset to hospital admission (median of 7 days) were associated with moderate, severe, and critical cases. Although univariate and multivariate analysis did not show any association with the disease severity.

The top three self-reported symptoms by the patients with confirmed COVID-19 infection were non-productive cough, dyspnea and fever. These three symptoms were commonly manifested by patients with moderate to critical cases as compared to mild cases which was comparable with the reports in other literatures [4,9,10,17,42]. Among these three prominent symptoms, dyspnea was reported by more than 90% of the patients classified under the severe and critical category. Those reporting dyspnea as an initial symptom were significantly associated with higher odds (OR:4, CI 1.6,10.8, p=0.003) of having severe and critical cases as compared to those who did not. This was similarly reported by Jiang Xie et. al. and Lang Wang et. al. in their study wherein dyspnea was identified as an independent predictor for mortality in patients with COVID-19 [9,42]. Extensive inflammation of the bilateral and respiratory bronchioles in patients with COVID-19 infection due to excessive activation of pro-inflammatory

cytokines and chemotactic aggregation of T-lymphocytes at the site of inflammation were possible mechanisms which underlie chest distress and dyspnea among infected patients. Continuous and unresolved dyspnea often indicates the progression of lung lesions [43].

Adjusted logistic regression analysis showed that physical examinations that had higher odds of having severe or critical COVID-19 infection were increased SBP, pulse rate, respiratory rate, oxygen support requirement and decreased oxygen saturation. A study done in London showed that among the physical examination findings, body temperature of more than 38°C has the strongest association with increased mortality among COVID-19 patients while pulse rate, respiratory rate, and BP did not show any association with disease severity [44]. As reported in other studies, fever was one of the common presentations of COVID-19 infection [4,5,8,9,10,44]. However, most of the patients in our study were afebrile during admission and our results did not show significant association with disease severity as compared to what were seen from other reports.

All moderate to critical patients enrolled in the study had respiratory alkalosis with mild to moderate hypoxemia on ABG, however, it did not show significant association. Oxygen saturations of ≥ 94% among COVID-19 patients notably decreased the odds of having severe or critical COVID-19 infection after adjusting for dyspnea, respiratory rate, age, oxygen support and PF ratio. The result of our study was somehow similar to the study by Xie Jiang et. al. which demonstrated that higher $SpO_2$ levels after oxygen supplementation were associated with reduced mortality independently regardless of age and sex (hazard ratio per 1 unit SpO2, 0.93; 95% CI, 0.91, 0.95; p=<.001) [42]. Hence, it was prudent to maintain higher oxygenation saturation of more than 93% among COVID-19 patients. It was also noted that an increased PF ratio had decreased the odds of having severe or critical COVID-19 infection while a decreased PF ratio of less than 215 was associated with increased risk of severe to critical COVID-19. This was supported by other study which showed a low $PaO_2/FiO_2$ ratio ≤200 mmHg as one of the independent risk factors for mortality (HR 3.57; 95% CI 2.20, 5.77, p<0.0001) and the in-hospital mortality proportionally increased with increasing impairment of gas exchange (p<0.001) [42]. The inflammatory process in COVID-19 causes a hypercoagulable state that results in microvascular thrombosis creating a dead space with reduced or absent pulmonary capillary flow leading to a high ventilation/perfusion(V/Q) ratio. The overt inflammatory process in COVID-19 cause capillary hyperperfusion and uneven distribution of capillary perfusion cause VQ mismatched and hypoxemia. Precapillary shunts cause a decreased or absent capillary perfusion leading to hypoxemia.The said mechanisms may contribute to hypoxemia, low P/F ratios, and high A-a gradient seen in COVID-19. Hypoxemia leads to the stimulation of the peripheral and central chemoreceptors which cause increased respiratory drive and thus increased respiratory rate (RR).[45] Increased RR was a sign of hypoxemia, therefore, it is important to maintain a higher PF ratio among COVID-19 patients, while a decreasing PF ratio should alert clinicians to be aggressive with the management to avoid fatal outcomes [45].

## LIMITATIONS

Our study has some notable limitations. This was a cross-sectional study design which involved a retrospective chart review, with all information based on what was recorded on the chart. Hence, some vital information might be omitted, thus we may have missed important associations with disease severity. Another limitation of this study was self-reporting of comorbidities and symptoms on admission. Self-reporting of comorbidities and symptoms could be underestimated due to lack of awareness and/or the lack of diagnostic testing, which may contribute to the underestimation of the true strength of association with the severity of COVID-19 infection.

## CONCLUSION

This study showed that advanced age, dyspnea, tachypnea and increase in oxygen support requirement were significantly associated with disease severity of COVID-19. Higher oxygen saturations and PF ratios were significantly associated with decreased odds of having severe or critical COVID-19 infection. Hence, clinicians should always be mindful of these contributing factors to recognize the disease severity of COVID-19 during initial evaluation and to enable them to give immediate appropriate measures and avoid poor outcomes with these patients.

## RECOMMENDATION

The proponents of this study recommend that factors such as advanced age, dyspnea, tachypnea, and increased in oxygen support requirement, oxygen saturations, and PF ratios which were associated with more severe COVID-19 be closely monitored during the initial evaluation of patients at the emergency room department to immediately recognize severe and critical cases and provide personalized management.

## REFERENCES


1. Yi-Chi Wua, Ching-Sung Chena, Yu-Jiun Chana et al. The outbreak of COVID-19: An overview. *J Chin Med Assoc.*
2. WHO announces COVID-19 outbreak a pandemic. March 2020. http://www.euro.who.int/en/health-topics/health-emergencies/coronavirus-covid-19/news/news/2020/3/who-announces-covid-19-outbreak-a-pandemic
3. https://coronavirus.jhu.edu/
4. Zhou F, Yu T, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet.* 2020; 395: 1054–62.
5. Grasselli G, Zangrillo A, et al. Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy. *JAMA*. 2020;323 (16):1574–1581. doi:10.1001/jama.2020.5394
6. Li L, Huang T, et al. COVID-19 patients' clinical characteristics, discharge rate, and fatality rate of meta-analysis. *J Med Virol*. 2020;1–7. https://doi.org/10.1002/jmv.25757
7. Kim ES, Chin BS, et al. Clinical Course and Outcomes of Patients with Severe Acute Respiratory Syndrome Coronavirus 2 Infection: a Preliminary Report of the First 28 Patients from the Korean Cohort Study on COVID-19. *J Korean Med Sci*. 2020;35(13):e142. 2020. doi:10.3346/jkms.2020.35.e142
8. J Richardson, J Hirsch, et al. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. *JAMA*. doi:10.1001/jama.2020.6775
9. Wang, L. He, W, et al. Coronavirus disease 2019 in elderly patient's: Characteristics and prognostic factors based on 4-week follow-up. *The Journal of infection*. 80(6), 639–645. https://doi.org/10.1016/j.jinf.2020.03.019
10. Guan WJ, Ni ZY, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med.* 2020;382 (18):1708-1720. doi:10.1056/NEJMoa2002032
11. WHO. World Health Organization Clinical Management Guidance: Interim Guidance. May 18, 2020. https://
12. www.worldometers.info/coronavirus/
13. He, F, Deng, Y, Li, W. Coronavirus disease 2019: What we know? *J Med Virol.* 2020; 1– 7. https://doi.org/10.1002/jmv.25766
14. Channappanavar, R., Fett, C., Mack, M., Ten Eyck, P. P., Meyerholz, D. K., & Perlman, S. Sex-Based Differences in Susceptibility to Severe Acute Respiratory Syndrome Coronavirus Infection. *Journal of immunology (Baltimore, Md. : 1950)*. 2017. 198 (10), 4046–4053.

15. Marjolein F. Q. Kluytmans-van den Bergh, et al. Prevalence and Clinical Presentation of Health Care Workers With Symptoms of Coronavirus Disease 2019 in 2 Dutch Hospitals During an Early Phase of the Pandemic. *JAMA Network Open.* 2020;3(5):e209673. doi:10.1001/jamanetworkopen.2020.9673 May 21, 2020
16. Xiaoquan L, Minghuan W, et al. Coronavirus Disease 2019 (COVID-2019) Infection Among Health Care Workers and Implications for Prevention Measures in a Tertiary Hospital in Wuhan. *China JAMA Netw Open.* 2020;3(5):e209666. doi:10.1001/jamanetworkopen.2020.9666
17. Huang C, Wang Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet.* 2020;395(10223):497-506. Epub 2020/01/28.
18. Guan WJ, Liang WH, et al. Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. *Eur Respir J.* 2020;55(5):2000547. Published 2020 May 14. doi:10.1183/13993003.00547-2020
19. Gémes, K, Talbäck, M, et al. Burden and prevalence of prognostic factors for severe COVID-19 in Sweden. *Eur J Epidemiol.* 35, 401–409 (2020). https://doi.org/10.1007/s10654-020-00646-z
20. Pennington, E. Asthma increases risk of severity of COVID-19 [published online ahead of print, 2020 May 5]. *Cleve Clin J Med*. 2020;10.3949/ccjm.87a.ccc002. doi:10.3949/ccjm.87a.ccc002
21. Leung JM, Yang CX, COVID-19 and Nicotine as a Mediator of ACE-2 [published online ahead of print, 2020 Apr 29]. *Eur Respir J.* 2020;2001261. doi:10.1183/13993003.01261-2020
22. Gao, Y, Liu, M, Chen, Y, Shi, S, Geng, J, Tian, J. , Association between tuberculosis and COVID-19 severity and mortality: A rapid systematic review and meta-analysis. *J Med Virol.* 2020. https://doi.org/10.1002/jmv.26311
23. Sy, K, Haw, N, Uy, J. Previous and active tuberculosis increases risk of death and prolongs recovery in patients with COVID-19. 2020. *Infectious Diseases*. 52:12, 902-907, DOI: 10.1080/23744235.2020.1806353
24. Western Cape: COVID-19 and HIV/tuberculosis 2020. Available from: https://storage.googleapis.com/stateless-bhekisisa-website/wordpress-uploads/2020/06/94d3ea42-covid_update_bhekisisa_wc_3.pdf
25. Li X, Xu S, et al. Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan [published online ahead of print, 2020 Apr 12]. J *Allergy Clin Immunol.* 2020;S0091-6749(20)30495-4. doi:10.1016/j.jaci.2020.04.006
26. Brake SJ, Barnsley K. Smoking Upregulates Angiotensin-Converting Enzyme-2 Receptor: A Potential Adhesion Site for Novel Coronavirus SARS-CoV-2 (Covid-19). *J Clin Med*. 2020;9(3):841. Published 2020 Mar 20. doi:10.3390/jcm9030841
27. Liu W, Tao ZW, Wang L, et al. Analysis of factors associated with disease outcomes in hospitalized patients with 2019 novel coronavirus disease. *Chin Med J.* 2020 May 5;133(9):1032-1038. doi: 10.1097/CM9
28. Vardavas C, Nikitara, K, et al. COVID-19 and smoking: A systematic review of the evidence. *Tobacco Induced Diseases.* Published March 20, 2020 DOI: https://doi.org/10.18332/tid/11932
29. Miyara, Makoto et.al. Low incidence of daily active tobacco smoking in patients with symptomatic COVID-19 infection. 2020. *Qeios.* 10.32388/WPP19W.
30. Zhu J, Zhong Z, et al. Clinicopathological characteristics of 8697 patients with COVID-19 in China: a meta-analysis [published correction appears in Fam Med Community Health. 2020 May;8(2):]. *Fam Med Community Health*. 2020;8(2):e000406. doi:10.1136/fmch-2020-000406

31. Bezuidenhout M,Wiese O, et al. Correlating arterial blood gas, acid–base and blood pressure abnormalities with outcomes in COVID-19 intensive care patients. 2020. *PubMed.* https://doi.org/10.1177/0004563220972539
32. Force ADT, Ranieri VM, et al. Acute respiratory distress syndrome: the Berlin Definition. *JAMA.* 2012;307(23):2526-33. Epub 2012/07/17.
33. Ferguson, N.D, Fan, E, et al. The Berlin definition of ARDS: an expanded rationale, justification, and supplementary material. *Intensive Care Med.* 38, 1573–1582 (2012). https://doi.org/10.1007/s00134-012-2682-1
34. Kasper DL, Fauci AS, et al, editors. Harrison's principles of internal medicine, 20th ed. New York: The McGraw-Hill Companies, Inc.; 2018. Available from: http://www.accesspharmacy.com.
35. Brown, M, Grissom, K, et al. Nonlinear Imputation of Pao2/Fio2 From Spo2/Fio2 Among Patients With Acute Respiratory Distress Syndrome. 2016. *Chest.* 150(2), 307–313. https://doi.org/10.1016/j.chest.2016.01.003
36. Pisani, L, Roozeman, et.al. Risk stratification using SpO2/FiO2 and PEEP at initial ARDS diagnosis and after 24 h in patients with moderate or severe ARDS. *Annals of intensive care*. 7(1), 108. 2017. https://doi.org/10.1186/s13613-017-0327-9
37. Chen, W, Janz, R, Shaver, M, Bernard, R, Bastarache, A, & Ware, B. Clinical Characteristics and Outcomes Are Similar in ARDS Diagnosed by Oxygen Saturation/Fio2 Ratio Compared With Pao2/Fio2 Ratio. *Chest.* 2015. 148(6), 1477–1483. https://doi.org/10.1378/chest.15-0169
38. CDC. Coronavirus Disease 2019 (COVID-19). Centers for Disease Control and Prevention. https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019-ncov%2Fneed-extra-precautions%2Fgroups-at-higher-risk.html. Published June 25, 2020. Accessed June 27, 2020.
39. Gallo Marin, B, Aghagoli, G, Lavine, K, et al. Predictors of COVID-19 severity: A literature review. *Rev Med Virol.* 2020;e2146. https://doi.org/10.1002/rmv.2146
40. Mueller A, McNamara M, et al. Why does COVID-19 disproportionately affect older people? *Aging (Albany NY).* 2020 May 31; 12(10): 9959–9981. Published online 2020 May 29. doi: 10.18632/aging.103344
41. Limbu D, Piryani R, et al. Healthcare workers' knowledge, attitude and practices during the COVID-19 pandemic response in a tertiary care hospital of Nepal Published: November 6, 2020 https://doi.org/10.1371/journal.pone.0242126
42. Xie J, Covassin N, et al. Association between hypoxemia and mortality in patients with COVID-19. *Mayo Clin Proc*. 2020;95(6): 1138-1147. https://doi.org/10.1016/j.mayocp.2020.04.006.
43. Shuke Nie et al. Coronavirus Disease 2019-related dyspnea cases difficult to interpret using chest computed tomography Respiratory Medicine April 2020 167:105951 DOI: 10.1016/j.rmed.2020.105951
44. Pablo, N, et al. Clinical Characteristics and Predictors of Outcomes of Hospitalized Patients With Coronavirus Disease in a Multiethnic London National Health Service Trust: A Retrospective Cohort Study. *Clinical Infectious Diseases.* 2019 https://doi.org/10.1093/cid/ciaa1091
45. Nitsure M, et al. Mechanisms of Hypoxia in COVID-19 Patients: A Pathophysiologic Reflection. *Indian J Crit Care Med.* 2020 Oct; 24(10): 967–970. doi: 10.5005/jp-journals-10071-23547

# Impact of COVID-19 Pneumonia on Pulmonary Function, Radiology and Quality Of Life in a Cohort of Survivors

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PAPER PRESENTED IN THE FOLLOWING CONFERENCES: Philippine College of Chest Physicians (PCCP) Research Contest March 2021 (Consolation Prize Winner, Original Research Category) and Poster Presentation at European Respiratory Society (ERS) International Congress September 2021 (Consolation Prize Winner)

## ABSTRACT

**BACKGROUND:** The extent and severity of the long-term respiratory complications of COVID-19 infection remains to be ascertained, but emerging data reveals that many patients experience persistent respiratory symptoms months after their initial illness and also had imaging abnormalities such as pulmonary fibrosis and impaired lung function weeks after being discharged. Given that persisting imaging abnormalities correlate with physiological impairment, it is likely that these patients are at a greater risk of long-term parenchymal lung disease in whom closer follow-up and further investigation are indicated.

**OBJECTIVE:** To report the pulmonary function and chest CT changes in this cohort of survivors in correlation with their symptoms .

**METHODS:** We conducted a single-centered retrospective analysis on an original cohort of 19 survivors who underwent chest CT-scan upon admission and 10-12 weeks upon discharge. The study included the measurement of static and dynamic lung volumes, determination of the diffusing capacity of the lung for carbon monoxide (DLCO), and a health status evaluation using the St. George Respiratory Questionnaire (SGRQ) during follow-up .

**RESULTS:** Study has shown that significant radiographic and alterations in lung functions, with mainly restrictive pattern in severe illness group (decrease DLCO and total lung capacity), still existed in a proportion of COVID-19 patients 3 months after discharge. There is a positive correlation between the CT scores and SGRQ scores suggesting that the higher the inflammatory load as evidenced on CT, the more symptomatic the patient was. On the other hand, there was a negative correlation between pulmonary function test and SGRQ as well as CT scores. The higher the CT scores and SGRQ scores, the lower the pulmonary function predicted .

**CONCLUSION:** After three months of recovery from COVID-19 pneumonia, the lung functions are affected in terms of minor diffusion defect and restrictive lung impairment. The aberration might be connected to the COVID-19's severity. As a result, it is advised that post-COVID-19 survivors, particularly those who suffered from severe illness, have long-term follow-up .

**KEYWORDS:** *COVID-19, pulmonary fibrosis, pulmonary function, DLCO, health status, SGRQ*

## INTRODUCTION

The first report of a novel respiratory virus emerged from Wuhan, China on December 2019 and was shown to be a coronavirus causing severe acute respiratory syndrome.[1] The highly transmissible virus spread rapidly and on 11 March 2020, coronavirus disease 2019 (COVID-19) was declared a global pandemic by the World Health Organization. As of December 2020, more than 68 million cases have been confirmed worldwide with 1.5 million reported deaths.[2]

COVID-19 due to SARS-CoV-2 may have multiple organ failure and lung injury is one of the most common clinical manifestations. The entry route of SARS-CoV-2 into the human cells is mainly facilitated by the angiotensin-converting enzyme-2 (ACE2) receptors, which seems to be expressed by type 2 pneumocytes. The binding of SARS-CoV-2 to the ACE2 receptors could arise into acute systemic inflammatory responses and cytokine storm, consequently leading to lung-resident dendritic cells (rDCs) activation, to produce T lymphocytes and release antiviral cytokines into the alveolar septa and interstitial compartments. However, the knowledge about the sequelae of SARS-CoV-2 infection remains limited.[3]

In light of the widely documented lung injuries related with COVID-19, concerns are raised regarding the assessment of the lung injury for discharged patients. Predicting the likely respiratory consequences of COVID-19 is challenging but reviewing data from this and other coronavirus infections provide insights. The optimal time for follow-up imaging to assess for radiological clearance in COVID-19 is unknown. Retrospective study showed that many patients had imaging abnormalities when discharged, a few patients even had pulmonary fibrosis.[4] A recent report showed that discharged patients with COVID-19 pneumonia still has residual abnormalities in chest CT scans, with ground-glass opacity as the most common pattern. The rate of radiological abnormalities (74.55%) is lower than that reported in an earlier study (83%) over 7 days after admission.[5] The lung pathology of fatal COVID-19 was dominated by diffuse alveolar damage with fibrin rich hyaline membranes and a few multinucleated giant cells. The aberrant wound healing may lead to severe scarring and fibrosis. The patchy glass opacification classically observed in COVID-19 pneumonia is, however, much less suspicious of harboring a malignancy, particularly in the context of a pandemic.[6]

A 6-week follow-up chest x ray is, therefore, not advised and the 12-week time point is considered to be optimal in providing sufficient time for imaging resolution while also ensuring that non-resolving changes are addressed sufficiently early. Guidelines published by the British Thoracic Society recommends chest radiography three months after discharge for all admitted COVID-19 patients, especially for those with a history of moderate or severe disease, with persisting symptoms.[7] If patients with COVID-19 pneumonia recover similarly like those with Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS), it is envisaged that at 12 weeks post-discharge, approximately 65% of these patient had full CXR resolution.[8]

The post-hospitalization COVID-19 study in the United Kingdom (UK) aims to recruit 10,000 patients to identify the medical, psychological, and rehabilitation needs of patients admitted to hospital with COVID-19 and to provide a comprehensive picture of the longer term effects of infection.[9] among survivors and non-survivors. This will help identify preventable causes of death among patients with COVID-19 and also prognosticate patients with advanced disease.

Given that persisting imaging abnormalities correlate with physiological impairment, it is likely that these patients are at a greater risk of long-term parenchymal lung disease necessitating closer follow-up and further investigation. Persistent impairment of pulmonary function and exercise capacity have been

known to last for months or even years in the recovered SARS and MERS survivors. However, post discharge imaging or lung functional data are limited for COVID-19 survivors. Preliminary evidence suggests that impaired lung function in coronavirus pneumonia could last for several months or even years, with the impairment of diffusing capacity (DLCO) as the most common abnormality followed by decreased in total lung capacity.[10]

The extent and severity of the long-term respiratory complications of COVID-19 infection remains to be seen, but emerging data indicate that many patients experience persistent respiratory symptoms months after their initial illness.

As effective vaccines and treatments for SARS-Cov-2 emerge, a key objective will be to identify and proactively manage complications from the infection and support patients through the recovery phase with the goal of preserving their health status. Few reports have described the sequelae of COVID-19 survivors, and until now, no study has reported early prognosis in relation to the degree of lung injury and rehabilitation in patients with COVID-19. To the best of our knowledge, this is the first local study to investigate the long term effects on changes in both pulmonary function, CT imaging, and health status in patients with COVID-19. Such data will allow the design of appropriate follow-up protocols in a healthcare system with large waiting lists and limitations on face-to-face appointments. There is a need for a unified pathway for the respiratory follow-up of patients with COVID-19 and balancing the delivery of high-quality clinical care with stretched resources. In this guidance document, it will help provide a suggested structure to achieve these aims with a focus on the respiratory follow-up of patients with clinico-radiological confirmation of COVID -19 pneumonia.

## OBJECTIVES

To report the pulmonary function and chest CT changes in this cohort of survivors 12 weeks post discharge in correlation with their symptoms and to compare severe patients with non-severe patients by outcome parameters.

## METHODS

### Study Design, Target Population, Inclusion & Exclusion Criteria

The study was an observational cohort study of all COVID-19-confirmed patients admitted at Cardinal Santos Medical Center from March to September 2020. In all patients, nasopharyngeal and oropharyngeal swabs were collected, followed by RT-PCR assay to confirm the diagnosis. It was a single-centered retrospective analysis conducted on an original cohort of 19 survivors who underwent chest CT scan upon admission and 10-12 weeks upon discharge and whose follow-up pulmonary function test was done as well. The outcome included the measurement of static and dynamic lung volumes, the determination of the diffusing capacity of the lung for carbon monoxide, and a health status evaluation using the St. George Respiratory Questionnaire (SGRQ) during follow up as well along with the repeat CT scan. Charts with incomplete data and those who died due to COVID-19 or any reason during admission and on follow-up were excluded from the study.

### Sampling Scheme

Purposive sampling was used. All patients, male and female, who fulfill the inclusion criteria were included in the study. The protocol was submitted to the Research Center and Research Ethics Review Committee for technical & ethical review. Request approval to collect medical records from the Radiology Department and Pulmonary Unit was done. Data collection was done via chart and image review of chest CT scan of patients. A self-administered questionnaire was sent online. All data collected will be confidential and typed into a password-protected computer. Only the researcher has access to the patient's data. Data was encoded without the patients' names. Electronic data will be kept for 5 years and then deleted thereafter.

### Disease Severity

Disease severity was categorized among the population group stated in the WHO interim guidance[2], as mild illness (i.e., mild symptoms without radiographic appearance of pneumonia), moderate pneumonia (i.e., having symptoms and the radiographic evidence of pneumonia, with no requirement for supplemental oxygen), severe pneumonia (i.e., having pneumonia, including one of the following: respiratory rate > 30 breaths/minute; severe respiratory distress; or SpO2 ≤ 93% on room air at rest), or critical cases (i.e., respiratory failure requiring mechanical ventilation, septic shock, other organ failure occurrence or admission into the ICU).

### Lung Function Testing

Pulmonary function tests (PFTs) were performed by respiratory therapists in the Pulmonary Unit of Cardinal Santos Medical Center. Spirometry was performed in accordance with recommended standards. The following parameters were measured by means of the single-breath test: forced vital capacity (FVC), forced expiratory capacity at the first second of exhalation (FEV1), total lung capacity (TLC), and diffusion capacity of the lung for carbon monoxide (DLCO). All PFT measurements were expressed as percentages of predicted normal values. Diffusion deficit was considered as DLCO < 80% of predicted value. To protect lung function laboratory staff, extra exhaust fans were installed in the lung function room and staff wore personal protective equipment such as N95 respirators, protective goggles, gloves, and gowns.

### Health Status Measurement

All of the eligible patients completed the Singapore-English version of the SGRQ. The SGRQ is a standardized, self-administered, pulmonary-specific health status questionnaire containing 50 items and 76 weighted responses that is divided into three subscales: (1) symptoms (8 items); (2) activity (16 items); and (3) impacts (26 items). SGRQ scores were calculated using score calculation algorithms and missing data imputation recommended by its developer. For each subscale and for the overall questionnaire, scores range from 0 (no impairment) to 100 (maximum impairment). Mean scores obtained from a sample of persons (n = 74) between 17 and 80 years of age (mean age, 46 years) who had no history of respiratory disease (mean FEV1, 95%) served as reference values.[11]

### Radiologic Findings

A radiologist who was blinded to the clinical data, reviewed all the chest CT images. Chest CT images were scored according to the pulmonary inflammation index (PII). Each of the five lung lobes was assessed for degree of involvement and classified either as none (0%), minimal (1%–25%), mild (26%–50%), moderate (51%–75%), or severe (76%–100%). No involvement corresponded to a lobe score of 0, minimal involvement to a lobe score of 1, mild involvement to a lobe score of 2, moderate involvement to a lobe score of 3, and severe involvement to a lobe score of 4. An overall lung "total severity score" was reached by summing the five lobe scores (range of possible scores, 0–20). Additional scores consisted of presence of consolidation, presence of pleural effusion, presence of lymphadenopathy (>10mm) and presence of fibrosis. The higher the value, the heavier the inflammatory load.

### Outcome Measures

Continuous variables were described using mean with standard deviation (SD) or median with interquartile range (IQR), followed by unpaired T-test or Mann-Whitney test. Categorical variables were described as percentage and compared using the Chi-square test. The correlation of different variables were analyzed using Spearman's correlation. The conventional level of statistical significance of 0.05 was used for all analyses. Statistical analysis was performed using STATA Version 15.1.

### Ethical Considerations

Individual patient records and all data collected were kept confidential. There is no

conflict of interest for the author. A waiver of informed consent was submitted to the RERC since this study entails record review with no interaction with the patient. Vulnerability, recruitment, and assent are not applicable. There are no risks, benefits, and compensation for the participants. The study abided by the principles of the Declaration of Helsinki 2013 and conducted along the guidelines of the International Conference of Harmonization and Good Clinical Practice.

## RESULTS

One hundred eighty six survivors were evaluated for this study. One hundred fifty four patients were excluded due to the following reasons: 125 had no CT scan upon admission or upon follow-up, 4 had no PFT on follow-up, 22 were lost to follow-up, and 3 died. Only 19 had CT scan done at 10-12 weeks after hospital discharge out of the 32 remaining patients. Baseline characteristics of the patients included in the study were summarized in Table 1.

Table 2 showed the pulmonary function variable of patients that were studied. FEV1 and FVC were similar for both groups. The average TLC and DLCO were lower in the severe illness group compared to the moderate illness group though it was not statistically significant, however, it was significant at 0.10 in terms of DLCO. Number of patients whose TLC and DLCO with <80% of predicted were significantly higher in the severe illness group ($p < 0.05$).

CT scan at the time of the recovery showed persistent ground glass opacities in 15 patients but most of them had CT scores of <5, hence, mean CT score difference was statistically significant (Table 3). All of the 6 patients in the severe illness group developed pulmonary fibrosis, while 6 out of 9 patients from the moderate illness group were noted to have fibrosis as well on follow up scan. Nevertheless, an overall improvement in CT scores after 10-12 weeks after discharge was observed. Symptoms, on the other hand, were common at follow-up, with all the patients both from the moderate and severe illness group reporting at least one ongoing symptom since discharge from hospital. Most common of which were cough and breathlessness

**Table 1.** Demographics of COVID-19 survivors studied

| | Moderate Illness (n=12) | | Severe/Critical Illness (n=6) | |
|---|---|---|---|---|
| Age | 55 (37-92) | | 67 (44-83) | |
| | Frequency | % Frequency | Frequency | % Frequency |
| <60 y/o | 7 | 58 | 2 | 33 |
| >60 y/o | 5 | 42 | 4 | 67 |
| Sex | | | | |
| Male | 7 | 58 | 4 | 67 |
| Female | 5 | 42 | 2 | 33 |
| Comorbidities | | | | |
| Hypertension | 5 | 42 | 6 | 100 |
| Diabetes Mellitus | 2 | 17 | 4 | 67 |
| Bronchial Asthma/COPD | 2 | 17 | 1 | 17 |
| Cancer | 0 | 0 | 1 | 17 |
| Smoker | 3 | 25 | 2 | 33 |
| Average Number of Hospital Days | 11 (4-18) | | 24 (10-58) | |
| Intubated | N/A | | 2 | 33 |
| High Flow Nasal Cannula | N/A | | 4 | 67 |

**Table 2.** Pulmonary function test at 10-12 weeks after discharge

| | Moderate (N=12) | | | Severe (N=6) | | | p value (Mean) | p value (Frequency) |
|---|---|---|---|---|---|---|---|---|
| | Mean | SD (95% CI) | No. of Patients with <80% Predicted (% Frequency) | Mean | SD (95% CI) | No. of Patients with <80% Predicted (% Frequency) | | |
| FEV1 | 98 | 17 (89-107) | 2 (17) | 98 | 20 (76-119) | 1 (17) | 0.98 | 1 |
| FVC | 95 | 12 (87-102) | 1 (8) | 87 | 11 (74-99) | 1 (17) | 0.21 | 0.596 |
| TLC | 97 | 19 (85-109) | 1 (8) | 83 | 19 (63-103) | 3 (50) | 0.17 | 0.045 |
| DLCO | 88 | 18 (72-92) | 3 (25) | 71 | 15 (54-88) | 4 (67) | 0.07 | 0.009 |

**Table 3.** CT score difference and SGRQ score at 10-12 weeks after discharge

| | Moderate (N=12) | | Severe (N=6) | | p value |
|---|---|---|---|---|---|
| | Mean | SD (95% CI) | Mean | SD (95% CI) | |
| CT Score Difference | 4.75 | 4.2 (5.7-14.6) | 10.2 | 2.6 (3.1-6.4) | 0.0037 |
| SGRQ score | 19 | 10 (12-26) | 17 | 3.4 (13-20) | 0.61 |

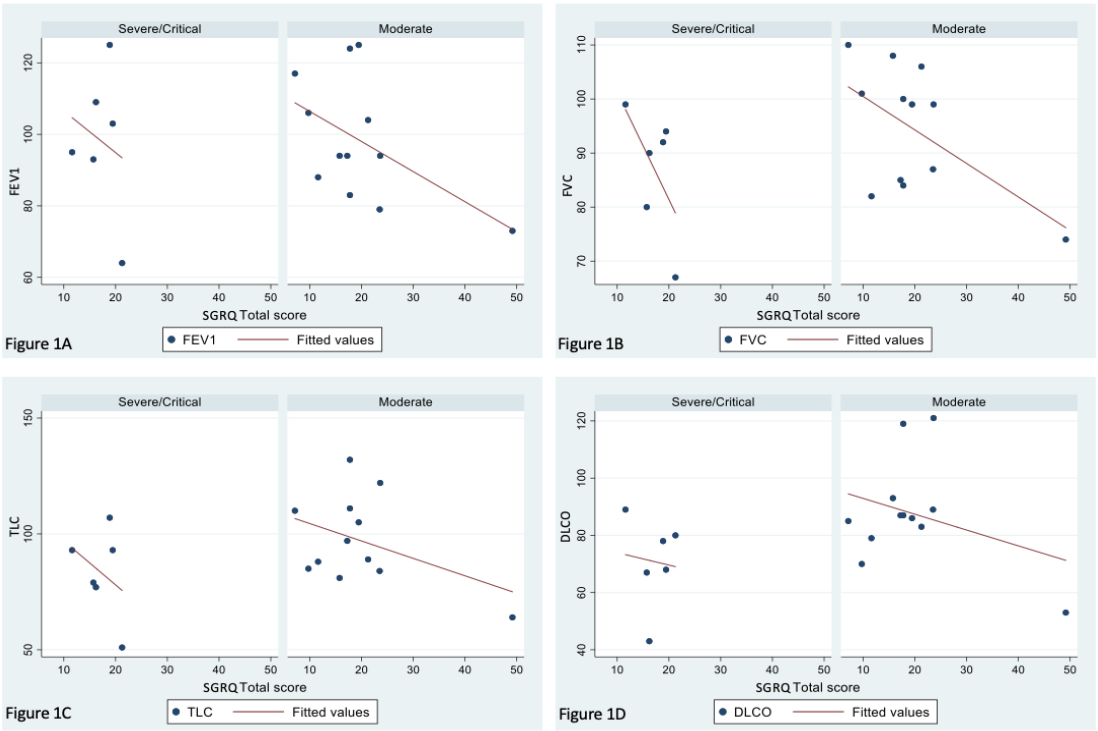


**Figure 1.** Scatter plot analysis for SGRQ score 10-12 weeks after discharge with pulmonary function: FEV1% predicted (A), FVC predicted (B), TLC% predicted (C), and DLCO% predicted (D).

upon activity. No difference in scores was seen between the moderate and severe illness group.

Correlation coefficient was computed to assess the relationship between the PFT and SGRQ scores. For the moderate illness group, there was a strong negative correlation seen between FEV1 (52%), FVC (57%) and moderate negative correlation on TLC (42%) and DLCO (32%) with the SGRQ scores. On the other hand, there was a moderate negative correlation seen between FEV1 (20%) and TLC (34%); weak negative correlation on DLCO (9%) and strong correlation on FVC (59%) with SGRQ scores in the severe illness group. Overall, there was a negative correlation between these two variables, meaning the lower the lung function, the higher the SGRQ score as seen in Figures 1a-1d. There appears to be 2 outliers in the data of the moderate illness group.

Scatter plot analysis between the PFTs and CT scores also showed a negative correlation between these two variables as shown in Figures 2a-2d. For the severe illness group, there was a strong correlation between FEV1 (68%), FVC (73%) and TLC (87%) and weak correlation on DLCO (17%) with the CT scores on follow-up. On the other hand, there was moderate correlation on FVC (29%), TLC (43%) and DLCO (34%) and weak correlation on FEV1 (2%) with the CT scores on follow up in the moderate illness group. Overall, the higher the CT score, the lower the lung function test was observed for both groups.

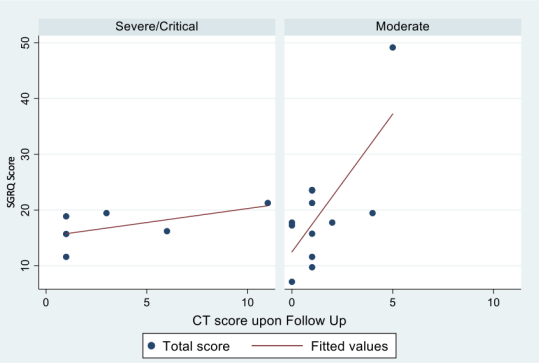


**Figure 3.** Scatter plot analysis for SGRQ score with CT score 10-12 weeks after discharge

CT scores on follow up were observed to have strong positive correlation with the SGRQ scores both for the moderate illness group (73%) and severe illness group (59%) as shown in Figure 3. The higher the inflammatory load as evidenced on CT, the more symptomatic the patient was.

## DISCUSSION

Severe COVID-19 leads to acute respira-

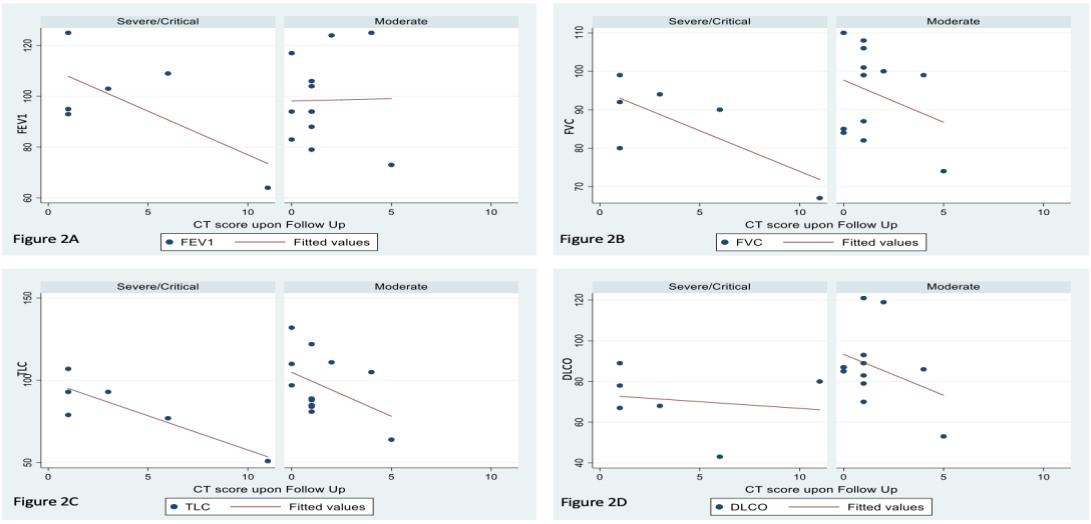


**Figure 2.** Scatter plot analysis for CT score 10-12 weeks after discharge with pulmonary function: FEV1% predicted (A), FVC predicted (B), TLC% predicted (C), and DLCO% predicted (D).

tory distress syndrome. Significant injury to type II alveolar epithelial cells induces pulmonary fibrosis through cytokine storm and immunopathology. The radiological changes in COVID-19 pneumonia do not appear to resolve fully in all patients but significantly improved as shown in our study.[12]

A significant proportion not only have CT evidence of residual pulmonary fibrosis but also functional impairment. The study by Mo et al. with a 110 COVID-19 patients demonstrated that at discharge, 91 (83%) of whom had a mild–moderate disease and 19 (17%) of whom had severe disease, almost half had impairment of the transfer factor of the lung for carbon monoxide.[10] In a study done by Huang et al. with fifty-seven patients who completed the serial assessments 1 month after hospital discharge, abnormalities were detected in the PFTs of 43 (75.4%) patients.

Six (10.5%), 5(8.7%), 25(43.8%) 7 (12.3%), and 30 (52.6%) patients had FVC, FEV1, FEV1/FVC ratio, TLC, and DLCO values less than 80% of predicted values, respectively. Thirty-one patients (54.3%) had abnormal CT findings.[13] At 3-months after discharge, residual abnormalities of pulmonary function were observed in 25.45% of the cohort in the study by Zhou et al, mostly demonstrating diffusion reductions in DLCO similar to our study.[14] Recovered patients with coronavirus pneumonia can be left with damaged lungs as seen on CT scan findings with pulmonary fibrosis. COVID-19 pneumonia may result in significant alterations in lung function, with a mainly restrictive pattern, partly persisting at 6 weeks after recovery. The DLCO was lower in patients with severe disease and was more sensitive to disease severity than other lung function measures such FVC and FEV1.

Another striking finding is the persistence of symptoms relating to COVID-19 more than two months after the onset of hospitalization, despite the improvement in radiological parameters. Critical illness, muscle weakness and deconditioning are likely to be the contributing factors. The persistence of symptoms following COVID-19 infection is widely reported in the media and several studies have shown that across the cohort, nearly three-quarters of patients had ongoing symptoms on questioning. Shortness of breath and excessive fatigue were the most predominant. In a study of patients discharged from an Italian hospital at a median of 60 days post discharge, patients were asked to recall their admission symptoms and health-related quality of life. It was found that 87% had at least 1 ongoing symptom with fatigue (53%) and shortness of breath (43%) predominating, similar to our study.[15,16] Though symptomatic, clinical abnormalities requiring action are infrequent. However, these patients should still be monitored for any changes in condition and symptoms over a longer period.

## CONCLUSION

This research has demonstrated that significant radiographic and alterations in lung functions, with a mainly restrictive pattern (i.e., decrease DLCO and TLC), still existed in a proportion of COVID-19 patients 3 months after discharge especially in the severe or critically ill patients. Therefore, repeat chest CT scan and PFT less than 12 weeks upon discharge is not advised to provide sufficient time for imaging resolution and lung function improvement while also ensuring that non-resolving changes are addressed sufficiently early. There is a positive correlation between the CT scores and SGRQ scores suggesting a significant radiographic abnormality correlated with more symptoms reported. On the other hand, there is a negative correlation between pulmonary function test and SGRQ as well as CT scores. The higher the CT scores and SGRQ scores, the lower the pulmonary function predicted. Impaired lung function might be related to pulmonary fibrosis.

## RECOMMENDATIONS

The small sample size was the main limitation of the present study. Additionally, PFTs before COVID-19 infection were not available for our patients. Nevertheless, our results may represent an important first step in the

knowledge of COVID-19 consequences in terms of pulmonary function in correlation with radiographic abnormality and in terms of quality of life and independence of patients. It highlighted the need to strengthen pulmonary function monitoring in these patients, and commence rehabilitation treatment if required in a more holistic approach.[17] Longer follow-up (i.e. 6 months, 1 year and 2 years) should be done as well, especially in the severe illness group.

## REFERENCES


1. Du Toit A. Outbreak of a novel coronavirus. *Nat Rev Microbiol. 2020;18 (3):123.*
2. World Health Organization. COVID-19 dashboard. 2019. Accessed December 14, 2020. https://covid19.who.int/.
3. Bassetti M, Vena A, Giacobbe DR. The novel Chinese coronavirus (2019-nCoV) infections: challenges for fighting the storm. *Eur J Clin Invest. 2020;50 (3):e13209.*
4. Yu M, Liu Y, Xu D, Zhang R, Lan L, Xu H. Prediction of the Development of Pulmonary Fibrosis Using Serial Thin-Section CT and Clinical Features in Patients Discharged after Treatment for COVID-19 Pneumonia. *Korean J Radiol. 2020;21(6):746-755.*
5. Han X, Cao Y, Jiang N, et al. Novel Coronavirus Pneumonia (COVID-19) Progression Course in 17 Discharged Patients: comparison of Clinical and Thin-Section CT Features During Recovery. *Clin Infect Dis.* 2020;71(15):723-731.
6. Dai H, Zhang X, Xia J, et al. High-resolution Chest CT Features and Clinical Characteristics of Patients Infected with COVID-19 in Jiangsu, China. *Int J Infect Dis.* 2020;95:106–12.
7. British Thoracic Society. Guidance on respiratory follow up of patients with a clinico-radiological diagnosis of covid-19 pneumonia. 2020. www.brit-thoracic.org.uk
8. Ngai JC, Ko FW, Ng SS, To KW, Tong M, Hui DS. The long-term impact of severe acute respiratory syndrome on pulmonary function, exercise capacity and health status. *Respirology.* 2010;15 (3):543–50.
9. 15 PHOSP-COVID. Improving long-term health outcomes. https://www.phosp.org/.
10. Mo X, Jian W, Su Z, et al. Abnormal pulmonary function in COVID-19 patients at time of hospital discharge. *Eur Respir J.* 2020;55(6):2001217.
11. Barr JT, Schumacher GE, Freeman S, LeMoine M, Bakst AW, Jones PW. American translation, modification, and validation of the St. George's Respiratory Questionnaire. *Clin Ther.* 2000;22 (9):1121-1145.
12. Salehi S, Abedi A, Balakrishnan S, Gholamrezanezhad A. Coronavirus disease 2019 (COVID-19): a systematic review of imaging findings in 919 patients. *AJR Am J Roentgenol.* 2020;215 (1):87-93.
13. Huang Y, Tan C, Wu J,. et al. Impact of coronavirus disease 2019 on pulmonary function in early convalescence phase. *Respir Res.* 2020;21(1):163.
14. Zhao YM, Shang YM, Song WB, et al. Follow-up study of the pulmonary function and related physiological characteristics of COVID-19 survivors three months after recovery. *EClinicalMedicine*. 2020;25:100463.
15. Masclans JR, Roca O, Muñoz X, et al. Quality of life, pulmonary function, and tomographic scan abnormalities after ARDS. *Chest.* 2011;139:1340–1346.
16. Arnold DT, Hamilton FW, Milne A, et al. Patient outcomes after hospitalization with COVID-19 and implications for follow-up: results from a prospective UK cohort. *Thorax.* 2021;76(4):399-401.
17. Liu K, Zhang W, Yang Y, Zhang J, Li Y, Chen Y. Respiratory rehabilitation in elderly patients with COVID-19: a randomized con- trolled study. *Complement Ther Clin Pract.* 2020;39:101166.
18. Wu Z, McGoogan JM. Characteristics of

and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. *JAMA.* 2020;323(13):1239– 1242.

Philippine Journal of Chest Diseases

Original Research

# The Prevalence of Smoking Among Physicians-in-Training and Its Association in Tobacco Control Interventions

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PAPER PRESENTED IN THE FOLLOWING CONFERENCE: Philippine College of Chest Physicians (PCCP) Research Contest March 2021 (Consolation Prize Winner, Original Research Category )

## ABSTRACT

**BACKGROUND:** Health care professionals, particularly physicians, are generally considered the most knowledgeable in health matters related to smoking and are expected to be role models in the hospital and community settings. However, in 2007, the WHO reported that the overall prevalence of tobacco use among physicians in the Philippines was as high as 63%. Despite this figure, to date, local data is still limited on how physicians smoking status influence their decision to interact with patients about smoking cessation.

**OBJECTIVE:** To determine the prevalence of cigarette smoking among residents and fellows-in-training of different specialties from the University of the Philippines-Philippine General Hospital and the relationship between their smoking status and attitude towards implementing the minimal intervention steps on tobacco control.

**METHODS:** We conducted a cross-sectional survey, analytical study among randomly selected residents and fellows-in-training from different departments at the UP-Philippine General Hospital. All respondents were asked to fill out a standardized questionnaire, adapted from the Global Adult Tobacco Survey (GATS), to extract data to measure tobacco smoking prevalence, consumption, cessation and impact of health warnings among physicians. A different set of questionnaire was used to assess the attitudes of physicians toward tobacco control on their patients based on the 5As approach recommended by the United States Department of Health and Human Services. Descriptive analyses of the data were performed on all variables using Fishers' exact test and Chi-square test.

**RESULTS:** Two hundred thirty (230) physicians from different departments participated in this study from November 2019 to March 2020. The respondents were predominantly females, with mean age of 28.5, and with relatively more of the participants coming from internal medicine (28.4%), surgery (19.6%) and pediatrics (15.7%). The prevalence of current smokers was 11.7%. Approximately seven out of ten or 71% of the respondents have never smoked. Sex and age were found to be significantly associated with smoking status.

**CONCLUSION:** Medical specialty did not show any significant association with smoking status. Smoking status significantly associated with attitude towards implementing the minimal intervention steps on tobacco control except in the aspect of assisting the patient to quit. Higher proportions of former and never smokers as compared to current smokers were found to ask their patients about tobacco use, advise about quitting tobacco use, and arrange for tobacco cessation services.

**KEYWORDS:** *tobacco control, smoking cessation*

## INTRODUCTION

The global prevalence of tobacco smoking is estimated to be over 1.1 billion.[1] In the Philippines, the prevalence of smoking among adults is estimated at 15.9 million or 22.7%.[2] Tobacco smoking is responsible for almost 6 million deaths worldwide each year with 12% of all deaths among adults aged 30 years and over were attributed to tobacco.[1,3,4] It is projected that the annual death toll could rise to more than eight million by 2030 unless urgent measures are taken.[5]

Health care professionals, particularly physicians, are generally considered the most knowledgeable in health matters related to smoking and are expected to be role models in the hospital and community settings. Many regard physicians as a reliable source of knowledge and advice on matters of health.[1] In fact, physicians have the potential to reach 80% of all tobacco users per year and can help 2-3% of all those who received advice quit successfully.[5]

Many physicians continue to be smokers themselves despite the obvious knowledge on the health consequences of smoking. The WHO reported in 2007 that the overall prevalence of tobacco use among physicians in the Philippines is 63%.[7] This is an alarming figure but local data is still limited on how physicians smoking status influence their decision to interact with patients about smoking cessation.

## OBJECTIVES

To determine the prevalence of tobacco smoking and the association between smoking status and attitudes toward tobacco control measures with their patients. Specifically, to determine the (1) demographic characteristics of the respondents (i.e., age, sex, and medical specialty); (2) their tobacco smoking status (i.e., current smoker, former smoker, non-smoker); (3) average number of tobacco used by current smokers and former smokers; (4) attitudes of current smokers towards smoking cessation and health care seeking behavior and health warning on cigarette packages; (5) association between the respondent's demographic characteristic and smoking status; and (6) association between the respondents smoking status and attitude towards the implementation of the minimal intervention steps on tobacco control (5A's) once they encounter patients who are ready to quit. This study may provide updated local data on the physicians' smoking rates and how their smoking habits impact medical interventions of smoking cessation among their respective patients.

## METHODS

We conducted a cross-sectional survey, analytical study. The respondents were randomly selected residents and fellows-in-training, from different departments all working at the UP-Philippine General Hospital. Prior data from the World Health Organization in 2007 showed that the prevalence of smoking was 63% among doctors. If the population size of physicians-in-training was around 800, the minimum required sample size was 248 to achieve 5% maximum tolerable error and 95% confidence. The actual sample size was 230, which corresponded to an error of 5.27%, and was considered acceptable. We used G*Power version 3.1.9.2 to estimate the minimum sample size.

Residents and fellows-in-training of different departments including Internal Medicine, Family Medicine, Pediatrics, Neurology, Dermatology, Psychiatry, Obstetrics and Gynecology, Otorhinolaryngology and General Surgery who handle cases involving adolescent and adult patients in the outpatient clinic of Philippine General Hospital were eligible for the study. Residents or fellows-in-training not holding outpatient clinics were excluded from the study.

The total number of physicians-in-training in Philippine General Hospital at the time of data collection was approximately 800. The respondents were selected by proportionate stratified random sampling. The

survey was conducted within a 5-month period from the time of approval (from November 2019 to March 2020). The participants were recruited during office hours at the outpatient clinic and were approached by the principal investigators. The invited participants were presented with the survey questionnaire with a cover letter discussing the study details and procedures. These were verbally explained to all participants. The principal investigator secured the informed consent. Participants were allowed to withdraw at any time during the survey administration and reasons for doing so was obtained.

The respondents were asked to fill out a survey questionnaire in English language. The questionnaire included demographic characteristics of the physicians. The standardized questionnaire, adapted from the Global Adult Tobacco Survey (GATS), was used to extract data to measure tobacco smoking prevalence, consumption, cessation and impact of health warnings among physicians. A different set of questionnaire was used to assess the attitudes of physicians toward tobacco control on their patients based on the 5As approach recommended by the United States Department of Health and Human Services. The estimated amount of time to complete the survey was 10-15 minutes.

The collected data were stored in a secured location and were encoded using Microsoft Excel. The descriptive analyses of the data were performed on all variables using Fishers' exact test and Chi-square test to determine the association between variables. A p-value of $<0.05$ was considered significant for all tests.

The protocol was submitted to the Clinical Research Division Technical Review Board (TRB) and to the University of the Philippines Manila Research Ethics Board (UPM REB) for review and approval. This study was conducted in accordance with principles of Good Clinical Practice upon approval of the protocol by both review boards. The investigators sought the consent from the study participants. The respondents were informed that participation was voluntary and that they have the option to refuse or withdraw at any time during the survey period.

To ensure utmost confidentiality, the respondents' personal data such as their names, birthday, address and contact numbers were not asked. The questionnaire was serially labeled with no other identifiers. Only the investigators had access to individual responses. The data obtained was electronically transcribed and encoded in a password-protected working spreadsheet. The data can only be accessed by the study investigators and the approving ethics committee. All the data collection forms were discarded properly after 1 year without possibility of recovery after the data were encoded in a working spreadsheet for analysis. Data handling and keeping were all in compliance with the Data Privacy Act of 2012.
The potential vulnerability that may arise from recognition of subordination in the hierarchy of training was avoided via frequent reminders and reassurance to all respondents of their right to refuse consent and participation at any point during the study.

In cases of breach in data privacy that was considered a potential risk, the responsible officer in the office of research compliance and IRB was immediately informed. Any form of privacy breach occurrence was well documented in writing and reported to authorities. Participants in the survey were not provided any material compensation. Since this was a cross-sectional survey, the investigators did not foresee any direct benefits associated with answering the questionnaire. However, the results may be used in developing a framework for a sustainable tobacco control strategy.

## RESULTS

A total of 230 physicians-in-training participated in this study, their ages ranging from 24 to 36 years with a mean of 28.5 +/- 2.2 years. Distribution in terms of sex was almost equal, with slightly more females. In terms of medical specialty, relatively more of the participants are from the field of internal medicine, surgery, and pediatrics (28.3%, 19.6%, and 15.7%, respectively) (Table 1). Approximately seven out of every 10 of the physicians-in-training (71.3%) have never smoked. Out of the three who have tried smoking, one is still currently smoking (Table 2).

The average number of cigarettes smoked per day by former smokers is significantly lower than the daily cigarette average of current smokers (p-value = 0.00). Current smokers mostly smoked 5 sticks or more per day while all the 39 former smokers smoked less than 5 sticks per day ([Table 3).

Two current smokers use vapes only so number of current smokers in Table 3 does not add up to the total number of current smokers, which is 27. Moreover, 8 current smokers use both cigarette and vape. Thus total number of current smokers who use vape is 10. Out of these 10, 6 consume 1 bottle or less per week while 4 use more than 1 bottle per week.

About 3 out of every 5 physicians-in-training (59.3%) who were categorized as current smokers tried to stop smoking during the 12 months preceding data collection but none of them visited a smoking cessation expert within the said period. Nearly half of them (48.1%) were advised to quit smoking during the same period. (Table 4).

**Table 1.** Demographic Characteristics of the Study Participants (n =230)

| Characteristics | |
|---|---|
| Age (years) | |
| Mean +/- Standard Deviation | 28.5 +/- 2.2 |
| Range | 24 to 36 |
| | n (%) |
| 20-30 | 193 (83.9) |
| 31-40 | 37 (16.1) |
| Sex | n (%) |
| Male | 107 (46.5) |
| Female | 123 (53.5) |
| Medical Specialty | n (%) |
| Internal medicine | 65 (28.3) |
| Family medicine | 17 (7.4) |
| Surgery | 45 (19.6) |
| Pediatrics | 36 (15.7) |
| Obstetrics and Gynecology | 24 (10.4) |
| Otorhinolaryngology | 17 (7.4) |
| Ophthalmology | 12 (5.2) |
| Neurology | 10 (4.3) |
| Dermatology | 1 (0.4) |
| Psychiatry | 3 (1.3) |

**Table 2.** Smoking Status of the Study Participants (n =230)

| Smoking Status | n (%) |
|---|---|
| Current smoker | 27 (11.7) |
| Former smoker | 39 (17.0) |
| Never smoker | 164 (71.3) |

**Table 3.** Cigarettes Smoked per Day among Current and Former Smokers

| Number of cigarettes smoked on average per day | Smoking status | | |
|---|---|---|---|
| | Current smoker | Former smoker | p-value |
| < 5 sticks | 2 (8.0%) | 39 (100.%) | 0.00[M] |
| 5-10 sticks | 12 (48.0%) | 0 (0.0%) | |
| > 10 sticks | 4 (16.0%) | 0 (0.0%) | |
| 20 sticks or more | 7 (28.0%) | 0 (0.0%) | |

***Significant (less than α = 0.05); M – Mann Whitney test*
**Two current smoker use vapes only hence total number does not add up to the total number of currents smokers (n=27)*

**Table 4.** Smoking cessation and health care seeking behavior among current smokers (n =27)

| | Yes | Not sure | Never |
|---|---|---|---|
| During the past 12 months, have you tried to stop smoking? | 5 (18.5%) | 6 (22.2%) | 16 (59.3%) |
| Have you visited a doctor or a smoking cessation expert in the past 12 months? | | | 27 (100.0%) |
| Were you advised to quit smoking in the past 12 months by any doctor? | 13 (48.1%) | | 14 (51.9%) |

For 4 out of every 5 current smokers (81.5%), the warning label in the cigarette package had no impact, as it did not lead them to think about quitting (Table 5).

**Table 5.** Impact of health warnings on cigarette packages among current smokers (n = 27)

| | Yes | Sometimes | Never |
|---|---|---|---|
| In the last 3 days, have warning labels in cigarette packages led you to think about quitting? | 2 (7.4%) | 3 (11.1%) | 22 (81.5%) |

**Table 6.** Demographics and smoking status

| Demographic Characteristics | Smoking Status | | | p-value |
|---|---|---|---|---|
| | Current smoker (n = 27) | Former smoker (n = 39) | Never smoker (n = 164) | |
| Sex | | | | |
| Male | 16 (15.0) | 25 (23.4) | 66 (61.7) | 0.01[C*] |
| Female | 11 (8.9) | 14 (11.4) | 98 (79.7) | |
| Age (years) | | | | |
| 20-30 | 27 (14.0) | 24 (12.4) | 142 (73.6) | 0.00[C*] |
| 31-40 | 0 (0.0) | 15 (40.5) | 22 (59.5) | |
| Medical specialty | | | | |
| Internal medicine | 3 (4.6%) | 9 (13.8%) | 53 (81.5%) | 0.21[F] |
| Family medicine | 4 (23.5%) | 1 (5.9%) | 12 (70.6%) | |
| Surgery | 8 (17.8%) | 9 (20.0%) | 28 (62.2%) | |
| Pediatrics | 7 (19.4%) | 5 (13.9%) | 24 (66.7%) | |
| Obstetrics and Gynecology | 2 (8.3%) | 5 (20.8%) | 17 (70.8%) | |
| Otorhinolaryngology | 1 (5.9%) | 5 (29.4%) | 11 (64.7%) | |
| Ophthalmology | 1 (8.3%) | 3 (25.0%) | 8 (66.7%) | |
| Neurology | 0 (0.0%) | 2 (20.0%) | 8 (80.0%) | |
| Dermatology | 1 (100.0%) | 0 (0.0%) | 0 (0.0%) | |
| Psychiatry | 0 (0.0%) | 0 (0.0%) | 3 (100.0%) | |

**Significant (less than α = 0.05); C- chi square test; F – Fisher's exact test*

Smoking status was found to have a significant association with attitude towards implementing the minimal intervention steps on tobacco control (p-values < 0.05) except in terms of assisting the patient to quit (p-value > 0.05). Specifically, higher proportions of former and never smokers as compared to current smokers were found to ask their patients about tobacco use, advice about quitting tobacco use, and arrange for tobacco cessation services (Table 7).

## DISCUSSION

The prevalence of smoking among physicians is a public health issue since they play

**Table 7.** Logistic Smoking Status and Attitude Towards Implementing the Minimal Intervention Steps on Tobacco Control

| | Smoking status | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Current smoker | | | Former smoker | | | Never smoker | | | p-value |
| | Y | S | N | Y | S | N | Y | S | N | |
| Are you willing to ask your patients about tobacco use? | 12 44.4% | 9 3.3% | 6 22.2% | 31 79.5% | 8 20.5% | 0 0% | 133 81.1% | 25 15.2% | 6 3.7% | 0.00 F |
| Are you willing to give advice about quitting tobacco use? | 10 37.0% | 17 63.0% | 0 0% | 27 69.2% | 12 30.8% | 0 0% | 127 77.4% | 35 21.3% | 2 1.2% | 0.00 F |
| Are you willing to assess a patient's willingness to quit? | 13 48.1% | 4 14.8% | 10 37.0% | 19 48.7% | 12 30.8% | 8 20.5% | 59 36.0% | 94 57.3% | 11 6.7% | 0.00 F |
| Are you willing to assist the patient to quit? | 4 14.8% | 19 70.4% | 4 14.8% | 11 28.2% | 24 61.5% | 4 10.3% | 31 18.9% | 93 56.7% | 40 24.4% | 0.19 C |
| Are you willing to arrange for tobacco cessation services? | 0 0% | 2 7.4% | 25 92.6% | 3 7.7% | 11 (28.2 %) | 25 64.1% | 10 6.1% | 60 36.6% | 94 57.3% | 0.01 F |

**Significant (less than α = 0.05); C- chi square test; F – Fisher's exact test; Y – Yes; S – Sometimes; N – Never*

an an important role in efforts to promote smoking cessation.[6] It has shown that physician-initiated interventions were found to be efficacious and cost-effective with regard to patient smoking cessation outcomes.[8] The prevalence of smoking among physicians across different studies ranges from as high as 62% to as low as 3%.[7] In the last national prevalence study conducted in 1987, 63% of male physicians and 37% of female physicians were smokers. The result of our study only shows 11.7% of physicians are current smokers. The lower prevalence rate may be due to the lack of physicians who belong to older age groups since most of the study respondents are younger doctors in training with a mean age of 28 years. Recent reports have shown that physicians who smoke are mostly between the ages of 40 to 50 years.[8-9]

Our study showed that sex and age were found to be significantly associated with

smoking status, with a greater proportion of males being current or former smokers. These findings were consistent with the literature review on tobacco use and smoking cessation practices of physicians in developing countries which shows higher smoking prevalence among male physicians.[10] In the Philippines, smoking rates are among the highest in Asia for both men, with 54%, and women, with 12.6%.[11]

Several studies have reported that some medical specialties may be considered at higher risk of smoking due to the condition of work, the load and the stress that comes with it. The highest smoking prevalence was reported among surgeons (60.2%), internal medicine doctors (35%) and other specialists (39.6%). In an international review of tobacco smoking in the medical profession, family physicians were found to smoke less and general practitioners were found to smoke more often than specialists.[12-13] Our study did not find a significant association between smoking status and medical specialty. These could be influenced by several factors such as patients and administrative workload and possibly the setup of training institutions (public or private).

It is reported in several studies that the promotion of minimum smoking cessation interventions was likely to be influenced by the smoking status of physicians. Our study also shows significant association with attitude towards implementing the minimal intervention steps on tobacco control except in terms of assisting the patient to quit. The plausible explanation why physicians are less involved in tobacco control and smoking cessation efforts is perhaps a substantial proportion of them are smokers' themselves.[14] Even among pulmonary specialists, they found that current smoking was associated with a low rate of making efforts in promoting smoking cessation.[14]

Building physicians capacity to engage in tobacco prevention and cessation activities has been found to be an essential measure for tobacco control. The quitting rates were low among physicians, and the delivery of advice on quitting smoking was not common across the studies.[10] Meta-analyses concluded that smoking status of doctors might have an impact on them advising their smoking patients to quit.[15] Smoking doctors were found to have 17% increase risk of not advising their patients to quit, and 8% less likely to counsel their patients as well.[16] Ohida and colleagues[15], suggested that non- smoking physicians have more unfavorable views towards smoking and are more active in encouraging patients not to smoke. The rates of male nonsmoking physicians who gave affirmative responses to "I always ask new patients about their smoking history" and "I have succeeded in getting some of my patients to quit smoking during the past year" were significantly higher than that of the male physicians who smoke.

In conclusion, the prevalence of smoking among physicians-in-training is 11%. Smoking status was found to have a significant association with attitude towards implementing the minimal intervention steps on tobacco control except in terms of assisting the patient to quit.

## LIMITATIONS

The study included mostly young doctors who are residents and fellows in training in a public hospital. This may limit the generalization of the result.

## REFERENCES

1. World Health Organization: WHO Tobacco Free Initiative: The role of health professionals in tobacco control. Geneva, Switzerland; 2005.
2. Global Adult Tobacco Survey Philippines Executive Summary. 2015.
3. WHO, 2013 Tobacco. Fact sheet N339. Retrieved 22/05/2014, 2014, from http://www.who.int/mediacentre/factsheets/fs339/en/.
4. World Health Organization. Mortality attributable to tobacco: WHO Global Report. Geneva: WHO, 2012.

5. Toolkit for delivering the 5A's and 5R's brief tobacco interventions in primary care. World Health Organization (WHO), 2014. Available from http://www.who.int/tobacco/publications/smoking_cessation/9789241506953/en/
6. Lancaster, T.; Stead, L.; Silagy, C.; Sowden, A. Effectiveness of interventions to help people stop smoking: Findings from Cochrane Library. *Br. Med. J.* 2000, 321, 355–358.
7. Tobacco or Health: A global Status Report. Available online: http://whqlibdoc.who.int/publications/1997/924156184X_eng.pdf.
8. Ohida T, Sakurai H, Mochizuki Y, Kamal AM, Takemura S, Minowa M, et al.: Smoking prevalence and attitudes toward smoking among Japanese physicians. *JAMA.* 2001, 285:2643-2648.
9. Nardini S, Bertoletti R, Rastelli V, Donner CF: The influence of personal tobacco smoking on the clinical practice of Italian chest physicians. *Eur Respir J.* 1998, 12:1450-1453.
10. Abdullah, A.S.; Feng, Q.; Pun, V.; Stillman, F.; Samet, J.M. A review of tobacco smoking and smoking cessation practices among physicians in China: 1987–2010. *Tob Control.* 2013, 22, 9–14.
11. Dans, A., Fajutrao, L., Fernandez, L., Amarillo, M. L., Villaruz, M. V., Jadloc, S. M. et al. (2000) Monograph on Cigarette Smoking in the Philippines, 1999. WHO Regional Office for the Western Pacific.
12. Li, H.Z.; Fish, D.; Zhou, X. Increase in cigarette smoking and decline of anti-smoking counseling among Chinese physicians: 1987–1996. *Health Promot.* Int. 1999, 14, 123–131.
13. Smith DR, Leggat PA. An international review of tobacco smoking in the medical profession: 1974–2004. *BMC Public Health.* 2007;7:115.
14. Pazarli Bostan, P., Karaman Demir, C., Elbek, O., & Akçay, Ş. (2015). Association between pulmonologists' tobacco use and their effort in promoting smoking cessation in Turkey: a cross-sectional study. *BMC Pulmonary Medicine.* 15(1). doi:10.1186/s12890-015-0131-y
15. Ohida T, Sakurai H, Mochizuki Y, Kamal AM, Takemura S, Minowa M, et al. Smoking prevalence and attitude toward smoking among Japanese physicians. *JAMA.* 2001;285:2943–8.
16. Duaso, M. J., McDermott, M. S., Mujika, A., Purssell, E., & While, A. (2014). Do doctors' smoking habits influence their smoking cessation practices? A systematic review and meta-analysis. Addiction, 109(11), 1811–1823.

Philippine Journal of Chest Diseases

Original Research

# Fluticasone/Salmeterol Maintenance Plus Short-acting Beta Agonists Reliever Versus Budesonide/Formoterol Maintenance and Reliever Therapy Regimen in the Treatment of Uncontrolled Asthma in a Philippine Government Hospital Setting: Direct Cost Comparison

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PAPER ACCEPTED FOR ABSTRACT PRESENTATION: Asian Pacific Society of Respirology (APSR) Congress (November 2021)

## ABSTRACT

**BACKGROUND:** Combination inhaled corticosteroid/long-acting β2-agonist (ICS/LABA) has become standard treatment for uncontrolled asthma in Filipino adults. Local healthcare professionals believe available ICS/LABAs have similar efficacy. Price and access are issues in asthma therapy. A study in Thailand compared the cost of treatment between fixed-dose ICS/LABA versus ICS/LABA Maintenance and Reliever Therapy (MART) regimens.

**OBJECTIVE:** To compare direct health care costs between regular Fluticasone/Salmeterol (FP/Salm) with as-needed Short Acting Beta Agonist (SABA) dosing regimen versus Budesonide/Formoterol (Bud/Form) MART regimen in a Philippine government hospital setting.

**METHODS:** We conducted a direct healthcare costs estimation between two ICS/LABAs, regular fixed-dose FP/Salm twice daily plus as needed short-acting β2-agonist versus Bud/Form as MART regimen in uncontrolled asthma. The treatment cost impact on societal perspective was also considered. Three randomized controlled trials were referenced to calculate direct healthcare costs and these are AHEAD, COMPASS and COSMOS. These three RCTs were included because they reflected prospective data on resource utilization in asthma management as well as compared ICS/LABA treatments among patients aged 12 years and above with moderate/severe asthma.3 Estimated total direct healthcare cost was the sum of drug acquisition cost and other healthcare costs. Unit costs of different healthcare resources were obtained from a public hospital and medication costs were obtained from private pharmacies.

**RESULTS:** The FP/Salm group demonstrates a higher healthcare utilization cost, except in the AHEAD study. However, overall cost is lower in FP/Salm group. Savings in total cost was highest in FP/Salm (COMPASS study). Overall, FP/Salm showed more savings in total cost (8.91%) versus MART regimen. Furthermore, total direct treatment savings is more than the price of another inhaler.

**CONCLUSION:** The use of twice daily FP/Salm maintenance therapy plus as needed SABA in uncontrolled asthma results in lower total direct treatment costs versus Bud/Form MART because of lower medication costs.

**KEYWORDS:** *FP/Salm, SABA, Bud/Form, MART*

## INTRODUCTION

Asthma has been acknowledged to constitute a significant public health burden owing to it being one of the most prevalent non communicable chronic respiratory disease globally. According to the latest data from the World Health Organization (WHO) in 2019, asthma affected an estimated 262 million people and caused 461,000 deaths.[4] In comparison, it was estimated that more than 250 million people in the world may have chronic obstructive pulmonary disease albeit with higher deaths at 3.23 million in 2019.[5] According to the WHO, asthma was the 10th leading cause of death in the Philippines in 2018 and there were 12,749 deaths comprising 2.05% of total deaths. The age adjusted death rate is 18.42% per 100,000 population which ranks Philippines as number 14 in the world.[6]

Asthma is defined as wheezing in the past 12 months and it had an estimated prevalence of 8.7% in the country.[7] The aim of asthma management is to control the disease. Long term goals include good control of symptoms, maintaining normal activity levels, minimizing future risk of exacerbations, fixed airflow limitations and side effects.[8-9] Discrepancies between patient and physician understanding of asthma control has been observed in Asia. In the REcognise Asthma and LInk to Symptoms and Experience (REALISE) Asia study, patients consistently overestimate their level of asthma control rather than what their symptoms suggest. Health care providers are best positioned to educate patients on their condition, address the perception discrepancy, help patients overcome their anxieties, and influence their attitudes toward treatment.[10]

The Philippines has a dual health system composed of the public and private sector. The public sector is run by the government while the private sector is largely market-oriented where health services are paid for through user fees at point of service.[11] The Philippine Health Insurance Corporation (PHIC) or Philhealth is the national health insurance program for all citizens of the Philippines.[12] However, as of date, the coverage is limited and outpatient services and medications are not yet included. Therefore, the financial burden of asthma management is often borne out-of-pocket by the patient in the Philippines. Even with private health insurance, these medications for chronic disease such as asthma are usually not reimbursable. Price and access are real issues in asthma therapy,[1] hence the need for the most affordable yet effective treatment for Filipino asthma patients.

Combination of ICS/LABA has become the standard treatment for uncontrolled asthma in Filipino adults. Local healthcare professionals believe all the available ICS/LABAs have similar efficacy clinically. Stepwise treatment approach for asthma patients using ICS/LABA demonstrated higher efficacy than ICS alone.[13] Fixed-dose ICS/LABA regimen is a recommended maintenance treatment with a separate reliever therapy, usually a SABA. This is recommended as a stepwise approach depending on the presenting symptoms (Steps 3 -5, moderate-severe asthma).[9] MART is also recommended for moderate/severe asthma[14] and it relies on rapid as-needed adjustments in ICS/LABA with the aim of reducing severe exacerbations. A study in Thailand compared the cost of treatment between fixed-dose ICS/LABA versus ICS/LABA MART regimens.[2] Another similar cost comparison study involved three of the Philippine's neighboring countries, Thailand, Indonesia and, Vietnam.[15] Both of these studies showed medication cost was an important driver of direct costs and regular use of twice daily FP/Salm resulted in lower total total direct treatment costs due to lower cost of medication.[2, 15]

## METHODS

A direct healthcare cost estimation was performed comparing the two ICS/LABAs, regular fixed-dose FP/Salm twice daily plus as needed short-acting β2-agonist versus Bud/Form as MART regimen in uncontrolled asthma. Treatment cost impact on societal perspective was considered but this paper fo-

**Table 1.** Study design of the three referenced trials

| | AHEAD | COMPASS | COSMOS |
|---|---|---|---|
| Study Design | 6-month, randomized, double-blind, parallel group | 6-month, randomized, double-blind, double-dummy, parallel group | 12-month,randomized, open-label, parallel group |
| Countries/ Sites | 17/184 | 16/235 | 16/246 |
| Treatment comparison | - FP/Salm 500/50 µg x 1 inhalation bid + terb as needed<br><br>- Bud/form 160/4.5 µg x 2 inhalation bid + Bud/form as needed | - FP/Salm 125/25 µg x 2 inhalation bid + terb as needed<br><br>- Bud/form 320/9 µg x 1 inhalation bid + terb as needed<br><br>- Bud/form 160/4.5 µg x 1 inhalation bid + Bud/form as needed | - FP/Salm 250/50 µg x 1 inhalation bid (100/50 µg x 1 inhalation bid or 500/50 µg x 1 inhalation bid) + salb as needed<br><br>- Bud/form 160/4.5 µg x 2 inhalation bid (dose could be changed to 160/4.5 µg x 1 inhalations bid) + Bud/form as needed |
| Number of Randomized Patients | 2,309 | 3,335 | 2,143 |
| Mean Age (years) | 39 | 38 | 45 |
| Mean Baseline $FEV_1$% predicted (%) | 71 | 73 | 73 |
| Primary Endpoint | Time to first severe exacerbation | Time to first severe exacerbation | Time to first severe exacerbation |

cused only on direct healthcare costs. The costs were collected on a single time period during data gathering from the public hospital for the direct healthcare services and from the private drugstores for the price of medications.

The societal perspective is concerned with society's welfare and how to get the most benefit from the scarce resources available to a society.[16] It takes into consideration the impact of the cost estimates of the asthma management in the society. This paper mainly focused on direct healthcare cost and compare the two most commonly used regimens in the Philippines, fixed-dose combination using FP/Salm + SABA versus Bud/Form as maintenance and reliever therapy. These treatment regimens give a snapshot of the true situation of asthma management in the Philippines.

Three randomized controlled trials were referenced to calculate direct healthcare costs. The three trials - AHEAD[17], COMPASS[18] and COSMOS[19] were taken from the study by Wickstrom, et al. which included five trials (STAY and SMILE were excluded because of study design wherein only different doses of Bud/Form were compared). The three referenced trials actually compared FP/Salm + SABA versus MART which included asthma patients >12years comparing ICS/LABA treatments in moderate/severe asthma.[3] AHEAD and COMPASS were double-blind, 6-month studies and COSMOS was an open-label 12-month study.

The total direct healthcare cost was estimated as the sum of medication costs and

other healthcare costs such as ER consult, regular or ICU bed rate per day, healthcare practitioners fee, etc. Unit costs of different healthcare resources were obtained from a public hospital (See Supplementary Table 1:https://bit.ly/SupTablesAsthmaMeds) while the medication costs (See Supplementary Table 2) were obtained from the nearby private pharmacies in the Philippines where asthma patients from public hospitals usually buy their medicines. The total amount of the medication costs were computed based on the dosing regimen described for each therapy (FP/Salm plus SABA versus MART) in the three referenced studies in asthma patients (Table 2).

Savings in total cost is highest in FP/Salm group with a savings of 15.35% (COMPASS). Overall, FP/Salm shows more savings in total cost (8.91%) at Php 37,070.78 versus Php 40,695.00 for the MART regimen. Furthermore, total direct treatment savings could afford the patient an extra inhaler.

Similar results in terms of lower treatment or medication costs were observed in two previous studies by Torsak et al. and Aggarwal et al. In the study by Torsak, et al., the treatment savings using FP/Salm was higher by as much as 45% while the study by Aggarwal, et al. showed treatment saving favoring FP/Salm regimen.[2,15] As mentioned in the study by Aggarwal et al., the differences were basically driven by the costs of the medication of the treatment regimen – first, the fixed dose ICS/LABA maintenance plus SABA reliever and second, the maintenance and reliever therapy.[15]

**Table 2.** Average cost by treatment option in the three studies

| | Treatment Arm | Medication Costs (Php) | Healthcare utilization costs (Php) | Total direct treatment costs (Php) | % Savings in Total cost by FP/SALM |
|---|---|---|---|---|---|
| AHEAD | FP/Salm (500/50) | 47185.88 | 48.30 | 47234.18 | 4.24% |
| | MART (2x160/4.5) | 49625.02 | 61.80 | 49326.82 | |
| COMPASS | FP/Salm (250/50) | 27666.5 | 210.40 | 27876.90 | 15.35% |
| | MART (2x160/4.5) | 32816.2 | 115.50 | 32931.92 | |
| COSMOS | FP/Salm (250/50) | 36034.76 | 66.50 | 36101.26 | 9.36% |
| | MART (2x160/4.5) | 39783.6 | 44.50 | 39828.10 | |
| Overall (3 studies) | FP/Salm | 36962.38 | 108.40 | 37070.78 | 8.91% |
| | MART | 40621.61 | 73.93 | 40695.61 | |

**Data were calculated as cost per patient per year*

## RESULTS

The FP/Salm group demonstrates a higher healthcare utilization cost at Php 210.40 (COMPASS) and Php 66.50 (COSMOS) for FP/Salm vs Php 115.50 (COMPASS) and Php 44.50 (COSMOS) for MART except in the AHEAD study. However, overall medication costs are lower in the FP/Salm group.

## DISCUSSION

In the Philippines, cost of treatment is always a concern for patients. The public health insurance and/or public health institutions have limited coverage, that is, only for admitted patients. Private health insurance may cover outpatient diagnostics but medications are mostly out-of-pocket. Therefore, the issue of cost is always forefront in the management of chronic diseases such as asthma.

Physicians in the Philippines are always concerned about affordability as shown in the Asia-Pacific Survey of Physicians on Asthma and Allergic Rhinitis (ASPAIR) study. In the ASPAIR study, 200 health care providers treating asthma were surveyed about the factors influencing treatment choice, and about 70% chose affordability (highest among other countries surveyed which ranges from 33% to 55%), followed distantly by practice guidelines at 17% and availability (stock). These are real issues which are stumbling blocks in the optimum management of chronic asthma in the Philippines.[20]

Combination ICS/LABA is the standard treatment for chronic asthma and local health care professionals believe that available ICS/LABA have similar efficacy. The results of this price comparison study showed a very slight advantage of FP/Salm vs MART regimen. The actual cost difference may not be huge, but the savings can already buy the patient an extra inhaler.

If we were to compare with the results of the Thailand study[2], their results showed a sizable variation between the two regimens with 45% savings in total cost with FP/Salm vs. 8.9% in the Philippine study. A possible explanation for this is that the health infrastructure set up of the two countries are quite different. Thailand ranks 6th among 195 countries in the 2019 Global Health Security Index while the Philippines ranked 53rd; Indonesia and Vietnam ranked 45th and 65th respectively.[21] The latter two countries' results were similar, favoring the FP/Salm regimen.

In the methodology of the Thailand study, medication cost came from their national drug information, while in the Philippines, medication cost was from a private pharmacy. This alone creates an impact on affordability. But despite this, the results still showed an advantage in direct treatment cost for the FP/Salm regimen.

## CONCLUSION

FP/Salm shows more savings in total cost (8.91%) at Php 37,070.78 versus Php 40,695.00 for the MART regimen. Twice daily FP/Salm maintenance therapy plus as needed SABA in an uncontrolled asthma result in lower total direct treatment costs versus Bud/Form MART because of lower medication costs. Similar to the findings in the studies by Torsak and Aggarwal, this paper will add to the body of evidence and aid in the treatment decision for patients with uncontrolled asthma.[2,15]

## LIMITATIONS

This study is only limited to direct healthcare costs in a public hospital setting while the medication costs are from a private pharmacy. The basis for the computations of the economic costs were from clinical trial studies which may not represent real-life scenarios in the Philippine setting. Similarly, there was also limited data on efficacy and safety unlike in the other cost comparison studies.

## RECOMMENDATIONS

Future studies should include indirect costs as well as the efficacy and safety of both treatment regimens. A cost comparison of the two asthma treatment regimens in a private healthcare setting should also be undertaken to determine if the findings of the current analysis will extend to the private healthcare institutions.

## DISCLOSURE

This study was funded by Glaxo SmithKline (GSK study 213963). Drs. Pasay, Villasanta, Realiza, and Bibera are employees of GSK. Dr. Bibera holds GSK shares/stocks. Drs. Pagcatipunan and Agra are external ex-

perts and do not hold shares.

## DATA AVAILABILITY STATEMENT

Information on GSK's data sharing commitments and requesting access can be found at: https://www.clinicalstudydatarequest.com.

## ACKNOWLEDGEMENT

Medical writing support was provided by Dr. Janet Bautista, an independent medical writer, and was funded by GSK.

## REFERENCES

1. Philippine Consensus Report on Asthma Diagnosis and Management 2019 Update.
2. Bunupuradah T, Boonsawat W, Kamrapit J, Aggarwal B. Direct healthcare cost comparison of Fluticasone propionate/Salmeterol vs Budesonide/Formoterol Maintenance And Reliever Therapy for moderate/severe asthma: Results from Thailand. *Asian Pac J Allergy Immunol.* 2021 Sep 5. doi: 10.12932/AP-180421-1117. Epub ahead of print. PMID: 34542305.
3. Wickstrøm J, Dam N, Malmberg I, Hansen BB, Lange P. Cost-effectiveness of budesonide/formoterol for maintenance and reliever asthma therapy in Denmark--cost-effectiveness analysis based on five randomised controlled trials. *Clin Respir J.* 2009 Jul;3(3):169-80.
4. World Health Organization 2019. https://www.who.int/news-room/q-a-detail/chronic-respiratory diseases-asthma
5. Bhatt A, Cruz L, Ferguson L, et al. https://copd.net/statistics. Updated 2021
6. World Health Rankings. 2018.https://www.worldlifeexpectancy.com/country-health-profile/philippines.
7. Varona LL, Alava HA, Abong J, Castor MR, De Leon JC, Kwong SL. Prevalence of asthma among Filipino adults based on the National Nutrition and Health Survey (NNHeS). *Phil J Int Med*. 2014; 52(4):1-7.
8. British Guideline on the Management of Asthma: A National Clinical Guideline 2016. Available from: https://www.sign.ac.uk/
9. GINA (Global Initiative for Asthma). Global Strategy for Asthma Management And Prevention, 2021. Available from: https://ginasthma.org/
10. Price D, David-Wang A, Cho SH, et al. Time for a new language for asthma control: results from REALISE Asia. *J Asthma Allergy.* 2015 Sep 23;8:93-103.
11. Dayrit MM, Lagrada LP, Picazo OF, Pons MC, Villaverde MC. The Philippines health system review. World Health Organization, Regional Office for South-East Asia. 2018. Vol-8 No-2. 1-316.
12. Philippine Health Insurance Corporation. 2014. www.philhealth.gov.ph/about_us/mandate.php
13. Bateman ED, Boushey HA, Bousquet J, et al. Can guideline-defined asthma control be achieved? The Gaining Optimal Asthma ControL study. *Am J Respir Crit Care Med.* 2004 Oct 15;170(8):836-44.
14. Cloutier MM, Dixon AE, Krishnan JA, Lemanske RF Jr, Pace W, Schatz M. Managing Asthma in Adolescents and Adults: 2020 Asthma Guideline Update From the National Asthma Education and Prevention Program. *JAMA.* 2020 Dec 8;324(22):2301-2317.
15. Aggarwal B, Jones PW, Yunus F, et al. Direct healthcare costs associated with management of asthma: comparison of two treatment regimens in Indonesia, Thailand and Vietnam. *J Asthma.* 2022 Jun;59(6):1213-1220.
16. Bousquet J, Boulet LP, Peters MJ, et al. Budesonide/formoterol for maintenance and relief in uncontrolled asthma vs. high-dose salmeterol/fluticasone. *Respir Med.* 2007 Dec;101(12):2437-46.
17. Kuna P, Peters MJ, Manjra AI, et al. Effect of budesonide/formoterol maintenance and reliever therapy on asthma exacerbations. *Int J Clin Pract.*

2007 May;61(5):725-36.
18. Vogelmeier C, D'Urzo A, Pauwels R, et al. Budesonide/formoterol maintenance and reliever therapy: an effective asthma treatment option? *Eur Respir J.* 2005 Nov;26(5):819-28.
19. Aggarwal B, Shantakumar S, Hinds D, Mulgirigama A. Asia-Pacific Survey of Physicians on Asthma and Allergic Rhinitis (ASPAIR): physician beliefs and practices about diagnosis, assessment, and treatment of coexistent disease. J *Asthma Allergy*. 2018 Dec 11;11:293-307.
20. 20. Global Health Security Index. 2021. Available from https://www.ghsindex.org

Philippine Journal of Chest Diseases

Systematic Review/Meta-analysis

# A Systematic Review and Meta-Analysis of the Diagnostic Yield and Safety of Cryobiopsy Compared to Forceps Biopsy in Patients with Endobronchial Tumors

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PAPER AWARDED IN THE FOLLOWING CONTEST: Paper presented at the Philippine College of Chest Physicians (PCCP) Research Contest for Meta-Analysis and Case Report Categories (2020-2021, 3rd Prize Winner)

## ABSTRACT

**BACKGROUND:** Forceps biopsy (FB) via flexible bronchoscopy is now the diagnostic tool of choice for identifying endobronchial tumors. Significant failure rates were observed because of the small amount of tissue obtained and the mechanical damage to the specimen. Cryobiopsy (CB) allows for the recovery of a larger specimen sample, potentially increasing the diagnostic yield. However, CB has higher rate of bleeding which may reduce its attractiveness as a diagnostic tool of choice.

**OBJECTIVE:** To evaluate the diagnostic yield and safety of CB compared to FB.

**METHODS:** We conducted a systematic review of the literature using PUBMED, MEDLINE, and Cochrane Library. RCTs comparing CB and FB were considered. Two independent reviewers extracted data and assessed the quality of the studies.

**RESULTS:** Five randomized controlled trials (RCT) with a total of 987 participants were examined. The diagnostic yield of cryobiopsy is significantly better compared to that of forceps biopsy, with an odds ratio of 4.58 (95% CI 3.02-6.95). We observed that across all the studies, cryobiopsy provides larger tissue samples compared to forceps biopsy regardless of variables. There seems to be more bleeding in cryobiopsy compared to forceps biopsy, with a risk ratio of 1.16 (95% CI 1.03-1.31). Three (3) studies support this conclusion, but cited that overall severity is usually mild.

**CONCLUSION:** This systematic review and meta-analysis found that cryobiopsy has a higher diagnostic yield of about 21 cases per 100 when compared to forceps biopsy. In terms of bleeding, the cryobiopsy group has a slightly higher risk of about 5 cases per 100. However, the majority of cases of bleeding in the cryobiopsy group were mild.

**KEYWORDS:** *forceps biopsy, cryobiopsy, diagnostic yield, bleeding*

## INTRODUCTION

Flexible bronchoscopy allows us to see endobronchial lesions and gives us the ability to diagnose them under direct visualization. It is currently the diagnostic tool of choice for identifying endobronchial lesions.[1] Obtaining adequate tissue samples from a suspicious lesion is critical during flexible bronchoscopy for cytohistological examination.[1] Forceps biopsy has been the standard method to obtain tissue samples from an endobronchial lesion with diagnostic yield ranging between 65%-82%.[2,4] A significant failure rate was noted even if the specimen was obtained under direct visualization, therefore, a repeat bronchoscopy and biopsy are required to confirm the diagnosis.[3] The main disadvantage of the forceps biopsy technique is the small size of the obtained tissue and the mechanical damage to the specimen. [1]

Bronchoscopic cryobiopsy (BLC) is a novel technique for obtaining endobronchial lesion biopsy.[5] Cryobiopsy (CB) produces a larger tissue specimen than the traditional forceps biopsy resulting in a significantly higher diagnostic yield. Neoplasia and inflammation are promoters of vasogenesis, which is proportional to tumor size. The larger the tumor size the higher the rate of bleeding during cryobiopsy. Although some studies found significant bleeding, it was statistically insignificant. [6,7]

There have been number of randomized controlled trials (RCT) and prospective studies comparing forceps biopsy and cryobiopsy, but none of them have focused solely on endobronchial lesions. Patients with suspected endobronchial lesions who required a biopsy were recruited for the available studies. Concurrent parenchymal lung lesions were not specified in these studies. Gangnah et al. performed a meta-analysis in 2016 comparing cryobiopsy and forceps biopsy. In this study, however, the cryobiopsy involved transbronchial lung biopsy which had different expected complications than an endobronchial biopsy. In the last 5 years, cryobiopsy on endobronchial tumors has become more common so, there are newer RCTs and non-RCTs comparing cryobiopsy to forceps biopsy. The availability of newer studies provided more information about the benefits and drawbacks.

## OBJECTIVES

To compare the diagnostic yield and safety of cryobiopsy to forceps biopsy in patients with endobronchial tumors and lung tumors with endobronchial involvement. To determine (1) the diagnostic yield of cryobiopsy versus forceps biopsy in terms of specimen size and rate of definitive diagnosis, and (2) the safety of cryobiopsy versus forceps biopsy in terms of bleeding severity.

## METHODS

### Study Design

We included all randomized controlled trials that compared the diagnostic yield and safety of cryobiopsy versus forceps biopsy in patients with endobronchial tumors and lung tumors with endobronchial involvement. All identified RCTs were included until the date of this systematic review in November 2020.

### Types of Participants

We included studies with patients more than 18 years old who had endobronchial tumors or lung tumors with endobronchial involvement.

### Types of Interventions

We searched for studies that used cryobiopsy and forceps biopsy to obtain tissue samples from endobronchial tumor and lung tumor with endobronchial involvement.

### Types of Outcome Measures

The following outcome measures were included: (1) specimen size, (2) diagnostic yield, and (3) bleeding severity. Studies with varying sets of interest outcome measures were still included. Studies were included even if it did not include all the listed outcome measures of interests. The authors extracted and computed necessary effect measures if the study did not specifically

provide the exact outcome measure of interest.

### Criteria for Exclusion of Studies

Studies involving other modes of biopsy aside from cryobiopsy and forceps biopsy as well as studies involving biopsy of lung parenchyma (e.g., Transbronchial biopsy) besides from endobronchial lesion were excluded.

### Search Method

We conducted a thorough literature search in order to review available evidence. We searched the database of PubMed (MEDLINE) and Cochrane Library. For RCT, the maximum sensitivity was used. The search results were intersected with the intervention terms which were then filtered by the study design. The included studies references were manually searched.

### Selection of Studies

All selected studies were independently reviewed by the two (2) trained investigators. Any conflict on the review was resolved by the third party (research adviser).

### Data Extraction and Management

Language, first author, year of publication, patient characteristics, objectives of the study, type of the study, inclusion and exclusion criteria, randomization, blinding, intervention, follow-up, diagnostic outcomes, and severity of bleeding were independently extracted into the evidence table. Any disagreement about the review were resolved by a third party (research adviser). The authors extracted and computed necessary effect measures if the article did not specifically provide the desired outcome measure.

### Bias Risk Assessment in Included Studies

The two authors independently assessed the risk of bias in the included studies. The Cochrane handbook of systematic reviews template was used for risk assessment. Any disagreements about the review were resolved by a third party (research adviser).

### Treatment Effect Measurement

We determined the effect measure in the size of the specimen using a standardized mean difference with a 95% confidence interval. Odds ratio was used in measuring the diagnostic yield, and relative risk was used in the bleeding. The risk ratio in the bleeding was calculated based on the total reported bleeding, and each level of severity of bleeding (mild, moderate and severe) was sub-analyzed and reported separately (according to the same level of severity) between the cryobiopsy group and forceps biopsy group. In the subanalysis, an adjusted level of significance of 0.25 was used.

### Unit of Analysis Issues

For meta-analysis, the random effects model was used, with the assumption that the true size effect was similar but not identical across the included studies. By treating differences as if they were random, this model represents a lack of understanding about why real or apparent intervention effects differ.

### Assessment of Heterogeneity

The studies included in this meta-analysis were sufficiently homogeneous in terms of characteristics, interventions and outcomes providing a useful summary. The heterogeneity of all included studies was assessed. The identified sources of heterogeneity in between studies were the number of patients included in each study, size of the cryoprobe and forceps used during the biopsy, the length of freezing time used and the number of bites done. Heterogeneity was assessed using the Chi-square and quantified using the $I^2$ statistic. The $I^2$ statistic was used since it is not dependent on the number of studies or the type of outcome data, since there are only limited studies that were identified that can be included in this meta-analysis. A substantial heterogeneity was considered if the $I^2$ is $\geq$50%. According to Lee, $I^2$ values of 25%, 50% and 75% were considered low, moderate and high estimates of heterogeneity.[17]

### Assessment of Publication Bias

Studies that show positive effects are more frequently reported and published, than studies that show no significant results. The majority of meta-analysis includes only published studies which may overestimate the actual degree of effect and while underestimating harm. As a result, meta-analysis may be influenced by publication bias. We assessed the publication bias using the funnel plot which is a simple scatter plot of the intervention effect estimates from individual studies against some measures of each study size or precision. The precision of the estimated intervention effect increases as the size of the study increases. Effect estimates from small studies will therefore scatter more widely at the bottom of the graph with the spread narrowing among larger studies. In the absence of bias, the funnel plot produces a symmetrical inverted funnel, asymmetry being suggestive of a publication bias. If there is publication bias the investigators exhausted all means to retrieve unpublished studies.

## Data Synthesis

All of the selected studies and data were manually entered in the system. Analysis was performed on each listed outcome measure. A risk ratio for bleeding and odds ratio for diagnostic yield with corresponding forest plot were calculated. We used a 95% confidence interval in all of the analysis and generating output data.

## Sensitivity Analysis

Sensitivity analysis determines the strength of the observed outcomes to the assumptions made in performing the analysis. The principle is to repeat the primary analysis with an altered data set or statistical method to check for any effect on the combined outcome estimate. Studies sensed to be of lower quality were removed and the analysis was then repeated. The analysis was robust and there was little change in the overall outcome estimate. Small-study effects is the phenomenon that smaller studies sometimes show contrasting, but frequently larger treatment effects than bigger studies, which usually threatens the validity of meta-analysis. The most well-known reasons for small study effects include publication bias, outcome reporting bias and clinical heterogeneity. Sensitivity analysis by study design and risk of bias were done in this meta-analysis.

## Description of Studies

Pubmed and Cochrane library were used to search for possible studies. A total of 186 studies were retrieved in the search using the search terms described earlier. Two additional studies were retrieved through Google scholar. After duplicates were removed, it yielded 187 studies. Abstracts were reviewed and 181 studies were found not compatible with our PICO and study design, thus they were excluded. Full text articles of the remaining 6 studies were retrieved and one study was further excluded (Figure 1).

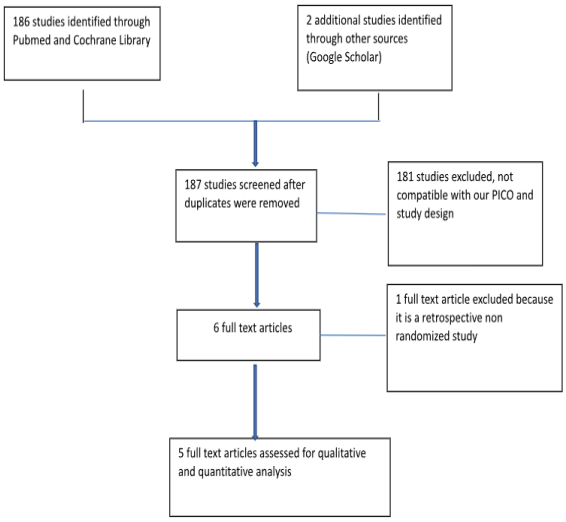


**Figure 1.** PRISMA Flow Diagram

We included five RCTs (N=987). The randomization in one prospective study was not clear. Two studies randomized patients in two groups (cryobiopsy group and frozen biopsy group). Three studies did simultaneous cryobiopsy and forceps biopsy in one patient. They were randomized as to whether cryobiopsy or forceps biopsy is done first. All studies included patients 18 years old and above with suspected endobronchial tumors. There were 182 initial studies that were excluded because

they did not fit our PICO and study design. A retrospective full text study done by Rubio et al was also excluded.

**Table 1.** Characteristics of Included Studies

| Author, Year | Study Design | Number of Subjects/ Characteristics | Intervention | Control | Outcome Measures |
|---|---|---|---|---|---|
| Aktas 2010 | Prospective Study | 41 Patients with older than 20 with endobronchial exophytic lesions | Cryobiopsy | Forceps biopsy | The median size of biopsies with cryoprobe and forceps. The diagnostic rate. Evaluation and control of complications—bleeding |
| Ehab 2017 | Prospective RCT | 47 Patients with clinically and radiographically suspected endobronchial lesions. | Cryobiopsy | Forceps Biopsy | The sum size of the forceps biopsy samples and size of cryobiopsy. The diagnostic yield. Adverse events: Post interventional bleeding |
| Hetzel 2011 | Prospective, randomized, single blinded, controlled, multicenter study | 593 patients, Patients age above 18 years suspected with endobronchial lesion based on clinical signs and radiologic images | Cryobiopsy | Forceps biopsy | Diagnostic yield. Durations of the biopsy The no. of samples taken The level of difficulty of positioning the probe Amount of bleeding |
| Mohamed 2015 | Randomized, single blinded | 40 patients, Patients suspected with endobronchial malignant lesions based on clinical and and enhanced chest CT | Cryobiopsy | Forceps Biopsy | Median size of biopsies and artifact free tissue area Diagnostic yield. |
| Schumann 2010 | Randomized, Poised, 2 arm study | 55 patients, Patients with exophytic endobronchial tumor | Cryobiopsy | Forceps Biopsy | Diagnostic Yield Safety in terms of bleeding |

### Assessment of the Risk of Bias

The included studies' risk of bias was assessed using the following criteria: random sequence generation and allocation concealment for selection bias, blinding of outcome assessment for detection bias, incomplete outcome data for attrition bias, blinding of outcome assessment and selective reporting for reporting bias. The performance bias was not included in the assessment since blinding

of personnel who perform the intervention is impossible to achieve, thus making all of the studies at risk for performance bias. Figure 2 shows the risk of bias graph while Figure 3 shows the risk of bias summary.

1. Selection Bias
   All of the studies cited that random sequence generation was done, except for the study done by Atkas 2010 which it was not quoted. Schummann 2010 and Atkas 2010, also failed to mention how allocation of concealment was done. All remaining studies utilized a closed envelope method to conceal allocation.
2. Performance Bias
   Performance bias is unavoidable since it is physically impossible to blind the person who performs the biopsy, and thereafter assess the bleeding. Thus, all of the included studies blinded only the participating patients and not the bronchoscopist.
3. Attrition Bias
   Attrition bias was not detected in any included studies. All of the randomized patients were totally accounted for and included in statistical analysis. No drop-outs were noted across all included studies.
4. Detection Bias
   The outcome measure of diagnostic yield in the included studies were performed by the pathologist which is usually independent and blinded. Detection bias was unlikely because of these third-party outcome assessors.
5. Reporting Bias
   Reporting biases were not noted in the included studies. A funnel plot was not generated since only 5 RCTs were included in this systematic review.
6. Other Biases
   All of the five studies that were included were investigator initiated and none were noted to be influenced by any product being investigated.

There was no standard size of the biopsy forceps and of the cryoprobe used across the studies. Also, no standardized protocol was used in performing both biopsies, especially on the number of bites for forceps biopsy and contact freezing time for the cryobiopsy. The mentioned variables can vary the size of the tissue sample, diagnostic yield and bleeding on both groups. In summary, random sequence generation and concealment biases were the identified potential biases of the included studies. Two (2) studies failed to either elaborate or mention how they randomized or concealed allocation of the participants, thus considered a likely source of bias.

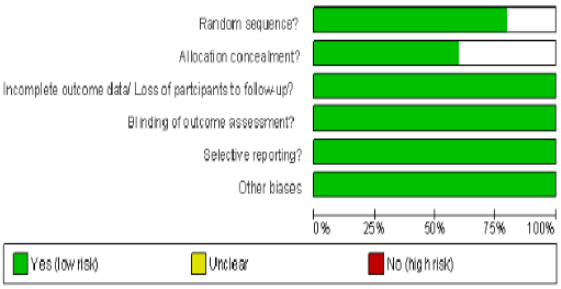


**Figure 2.** Risk of bias graph of the included studies

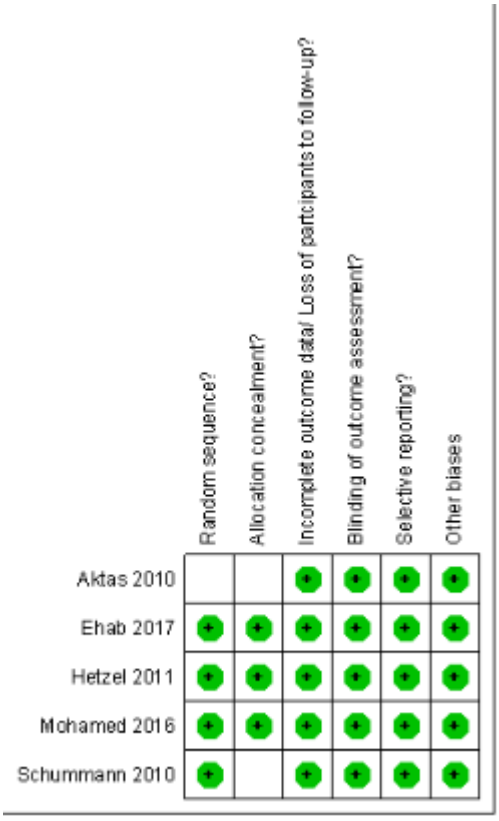


**Figure 3.** Risk of bias summary of the included studies

## RESULTS

### Effects of the Interventions

*Size of the specimen*

Upon review of the included studies, there was no standard size of the biopsy forceps and that of the cryoprobe used across the studies. There is also no standardized protocol used in performing both biopsies, especially on the number of bites for forceps biopsy and contact freezing time for the cryobiopsy. The mentioned variables can greatly vary the size of the tissue sample. There were different ways of measuring the size and units of measurement used to report the size of the obtained tissue sample as well. Noted reports were in units of diameter, square area or volume. The reviewers feel that heterogeneity is high in this outcome measure, thus meta-analysis was not done. We observe that it seems across all the studies, cryobiopsy provides larger tissue samples compared to forceps biopsy regardless of above variables. Refer to Table 2.

*Diagnostic Yield*

The diagnostic yield of cryobiopsy is significantly better compared to that of forceps biopsy, with an odds ratio of 4.58 (95% CI 3.02-6.95), and with insignificant heterogeneity as shown in Figure 4. All of the studies seem to favor cryobiopsy in providing higher diagnostic yield compared to forceps biopsy. But there are two (2) included studies that have fewer enrolled participants.

**Table 2.** Summary of the identified methodological differences and reported specimen size and conclusion of included studies

| Study Author/Year | Forceps biopsy and cryobiopsy probe size/Measuring Device | Conclusions |
|---|---|---|
| Atkas 2010 | Not mentioned | Mean diameters of samples taken with forceps biopsy and cryoprobe biopsy were 0.2 and 0.8 cm, respectively (*P < 0.001).* |
| Ehab 2017 | Cryoprobe- Erbokryo, ERBE 2.4mm diameter<br>Forceps- EndoFlex, Voerde 2.3 mm diameter<br>Measuring device- electronic caliper device | Samples obtained by cryobiopsy were significantly larger than that of the forceps biopsy (mean size in mm 5.9 ± 2.3 vs 2.5 ± 0.8, p = 0.001). |
| Hetzel 2010 | Not standardized per protocol | No reported specimen size outcome. |
| Mohamed 2016 | Cryoprobe - Erbokryo, ERBE (no diameter size specified)<br>Forceps - FB 21C or FB 52C-1, Olympus, Hamburg<br>Measuring device - Not mentioned | Median size of biopsies with cryoprobe and forceps were 1.7 cm (0.8–2.2 cm), and 0.6 cm (0.2–1.1 cm) respectively (p < 0.001). |
| Schumann 2010 | Cryoprobe- Erbokryo, ERBE 2.4mm diameter<br>Forceps - FB 21C or FB 52C-1, Olympus, Hamburg<br>Measuring device -Quantitative image analysis | Cryobiopsy had significantly larger mean total tissue area (10.4 vs 5.2 mm2; P < .0001) |

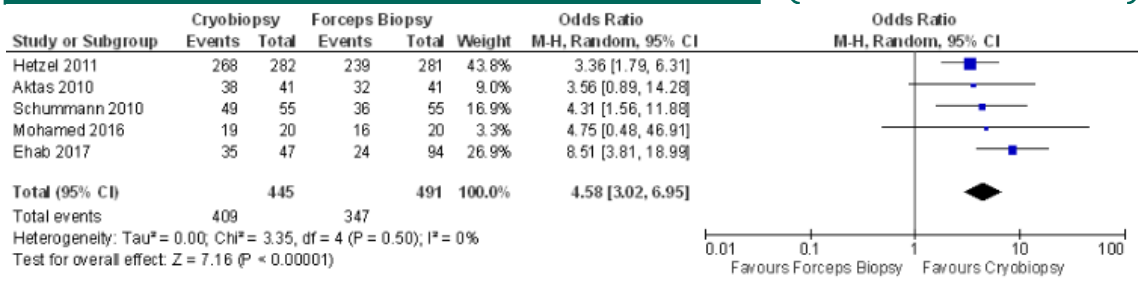


**Figure 4.** Forest plot of diagnostic yield of CB versus FB in patients with endobronchial tumors

*Bleeding*

There was more bleeding in cryobiopsy compared to forceps biopsy, with a risk ratio of 1.16 (95% CI 1.03-1.31) and with insignificant heterogeneity (Figure 5). Three (3) studies affirm this conclusion, but cited that overall severity is usually mild. One (1) study demonstrated otherwise and showed more bleeding in the forceps biopsy group, but this study reported low rate of bleeding and only mild in severity. but one (1) study contradicted it by reporting milder bleeding in the forceps biopsy. The actual incidence of mild bleeding was 218/390 (55.89%) in the cryobiopsy versus 185/389 (47.55%) in forceps biopsy.

There seems to be no significant difference in moderate bleeding between the cryobiopsy and forceps biopsy, with a risk ratio of 1.06 (95% CI 0.76-1.48) and with insignificant heterogeneity. The actual incidence of moder-

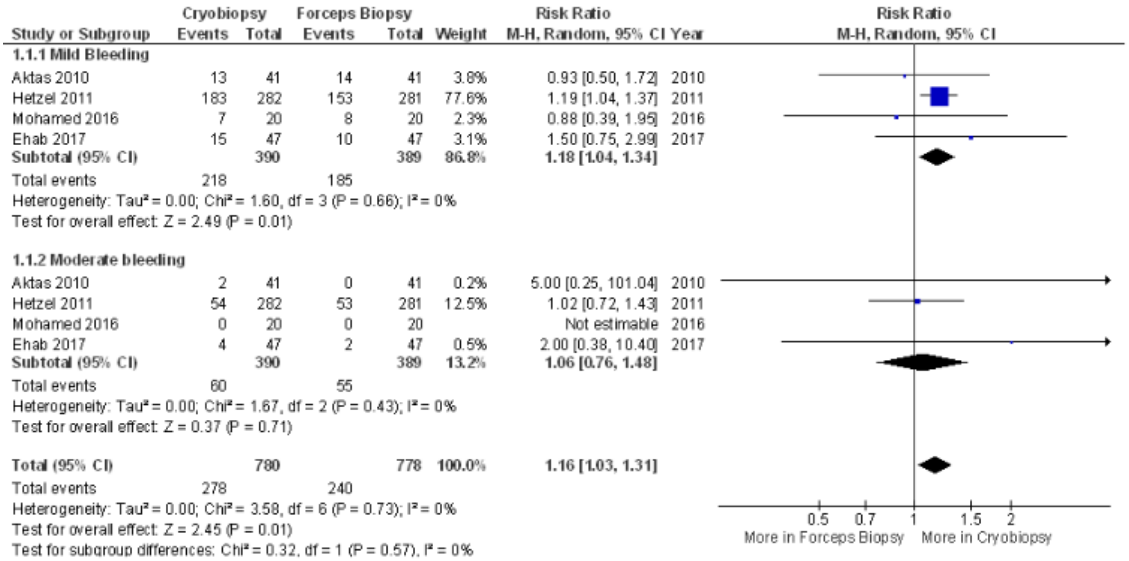


**Figure 5.** Meta-analysis and sub-group analysis of bleeding between CB and FB in patients with endobronchial tumors

*Subgroup Analysis (For Bleeding)*

Subgroup analysis was done on bleeding to demonstrate if there is difference in the bleeding events between the forceps biopsy and cryobiopsy if severity of bleeding is considered. The results showed that the cryobiopsy had more mild bleeding events than the forceps biopsy, with a risk ratio of 1.18 (95% CI 1.04-1.34) and no significant heterogeneity. Three (3) studies supported this conclusion, ate bleeding was 60/390 (15.38%) in the cryobiopsy versus 55/389 (14.14%) in forceps biopsy. Two (2) studies did not report any event of moderate bleeding in the forceps biopsy. While one (1) study did not report an event of moderate bleeding in the cryobiopsy group.

*Sensitivity Analysis*

Table 3 shows the results of a sensitivity analysis that took the study design into con-

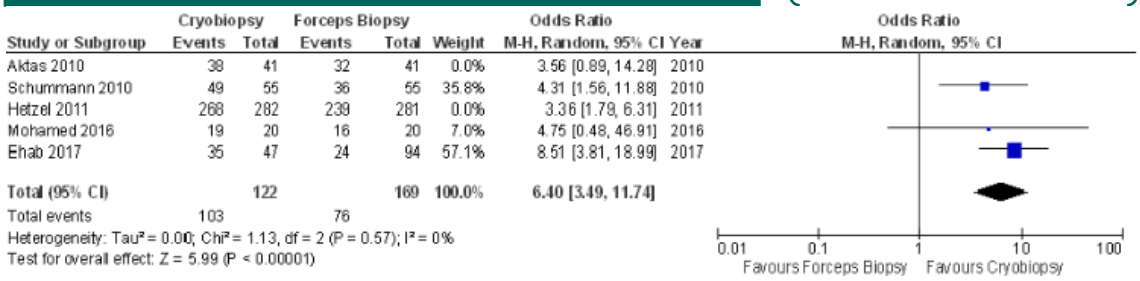


**Figure 6.** Sensitivity analysis -removed 2 studies with no or different biopsy protocol

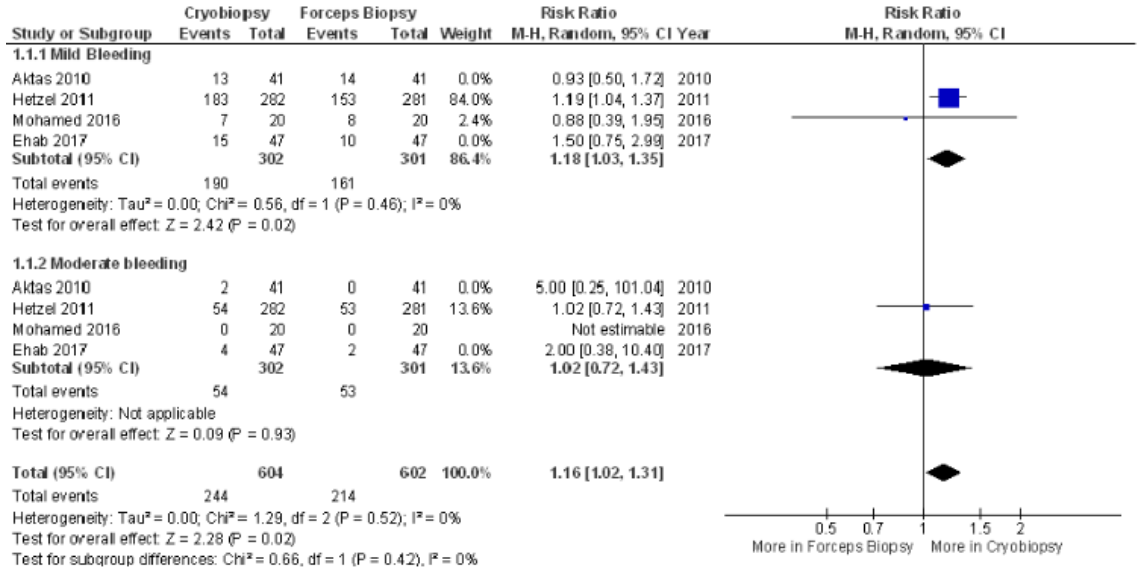


**Figure 7.** Sensitivity analysis --removed 2 studies that randomize the patient base on the sequence of biopsy

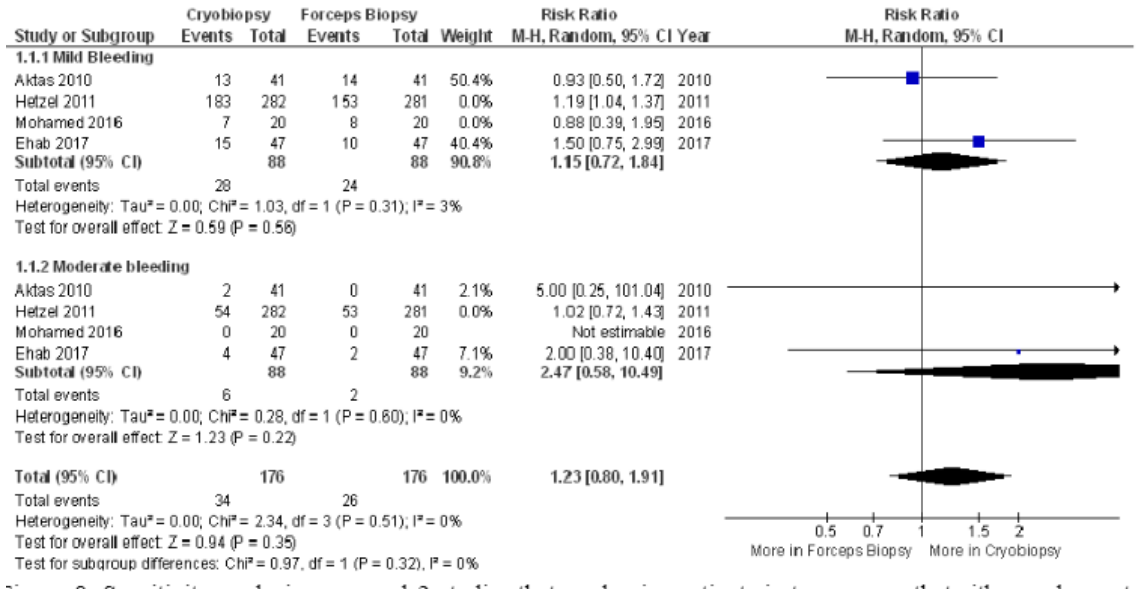


**Figure 8.** Sensitivity analysis -emoved 2 studies that randomize patients in two groups that either underwent forceps or cryobiopsy

sideration. For diagnostic yield, two studies with no biopsy protocol or protocols that

differed from the other studies were excluded. The remaining three studies had a higher diagnostic yield OR of 6.40 (95% CI 3.49, 11.74). This implies that the non-uniformity in the biopsy procedure had a significant impact on the magnitude of the pooled estimate, but the direction remained unchanged.

We also analyzed the effect of different types of randomization to the relative risk of bleeding. First, we considered only the studies that randomized patients in two groups that either underwent forceps or cryobiopsy. The RR is 1.16 (95% CI 1.02, 1.31). The RR is almost the same to the original estimate of 1.16 (95% CI 1.03, 1.31). Second, we consider studies that randomized the patient based on the sequence of biopsy but undergoing both biopsies. The RR for bleeding is higher (RR 1.23 (95% CI 0.80, 1.91)), but the confidence interval was noted to be wider, thus contributing to imprecision. This is probably the effect of the weight of the excluded studies, with higher number participants. We concluded that the results regarding bleeding are robust because even with the sensitivity analysis, RR are similar. Refer to Table 3 for the sensitivity analysis.

**Table 3.** Summary of sensitivity analysis for the studies included

| Criteria | OR/ RR |
|---|---|
| Original diagnostic yield | OR 4.58 (3.02, 6.95) |
| By study design<br>-removed 2 studies with no or different biopsy protocol<br>-included 3 studies | OR 6.40 (3.49, 11.74) |
| Original bleeding risk | RR 1.16 (1.03, 1.31) |
| By study design<br>-removed 2 studies that randomize the patient base on the sequence of biopsy<br>-included 2 studies | RR 1.16 (1.02, 1.31) |
| By study design<br>-removed 2 studies that randomize patients in two groups that either underwent forceps or cryobiopsy<br>-included 2 studies | RR 1.23 (0.80, 1.91) |

**OR—odds ratio; RR—risk ratio*

*Quality of Evidence*

Using the GRADE methodology, there is high quality of evidence. We are very confident that the true effect lies close to that of the estimate of the effect. Further research is likely to affirm our confidence in the estimate of effect. Refer to Table 4 for the summary of findings. In summary, cryobiopsy is more efficient in providing a definitive diagnosis versus

**Table 4.** GRADE Evidence Profile

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Cryobiopsy | Forceps Biopsy | Relative (95% CI) | Absolute (95% CI) | | |
| **Diagnostic yield (assessed with: Diagnosis )** | | | | | | | | | | | | |
| 5 | randomised trials | not serious | not serious | not serious | not serious | none | 409/445 (91.9%) | 347/491 (70.7%) | **OR 4.58** (3.02 to 6.95) | **21 more per 100** (from 17 more to 24 more) | ⊕⊕⊕⊕ HIGH | |
| **Total Bleeding (assessed with: Bleeding)** | | | | | | | | | | | | |
| 4 | randomised trials | not serious | not serious | not serious | not serious | none | 278/780 (35.6%) | 240/778 (30.8%) | **RR 1.16** (1.03 to 1.31) | **5 more per 100** (from 1 more to 10 more) | ⊕⊕⊕⊕ HIGH | |
| **Mild Bleeding (assessed with: Bleeding)** | | | | | | | | | | | | |
| 4 | randomised trials | not serious | not serious | not serious | not serious | none | 218/390 (55.9%) | 185/389 (47.6%) | **RR 1.18** (1.04 to 1.34) | **9 more per 100** (from 2 more to 16 more) | ⊕⊕⊕⊕ HIGH | |
| **Moderate Bleeding (assessed with: Bleeding)** | | | | | | | | | | | | |
| 4 | randomised trials | not serious | not serious | not serious | not serious | none | 60/390 (15.4%) | 55/389 (14.1%) | **RR 1.06** (0.76 to 1.48) | **1 more per 100** (from 3 fewer to 7 more) | ⊕⊕⊕⊕ HIGH | |

forceps biopsy with an OR of 4.58. In practice, it means that we can diagnose 21 patients more in every 100 cases compared to forceps biopsy. There is a slight increase in the chance of bleeding for cryobiopsy (RR of 1.16) versus forceps biopsy. Mild bleeding is the most commonly reported severity. We computed the number needed to harm for both mild and moderate bleeding, results were 12 and 81, respectively. In actual practice, there will be 9 more mild bleeding in every 100 cases and 1 more moderate bleeding in every 100 cases, if cryobiopsy will be used in doing endobronchial biopsy.

## RESULTS

### Summary of findings

Cryobiopsy has a significantly higher diagnostic yield than forceps biopsy. Cryobiopsy, on the other hand, has a slightly higher risk of bleeding, specifically mild bleeding. There is no statistically significant difference in the risk of moderate bleeding between the two biopsy methods. Patients in both groups with moderate bleeding resolved spontaneously after electrocautery or argon plasma coagulation (APC). There was no note of severe bleeding in both groups.

### Overall completeness and applicability of evidence

The reviewers searched studies using the usual medical database (PUBMED and COCHRANE) to retrieve the published data. In addition, a manual search using Google was utilized used to search and retrieve the studies. The following are the strong points of this study: it included only RCT for good methodological quality, the population was homogeneous, a head-on comparison of intervention to the standard of care, and almost similar reporting of outcome measures of the included studies.

The limitations of this study include a different randomization process in each study, non-standardized material (size of cryoprobe and forceps) and methods between the studies, and a small number of enrolled participants in most of the included studies. Furthermore, a meta-analysis on specimen size was not performed due to concerns about the non-uniformity of biopsy materials and methods, as well as the units of measurement used in reporting.

To further strengthen the claim of an intervention to be applicable, it is essential to enroll a higher number of participants and standardize materials and methods of the biopsy procedure.

### Potential review process biases

The two authors searched three (3) databases. We also conducted a manual search for the related articles on through Google. Random sequence generation and concealment biases were identified as potential biases following a review of the included studies. The reviewer did not notice other biases during review.

### Agreements and disagreements as well as reviews

The conclusion of this review suggested that cryobiopsy has a higher diagnostic yield than forceps biopsy, and is in agreement with the latest systematic review published in 2016. However, the quality of evidence for the said review was graded low due to methodological flaws such as variable study type inclusion (i.e., retrospective, non-randomized prospective, and RCT), non- homogeneous population (i.e., ILD, peripheral and central lung tumors, endobronchial tumors) and variable biopsy location (i.e., endobronchial and peripheral lung biopsy). On the other hand, this systematic review and meta-analysis has a more homogeneous population, uses the same biopsy location and procedures, and only includes included RCTs. The number of included studies, however, limited this.

## CONCLUSION

This systematic review and meta-analysis found that cryobiopsy has a higher diagnostic yield of about 21 cases per 100 when compared to forceps biopsy. In terms of

bleeding, the cryobiopsy group has a slightly higher risk of about 5 cases per 100. However, the majority of cases of bleeding in the cryobiopsy group were mild.

### Practice Implications

Cryobiopsy is an effective and safe preliminary tool in diagnosing endobronchial tumors. Although there is an increased risk of bleeding in cryobiopsy, it is usually mild. The use of cryobiopsy as an initial tool in diagnosing suspected endobronchial tumors can be incorporated into our institutional protocol. This will allow us to improve our diagnostic yield while also lowering costs associated with subjecting our patients to more invasive procedures if the initial diagnostic procedure is inconclusive. Furthermore, this will reduce the possibility of adverse events or morbidity in patients as a result of complications from multiple invasive diagnostic procedures.

Unfortunately, the cost of the technology, machine utilization costs, and the need for a well-trained bronchoscopist (an interventional radiologist) limit the availability of cryobiopsy.

The above factors are plausible reasons why cryobiopsy is impractical and inaccessible to low income and remote communities.

### Implications for future research

If future RCTs comparing cryobiopsy to forceps biopsy can be done , they should be conducted in a two-arm randomized controlled trial using standardized materials (size of cryoprobe and forceps) and methods (standardized measurement of biopsy specimen) for more homogenous data. Another meta-analysis comparing cryobiopsy and forceps for transbronchial lung biopsy (lung tissue biopsy) can be performed.

## ACKNOWLEDGMENT

We would like to thank our research advisers Dr. Paul Rilhelm Evangelista and Dr. Cecilia Jocson for their help with this study. We would like to thank Dr. Raquel Ibañez and Dr. Cecile Jimeno for teaching us and guiding us through the process of writing this research paper in making this research paper.

## REFERENCES

1. Mohammed AS, Sharshar RS, Wasfy RE, et al. The diagnostic yield of cryobiopsy versus forceps biopsy of malignant endobronchial lesions. *The Egyptian Journal of Chest Diseases and Tuberculosis*. 2016;65 (1):267-270
2. Aktas Z, Gunay E, Hoca NT, et al. Endobronchial cryobiopsy or forceps biopsy for lung cancer diagnosis. *Annals of Thoracic Medicine.* 2010; 5(4):242-246.
3. Hetzel J, Eberhardt R, Herth FJF, et al. Cryobiopsy increases the diagnostic yield of endobronchial biopsy: a multicenter trial. *European Respiratory Journal.* 2012;39(3):685-690.
4. Ehab A, El-Badrawy MK, Moawad AA, et al. Cryobiopsy versus forceps biopsy in endobronchial lesions, diagnostic yield and safety. *Advances in Respiratory Medicine.* 2017; 85(6):301-306.
5. Dhooria S, Agarwal R, Sehgal IS. Bronchoscopic lung cryobiopsy: An Indian association for bronchology position statement. *Lung India*. 2019;36(1):48-59.
6. Dalar L, Ozdemir C, Sokucu SN, et al. Bronchoscopic treatment of benign endoluminal tumors. *Canadian Respiratory Journal*. 2019;5269728.
7. Udugawa H, Kirita K, Naito T, et al. Feasibility and utility of transbronchial cryobiopsy in precision medicine for lung cancers: prospective single arm study. *Cancer Science.* 2020;111(7): 24882498.
8. Li Z, Zarogoulidis P, Kougioumtzi I, et al. Surgical approaches of endobronchial neoplasms. *Journal of Thoracic Disease*. 2013;5(Supp14): 5378-5382.
9. Wilson RW, Kirejczyk W. Pathological and radiologic correlation of endobronchial neoplasms: part 1, benign tumors. *Ann Diagn Pathol.* 1997;1 (1):31-46.

10. Shahzad T, Irfan M. Endobronchial tuberculosis: a review. *Journal of Thoracic Disease.* 2016;8(12): 3797-3802.
11. El-Dahdouh S, Abd Elaal GA, El-kady N, et al, Comparison between endobronchial forceps biopsy and cryobiopsy by flexible bronchoscopy. *Egyptian Journal of Chest Diseases and Tuberculosis*. 2016;65(1):325-329.
12. Aktas Z, Gunay E,Hoca NT, et al. Endobronchial cryobiopsy or forcep biopsy for lung cancer diagnosis. *Ann Thoracic Med.* 2010;5(4):242–246.
13. Kim JH, Choi JM, Song SE et al. Comparison of forcep biopsy and cryobiopsy by a flexible bronchoscopy. *Tuberculosis Respir Dis.* 2009; 66(2):110-115.
14. Aktas Z, Gunay E, Hoca NT, et al. Endobronchial cryobiopsy or forceps biopsy for lung cancer diagnosis. *Annals of Thoracic Medicine.* 2010; 5(4): 242–246.
15. Hetzel J, Eberhardt R, Herth FJF et al. Cryobiopsy increases the diagnostic yield of endobronchial biopsy: a multicentre trial. *European Respiratory Journal.* 2012;39: 685-690
16. Lee YH. Overview of meta-analysis for clinicians. *Korean Journal of Internal Medicine.* 2018. 33:277-283.

Philippine Journal of Chest Diseases

Case Report

# Successful Reversal of Severe Pulmonary Arterial Hypertension After Transcatheter Closure of a Patent Ductus Arteriosus in a 47-Year-Old: A Case Report

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PAPER PRESENTED IN THE FOLLOWING CONFERENCE: American Thoracic Society (ATS) International Conference (May 2021)

## ABSTRACT

**BACKGROUND:** Patent Ductus Arteriosus (PDA) has an estimated prevalence of 1:2000 in children. However, the true prevalence amongst adults is not well-defined. Among patients with congenital heart disease (CHD), 5-10 % will subsequently develop pulmonary hypertension if untreated. Usual therapeutic options for adult PDA patients with severe pulmonary arterial hypertension (PAH) include targeted therapy aimed at reducing pulmonary pressures, such as phosphodiesterase-5 inhibitors, guanylate cyclase stimulators, and endothelin receptor antagonists. Closure of such lesions is not regarded standard of care because the pulmonary microvasculature is thought to have already begun irreversible changes, that lead to Eisenmenger syndrome. Only a few adult cases were done internationally, and to date, there have been no local cases of successful reversal of severe pulmonary arterial hypertension in PDA. Our case report shows that these patients can still undergo successful closure after treatment with targeted therapy.

**CASE PRESENTATION:** We present a case of a 47-year-old woman diagnosed with congenital heart disease during childhood but had refused treatment as she was asymptomatic. In her adult life, she was repeatedly admitted for dyspnea and had been on home oxygen for 2 years before she was admitted to our institution. Chest radiograph revealed cardiomegaly as well as pulmonary hypertensive changes. A two-dimensional echocardiogram (2D echo) revealed a Pulmonary Artery Systolic Pressure (PASP) of 155 mmHg by tricuspid regurgitation (TR) jet. Cardiac magnetic resonance imaging revealed a PDA, and a bidirectional flow was seen on transesophageal echocardiogram. Sildenafil 25mg thrice daily was started and she was referred for possible percutaneous closure. Catheterization showed an elevated mean pulmonary artery pressure (mPAP) of 97mmHg. A vasodilator challenge showed reversibility of the shunt (decrease of pulmonary vascular resistance (PVR) to 11.6 woods unit from 40.85 woods unit: Rp/Rs of 0.42 from 1.95), thus, closure was successfully done. Sildenafil was resumed at the same dose due to persistent elevation of PASP. Subsequent 2D echocardiography evaluation showed eventual normalization of the PASP. Sildenafil and home oxygen were eventually discontinued after one year. Two-year follow-up showed that the patient continued to remain asymptomatic with normal PASP on 2D echocardiography.

**CONCLUSION:** In the advent of targeted PAH therapies, such as Sildenafil, there is a growing role for a combined medical-surgical approach in patients who are either borderline operable, or initially inoperable.

**KEYWORDS:** *pulmonary vascular disease, patent ductus arteriosus, Sildenafil, Pulmonary arterial hypertension, congenital heart disease, reversal*

## INTRODUCTION

PAH is an eventual complication of untreated CHD, particularly in patients with left-to-right (systemic-to-pulmonary) shunts. Persistent exposure of the pulmonary vasculature to increased blood flow and pressure may result in vascular remodeling and dysfunction. This leads to increased pulmonary vascular resistance (PVR) and increased pressures in the right side of the heart.

Several patients with left-to-right shunts are still undiagnosed until childhood or even adulthood. In these patients, changes to the pulmonary vasculature have already occurred, and PAH has, to a certain extent, already developed. This continually growing cohort of adult PAH-CHD patients presents the clinician with a range of challenges associated with the management of complex cardiac and non-cardiac comorbidities. With the advent of PAH-specific therapies (such as Sildenafil) in recent years, there have been major advances in the treatment of patients with other forms of PAH, and comparable success is beginning to be seen in PAH-CHD as evidenced by studies done by Nazzareno et al.

## THE CASE

A 47-year old woman was diagnosed with an unrecalled congenital heart disease since childhood. The family was advised to get the CHD repaired, but they refused. Since then, the patient has been admitted several times for dyspnea and pneumonia. Four years prior to admission to our institution, the patient complained of exertional dyspnea while doing her daily activities. The patient then sought consult where a 2D echocardiography was performed revealing severe pulmonary hypertension (see Table 1). No congenital heart defect was noted in this 2D echocardiography. The patient was advised 2-liter oxygen supplementation via nasal cannula at home and was prescribed with unrecalled medications. In the interim, the patient was noted to have worsening dyspnea. The patient could no longer tolerate less than ordinary activities, thus sought admission in our institution.

The patient has no history of previous surgery. The patient is also a Gravida 1 Para 1 with uneventful pregnancy. She is a non-smoker, non-alcoholic beverage drinker, and denies illicit drug use. Heredofamilial diseases include hypertension, diabetes, and heart disease.

On examination, the patient is of normal build and nutrition (BMI: 20.78 kg/m2), afebrile and slightly tachypneic (23 cycles per minute), tachycardic (110 beats per minute), and has normal blood pressure (110/70 millimeters mercury). Oxygen saturation was 88% at room air. The patient was noted to have engorged neck veins, bibasal rales, and (occasional) wheeze, a grade 5/6 diastolic murmur was heard at the left parasternal border. No edema was noted. Laboratory tests were unremarkable except for erythrocytosis (RBC: 5.41 106/L) on CBC. Arterial blood gas (ABG) showed hypoxemia (pO2 65 mmHg at 4LPM, NV: >80 mmHg). Electrocardiogram (ECG) revealed sinus rhythm with left atrial abnormality, incomplete right bundle branch block with biventricular hypertrophy and ante-

**Table 1.** Echocardiographic Monitoring Pre- and Post-PDA closure

| | 2 Years pre-closure | 1 month pre-closure | Immediately post closure | 1 month post-closure | 3 month post-closure | 9 month post-closure | 24 month Post- closure |
|---|---|---|---|---|---|---|---|
| PASP (mmHg) | 156 | 155 | 45 | 82 | 73 | 23 | 19 |
| Interventions | O2 at 2LPM | Sildenafil 25mg 3x/day<br><br>O2 at 2LPM | O2 at 2LPM | Sildenafil 25mg 3x/day<br><br>O2 at 2LPM | Sildenafil 25mg 3x/day<br><br>O2 at 2LPM | Sildenafil 25mg 3x/day<br><br>O2 at 2LPM | none |

roseptal wall ischemia and/or right ventricular strain pattern. Chest radiograph revealed cardiomegaly with pulmonary hypertensive changes (Figure 1). Because of the patient's history of pulmonary hypertension, the patient was initially managed as a case of idiopathic PAH, and was worked-up. Computed tomography (CT) with pulmonary embolism protocol revealed a significantly dilated main pulmonary trunk and hypertrophy of the ventricular walls on both sides including the interventricular septum and no findings of pulmonary artery embolism. 2D echocardiography (Table 1) revealed dilated right-sided chambers, dilated main pulmonary artery diameter, severe tricuspid regurgitation, and severe pulmonary hypertension, and, no intra-cardiac nor extra-cardiac defects were seen on echocardiography. As there has been a history of an unrecalled CHD, a cardiac magnetic resonance imaging (MRI) was done which revealed a patent ductus arteriosus with a Qp: Qs (ratio of pulmonary blood flow to systemic blood flow) of 0.59 (Figures 2,3). Transesophageal echocardiography was done which revealed a PDA with bidirectional flow.

The patient was diagnosed to have PDA with severe PAH. This was supported by physical findings of engorged neck veins, diastolic murmur with (a finding of) hypoxemia, right ventricular hypertrophy, elevated PAP on 2D echocardiography, a PDA with the bidirectional flow and a Qp:Qs ratio of less than 1 on transesophageal echocardiogram and cardiac MRI. The patient was started on Sildenafil 25mg tab thrice daily, advised the use of 2L oxygen via nasal cannula, which relieved dyspnea. The patient was referred to the Philippine Heart Center for reversibility testing.

After a month, the patient was admitted to the Philippine Heart Center. Hemodynamic studies revealed (Table 2): (1) severely elevated pulmonary artery pressure; (2) elevated pulmonary vascular resistance (PVR) at 3,268 dynes/sec/cm5 (normal value: 20-130 dynes/sec/cm5), equivalent to 40.85 woods unit (normal value: <2-3 woods unit); and, (3) conical PDA (diameter of 3.3mm), Qp:Qs was 0.6:1.0 with Rp/Rs (ratio of pulmonary-to-systemic vascular resistance) of 1.95, indicative of moderate pulmonary vascular disease (Figure 4). 100% Oxygen challenge test was done which showed reversibility of the shunt (PVR of 928 dynes/sec/cm5, equivalent to 11.6 woods unit; Rp/Rs of 0.42 post-O2 challenge). Percutaneous device closure using Amplatzer™ Duct Occluder was done without periprocedural complications (Figure 5). The patient was then discharge and taken off sildenafil.

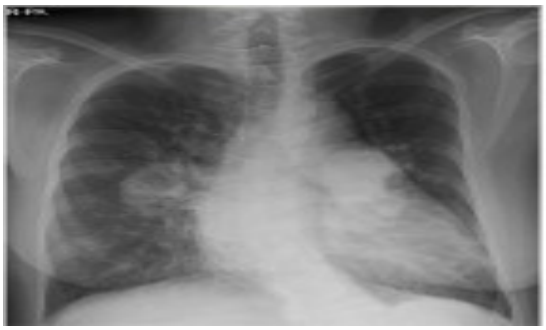

**Figure 1.** Chest radiograph showing cardiomegaly with pulmonary hypertensive changes

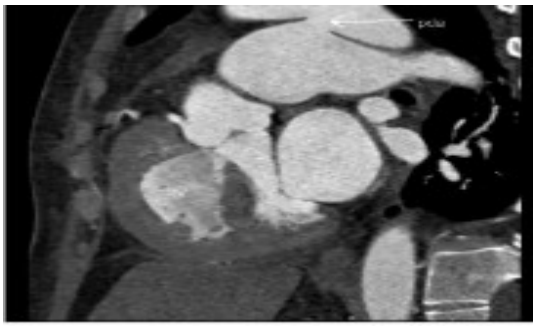

**Figure 2.** PDA (arrow) connecting the main pulmonary artery (MPA) and aortic arch

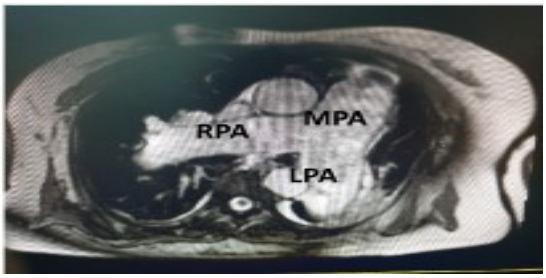


**Figure 3.** Dilated main and branch pulmonary arteries. MPA=3.9cm, right pulmonary artery (RPA) = 3.1cm, left pulmonary artery (LPA) = 3.6cm

Table 2 shows the serial pulmonary artery pressures along with interventions

done at 2 years pre-closure, 1 month pre-closure, immediately post-closure, and 1, 3, 9, and 24 months after closure. One month post-closure, (a) repeat 2D echocardiography still revealed residual pulmonary hypertension, with episodes of exertional dyspnea after performing daily activities and was still unable to tolerate without oxygen supplementation thus, sildenafil 25mg thrice daily was resumed and frequent follow-up was done. The subsequent 2D echocardiography revealed declining trend in pulmonary artery systolic pressure beginning at 3 months. At 9 months post-closure, patient was now noted to be asymptomatic and was able to tolerate without oxygen supplementation, thus sildenafil was discontinued. At 24 months post-closure, patient continued to be asymptomatic and pulmonary artery systolic pressure remained normal without medications.

## DISCUSSION

**Table 2.** Hemodynamic studies

| | Baseline | 100% Oxygen |
|---|---|---|
| PVR | 40.85 woods unit (NV: <2-3 woods unit) | 11.6 woods unit |
| Rp/Rs | 1.95 | 0.42 |
| MPAP | 97mmHg | 85mmHg |
| | (NV: 8-20mmHg) | |

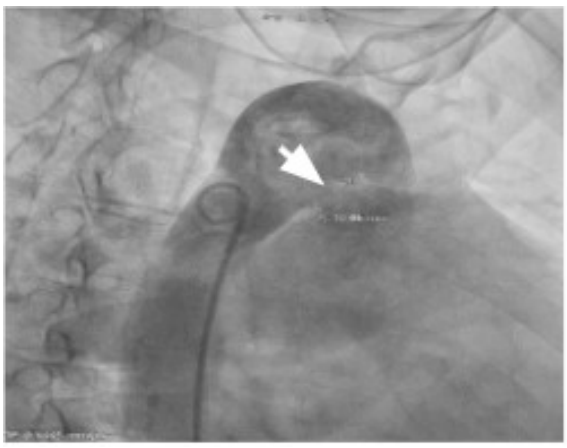

**Figure 4.** PDA

PDA in children has a prevalence of 1:2000, however, the prevalence amongst adults is not well-defined since it is usually discovered and treated during childhood1,2. Most cases presenting during adulthood show signs and symptoms of heart failure, edema, and pulmonary hypertension1. Although 2D echocardiography is the standard diagnostic modality3, with a sensitivity of as high as 83% 4, it still has significant operator variability, to which the late diagnosis of the lesion in this patient could be attributed to.

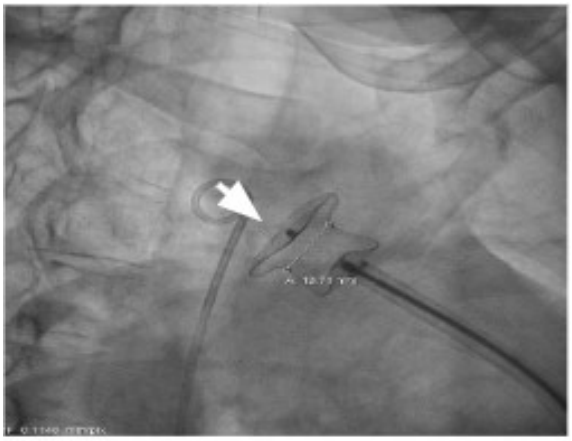

**Figure 5.** Device Closure

Left untreated, prolonged left-to-right shunting in a hemodynamically significant PDA can progress to pulmonary arterial hypertension, a disease of the small pulmonary arteries that is characterized by vascular proliferation and remodeling. It causes a progressive increase in pulmonary vascular resistance and, ultimately, right ventricular failure and death. PAH occurs in approximately 1.6% to as high as 12.5% of adult patients with CHD5. The current definition of PAH relies on a pulmonary arterial pressure ≥25 mmHg at rest, a left atrial pressure ≤15 mmHg, and normal resting cardiac output, suggesting a resting pulmonary vascular resistance of ≥3 Woods units. 5

Three factors are thought to cause the increased pulmonary vascular resistance that characterizes this disease: vasoconstriction, remodeling of the pulmonary vessel wall, and thrombosis in situ.6 The 3 major pathophysiological pathways, namely the endothelin pathway, nitric oxide pathway, and prostacyclin pathway, represent important signaling cas-

cades in PAH. These pathways also represent important therapeutic targets. PAH is subdivided into 4 clinical groups: (1) Eisenmenger syndrome; (2) PAH associated with systemic-to-pulmonary shunts; (3) PAH with small defects; and (4) PAH after surgical repair.6 Each clinical group has different management principles. Our patient belonged to the second category.

To date, advanced therapies, including endothelin receptor antagonists, phosphodiesterase type-5 inhibitors, prostacyclin, and prostacyclin analogs, which all serve to decrease pulmonary vascular resistance by inducing vasodilation of the pulmonary vasculature. Multiple trials such as BREATHE-5, SUPER, SERAPHIN, PHIRST have demonstrated their safety and efficacy in severe PAH, offering improvements in exercise capacity, functional class, and hemodynamics, without compromising oxygen saturation.7-10

According to 2020 ESC guidelines for the management of adult congenital heart disease, class I recommendation for PDA closure are in patients with evidence of LV volume overload and no PAH (no non-invasive signs of PAP elevation or invasive confirmation of PVR <3 WU in case of such signs), while in patients who have developed PAH with PVR 3 -5 WU, when there is still significant L-R shunt (Qp:Qs>1.5) is a class IIa recommendation. In patients who have developed PAH with PVR >/ = 5 WU, PDA closure may be considered when there is still significant L-R shunt (Qp:Qs>1.5) is a class IIb recommendation; lastly, PDA closure is not recommended in patients with Eisenmenger physiology and patients with lower limb desaturation on exercise.11 In our case, the patient did not have any evidence of LV volume overload. During right heart catheterization a significantly increased pulmonary vascular resistance (PVR 40.85 woods unit) was noted with a Qp:Qs was 0.6:1.0. All of these findings make this patient a poor candidate for interventional closure. Specifically, when PVR exceeds 10 woods unit, correction of defect is contraindicated .12 The latest European Society of Cardiology Guidelines for the Management of Adult Congenital Heart Disease also state that in PDA patients who have developed PAH with PVR >_5 WU, PDA closure may be considered when there is still significant left-to-right shunt (Qp:Qs >1.5)11 Thus, this patient falls into a gray area zone regarding the repair of the CHD. Medical therapy with the phosphodiesterase-5 inhibitor sildenafil was then instituted. However, on 100% oxygen challenge test, the Rp/Rs (ratio of pulmonary to systemic vascular resistance) decreased to 0.42 from 1.95, demonstrating reversibility of the hemodynamic profile should the lesion be closed.

Ultimately, the important determinant of management and prognosis is whether the PAH is reversible. The criteria for reversibility are as follows: 1) a fall in the pulmonary artery pressure or no elevation; 2) no decrease in the aortic pressure and SaO2; and 3) no worsening of signs and symptoms13,14. If all the criteria were satisfied, PAH is considered reversible, as what was seen in our case. There is a marked paucity of data regarding combined medical and interventional approaches; with only 7 reported successful cases, and no Philippine data has been noted.15 Two of these cases -- by Ussia et al and by Mitropoulos et al -- were patients with PDA and severe PAH who underwent successful closure after medical therapy. These 2 cases demonstrated patients initially deemed unoperable due to increased pulmonary vascular resistance and due to being a “non-responder” to vasoreactivity testing with NO. These patients were then prescribed with pulmonary vasodilator drugs (such as bosentan) for 3 months. Afterwhich, a significant improvement on pulmonary hemodynamics were noted on repeat right heart catheterization thus transcutaneous repair was successfully done. As mentioned above, since patient selection for PDA closure centers on the evidence of reversibility of the pulmonary vascular resistance, complete closure using Amplatzer duct occluder was decided by the health care team after proper explanation of the benefits and risks to

the patient. These risks include a small percentage of patients with borderline hemodynamic data with PDA and PAH that can deteriorate after PDA closure due to non-regression of pulmonary hypertension, progressive pulmonary vascular disease, and right sided heart failure. Thus, treatment with permanent closure must still be performed with caution.16 As was seen in our patient, PASP 1-month post-repair showed a rebound increase, albeit not as high as pre-intervention level, likely due to the persistence of a pulmonary vascular disease10,13-14. For this purpose, sildenafil was continued, as a pharmacological prophylaxis for a rebound pulmonary hypertension.17. Subsequent 2D echocardiography showed decreasing values in the PAP. To the best of the investigator's knowledge, this is the first reported case of a successful reversal of severe pulmonary hypertension following device closure in an adult patient with previously untreated CHD.

## CONCLUSION

With the advent of advanced interventional techniques, patients with severe PAH-CHD could still benefit from the repair of cardiac defect, even with suspected pulmonary vascular disease. The decision to repair the defect should be approached by taking into consideration multiple factors such as patient characteristics, functional capacity, hemodynamic findings, and most critically - evidence of reversibility on invasive testing.

In the advent of targeted PAH therapies, such as Sildenafil, there is a growing role for a combined medical-surgical approach to those patients that are either borderline operable, or initially inoperable, hereby identifying a larger number of potential appropriate candidates for corrective treatment.

## REFERENCES


1. Schneider DJ, Moore JW. Patent Ductus Arteriosus. *Circulation.* 2006;114 (17):1873-1882. doi:10.1161/CIRCULATIONAHA.105.592063
2. Wiyono SA, Witsenburg M, de Jaegere PPT, Roos-Hesselink JW. Patent ductus arteriosus in adults. *Neth Heart J.* 2008;16(7-8):255-259.
3. Galal MO, Ahmad Z, Hussain A, et al. Accuracy of Routine 2D Echocardiography to Estimate Patent Ductus Arteriosus Type and Dimension and Predict Device Selection for Successful PDA Occlusion. *J Saudi Heart Assoc.* 2021;33(4):339-346. doi:10.37616/2212-5043.1284
4. Gutgesell HP, Huhta JC, Latson LA, Huffines D, McNamara DG. Accuracy of two-dimensional echocardiography in the diagnosis of congenital heart disease. *The American Journal of Cardiology.*1985;55(5):514-518. doi:10.1016/0002-9149(85)90237-1
5. Simonneau G, Galiè N, Rubin LJ, et al. Clinical classification of pulmonary hypertension. *Journal of the American College of Cardiology.* 2004;43(12, Supplement):S5-S12. doi:10.1016/j.jacc.2004.02.037
6. Simonneau G, Gatzoulis MA, Adatia I, et al. Updated Clinical Classification of Pulmonary Hypertension. *Journal of the American College of Cardiology.* 2013;62 (25, Supplement):D34-D41. doi:10.1016/j.jacc.2013.10.029
7. Bosentan Therapy in Patients With Eisenmenger Syndrome. *Circulation.* Accessed December 1, 2022. https://www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.106.630715?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed
8. Ghofrani HA, D'Armini AM, Grimminger F, et al. Riociguat for the Treatment of Chronic Thromboembolic Pulmonary Hypertension. *N Engl J Med.* 2013;369 (4):319-329. doi:10.1056/NEJMoa1209657
9. Galiè N, Ghofrani HA, Torbicki A, et al. Sildenafil Citrate Therapy for Pulmonary Arterial Hypertension. *New England Journal of Medicine.* 2005;353(20):2148-2157. doi:10.1056/NEJMoa050010
10. Study With an Endothelin Receptor Antagonist in Pulmonary Arterial Hyperten-

sion to Improve Clinical Outcome | Clinical Trial. *American College of Cardiology.* Accessed December 3, 2022. https://www.acc.org/latest-in-cardiology/clinical-trials/2015/02/11/11/13/http%3a%2f%2fwww.acc.org%2flatest-in-cardiology%2fclinical-trials%2f2015%2f02%2f11%2f11%2f13%2fseraphin

11. Baumgartner H, De Backer J, Babu-Narayan SV, et al. 2020 ESC Guidelines for the management of adult congenital heart disease. *European Heart Journal.* 2021;42(6):563-645. doi:10.1093/eurheartj/ehaa554
12. The Task Force on the Management of Grown Up Congenital Heart Disease of the European Society of Cardiology, Deanfield J, Thaulow E, et al. Management of Grown Up Congenital Heart Disease. *European Heart Journal.* 2003;24(11):1035-1084. doi:10.1016/S0195-668X(03)00131-3
13. Ji Q, Feng J, Mei Y, et al. Transcatheter Closure of Adult Patent Ductus Arteriosus with Severe Pulmonary Hypertension. *Hypertens Res.* 2008;31(11):1997-2002. doi:10.1291/hypres.31.1997
14. Yan C, Zhao S, Jiang S, et al. Transcatheter closure of patent ductus arteriosus with severe pulmonary arterial hypertension in adults. *Heart.* 2007;93(4):514-518. doi:10.1136/hrt.2006.091215
15. Arvind B, Relan J, Kothari SS. "Treat and repair" strategy for shunt lesions: a critical review. *Pulm Circ.* 2020;10(2):2045894020917885. doi:10.1177/2045894020917885
16. Diller GP, Gatzoulis MA. Pulmonary Vascular Disease in Adults With Congenital Heart Disease. *Circulation.* 2007;115(8):1039-1050. doi:10.1161/CIRCULATIONAHA.105.592386
17. Nemoto S, Sasaki T, Ozawa H, et al. Oral sildenafil for persistent pulmonary hypertension early after congenital cardiac surgery in children. *European Journal of Cardio-Thoracic Surgery.* 2010;38(1):71-77. doi:10.1016/j.ejcts.2010.01.045


The Philippine Journal of Chest Diseases
An official publication of:
Philippine College of Chest Physicians
84-A Malakas St., Pinyahan Quezon City, Philippines
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