LUNG CENTER OF THE PHILIPPINES

Scientific Proceedings

Volume 11 Number 2 | December 2023 | ISSN 0117-9322

WHAT'S INSIDE

https://lcp.gov.ph

CLINICAL RESEARCH DEPARTMENT

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

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

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

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

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

LISTING AND BRIEF DESCRIPTION OF AVAILABLE SERVICES

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

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

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Scientific Proceedings

Volume 11 No. 2 | December 2023 | ISSN 0117-9322

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

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LUNG CENTER OF THE PHILIPPINES
Scientific Proceedings

CONTENTS

"WHAT'S IN IT FOR ME?"

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

As editor-in-chief, this thought has crossed my mind several times especially during the periods when we are putting up an issue. It seems a harmless benign sentence. However, I frequently tell myself that this may be the same question that crops up at the other end each time we ask for the authors' permissions to have their manuscripts published in the *Scientific Proceedings*. The process is never smooth and is always full of challenges. Bargaining is involved.... Probably some pleadings or persistence.... Some one-on-one talks *(wala pa namang threats)*.

It seems like a no-brainer for our research works to be published in already established journals or publications especially when they cater to our specialties or areas of interest. There's fame, prestige, possibility of being quoted in subsequent talks or publications, and of course, honor. *Sabi ko nga, nandoon na yung "kilig factor"*. The rewards need not be articulated. It is automatic and self-fulfilling.

But how about publishing one's work in a recently *"resuscitated"* journal from our institution? I will be the first to admit that it may have not crossed one's mind when he or she was embarking on the research. Perhaps the authors had other ideas what to do with the finished products and this may revolve around presentation in international conferences (some societies have strict regulations that accepted presentations should be submitted to their journals even if it does not mean automatic acceptance) most of the time. Some are quite honest in that they may not have time to fine-tune their manuscripts after all the comments during presentations or possibly peer reviews. Quite frankly, they were just in it to fulfill a requirement for graduation. The editorial staff addressed this by offering our technical services to make the necessary changes in terms of formatting the manuscript to make it compliant to the journal's specifications and technical reviews. Another frequently encountered reason is that they just want to wait some more for future conference opportunities which may be good venues for presenting their research output.

Unlike in academic universities or hospitals, the requirement for publications from the staff, translates to potential points when fulfilled. This scoring system will have promotion or tenure implications. Research studies are not considered finished and therefore cannot be counted unless published (i.e., made *"public"*). As the saying goes, *"publish or perish.... up or out."* It is relatively different in a non-academic setting.

Certainly, the editorial staff will introduce certain changes with the hospital's Research Department to facilitate publication in our journal. These may include automatic formatting that will be compliant with our manuscript guidelines by the authors of their research outputs when submitted as part of their requirement. Request for administrative support or possibly directive that will make investigations done in Lung Center (utilizing its patients or facilities) consider preferential submission to our journal if for local publication.
I remain optimistic that a *"culture"* or mindset change is possible. That just keeping our SP as a viable publication alternative within our awareness will translate to more LCP finished investigations to be showcased here.

As I was writing this piece, I would like to share some thoughts that also crossed my mind in terms of a recognition or reward system when one's research gets published in our SP.

- A potential point system that may be included in the staff evaluation. Probably, this may result to being included in a *"publication circle"* (an elite club) with its due recognition and the name to be displayed in a prominent signage possibly in the hospital lobby. Possibly, this may also be considered for our visiting staff in terms of renewal for their appointments.
- Possible individual access to a journal of one's choice after accumulating certain number of points. LCP may shoulder the annual fee.
- Possible individual access to a research scientific conference (sessions catering to manuscript writing, specifics of conducting a trial, etc.) of one's choice after accumulating certain number of points. LCP may shoulder the annual fee.
- Points that may translate to clinic rental discounts.
- Points may translate to additional research funding from LCP.

These are just my random thoughts. I know we can still be innovative and possibly more enticing.

I also believe that constant reminders are just needed. I would like to assure the LCP community that we are achieving great strides with our journal. We are on-track to hit our target of being recognized as a peer reviewed publication that will be ultimately indexed. We just must churn out substantial and quality issue after issue after issue.

In the end, we may have to go back and tackle for ourselves the question why we want our works published? Is it not to share with the scientific community the relevance of our work? Anything that is worth pouring your time and effort into is worth sharing. Publication is an important responsibility of a good physician. Ultimately, the rewards will just follow.

EDITORIAL POLICIES

ABOUT THE JOURNAL

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

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

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ORIGINAL ARTICLE

INCIDENCE AND CORRELATES OF STENT MIGRATION IN ADULT PATIENTS UNDERGOING SELF-EXPANDING METAL STENTING FOR CENTRAL AIRWAY OBSTRUCTION: A RETROSPECTIVE COHORT STUDY OF FILIPINO PATIENTS AT THE LUNG CENTER OF THE PHILIPPINES

Ruari K. Lee, MD and Edmund E. Villaroman, MD
Lung Center of the Philippines

ABSTRACT

Background. One of the most common complications of Self Expanding Metal Stent (SEMS) insertion for Benign and Malignant Central Airway Obstruction (CAO) is Stent Migration. Despite advancements in SEMS construction, this complication still persists, and hence, may be associated with other clinical factors. This study aims to identify significant clinical factors which may be associated with stent migration.

Methodology. This was a retrospective cohort study of all patients who underwent SEMS insertion for Benign and Malignant CAO in the Lung Center of the Philippines from January 2012 to July 2022. Patient, operative and stent factors were extracted and analyzed from subjects grouped into with stent migration and without stent migration. Time at risk was 30 days post operatively for patients without stent migration. Incidence rate for stent migration and repeat intervention were computed as person-time rate. Unadjusted hazards ratio was computed and analyzed for the different clinical factors.

Results. The study included 61 patients, wherein 65 SEMS were placed. Nine patients had stent migration within 30 days, while nine more patients had stent migration after 30 days. Incidence rate of stent migration within 30 days was 0.0074 per person-day (CI 0.0047-0.012), and incidence rate of stent migration at any time after insertion was 0.0050 per person-day (CI 0.0026-0.0096). Incidence rate for repeat intervention was 33.33%. No significant clinical factors were associated with stent migration within 30 days (all $p > 0.05$). For stent migration at any time after insertion, obesity (patient BMI range of 25.3 to 30.7) had a 252% increase in hazard for stent migration (HR = 3.52; 95% CI 1.12-11.11; p =0.032), while procedure duration of ≥ 110mins had an 80% decrease in hazard for stent migration (HR = 0.2; 95% CI 0.04-0.97; p = 0.046).

Conclusion. Obesity and procedure duration of ≥ 110mins were significant factors for stent migration. Further studies are needed to establish causality between these two factors and stent migration.

Keywords. Central airway obstruction, self-expanding metal stents, stent migration, stenting, stent complication

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Year Completed: 2022
Date Received: 25 May 2023
Date Accepted: 07 November 2023

INTRODUCTION

Central airway obstruction (CAO) is one of the most challenging diseases seen and managed at the Lung Center of the Philippines, being the apex hospital for chest and lung diseases in the country. One of the most established, time-tested armamentariums that thoracic surgeons utilize in the management of CAO is the use of self-expanding metal stents (SEMS). SEMS have been used in our institution since the year 2012. Indications for use of SEMS include cases of malignant CAO, and inoperable benign CAO cases such as in long segment tracheal stenosis, tracheomalacia and trauma.

The use of SEMS has evolved through time. Initially, there was indiscriminate use of these stents due to the numerous advantages seen in its use, such as immediate improvement of symptoms, respiratory physiologic outcomes[1] and ease of deployment.[2,3] However, the United States Food and Drug Administration4 has issued a warning in 2005 regarding the use of metallic stents for benign airway disease, due to reports of several post operative complications, including obstructive granulation tissue, stenosis at the ends of the stent, migration of the stent, mucous plugging, infection, and stent fracture.[4] Currently, these metal stents are used for malignant CAO, and for select cases of benign CAO.[5]

Despite the judicious use of SEMS, stent migration is still currently observed in some of our patients. This begs the question of whether there are other factors which lead to this complication. Through identification of these other possible risk factors, interventionalists may then plan ahead and take necessary steps to avoid stent migration.

Review of Related Literature and Significance of the Study

Central airway obstruction (CAO) is defined as a condition wherein there is luminal narrowing of the trachea or mainstem bronchi. Obstruction can be classified based on etiology – either benign or malignant. More common causes of benign CAO in our institution include post intubation and post tracheostomy tracheal stenosis, infection such as tuberculosis, or granulation tissue formation caused by foreign bodies, post trauma or surgery. Malignant causes of CAO include primary bronchopulmonary, mediastinal or metastatic malignancies from other organs.[6]

Airway stenting is an integral component of endoscopic management of benign and malignant CAO.[7] It has been shown to relieve dyspnea, improved functional status, and better quality of life.[8] Among the different types of stents, silicone stents and SEMS are more commonly used to address these cases. Silicone stents have the advantage of easy repositioning and removal,[10] which is ideal for temporary management of benign airway lesions, who will undergo eventual definitive resection. It has however several disadvantages, which include smaller internal to external diameter, and higher chance of migration[11] due to its smooth surface. On the other hand, SEMS have been shown to be more effective in opening up the airway, owing to its thinner internal-external diameter, and the radial force it exerts on the airway to maintain its patency. It offers several advantages including easier placement, lower migration rate,[12] and better conformation to irregular airways[9,13] to name a few. SEMS, however also has disadvantages to its use, which include higher rate of granulation tissue formation, increased infection rate, as well as increased difficulty in removal once it has incorporated into the mucosa of the airway.[14] Different kinds of SEMS have been described in literature. In contrast to earlier types of SEMS, which were stainless steel or cobalt-based, the newer types of SEMs are made up of nitinol alloy. Nitinol offers the advantage of being able to conform to the anatomy of the airway, hence, theoretically decreases risk of dislodgement. It also is more elastic, and is able to collapse with coughing which aids in airway clearance.[15]

There are no current studies regarding the expertise required for SEMS placement. However, several studies have shown that physicians with adequate training and experience on bronchoscopy perform this procedure. This includes thoracic surgeons,[16] interventional pulmonologists[17,18] and interventional radiologists19 with the help of anesthesiologists. SEMS may be placed under fiberoptic bronchoscopy guidance. However, in cases wherein there is doubt in the stability of the airway, rigid bronchoscopy is advocated, which provides airway security, as well as excellent control of oxygenation and ventilation.[6] After securing the airway, different modalities may be employed to initially address the obstructing lesion of the airway, prior to deployment of the SEMS. Placement of the stent may then be done via direct visualization through the bronchoscope or via fluoroscopy, and may be double-checked with post operative radiographic imaging.

Studies regarding SEMS use have reported good outcomes including excellent technical success, which is defined as restoration of endoluminal patency of ≥75%. In a study by Cosano, technical success rate in malignant CAO was 92% (n = 59/65), while in benign CAO was 96% (n = 69/72).[20] Intraoperative complications are rare, primarily because of the ease of deployment of SEMS, which only requires fiberoptic bronchoscopy in most cases. This is in contrast to silicone stents, which require rigid bronchoscopy for proper deployment.

In contrast to the high technical success rate, clinical success, defined as successful intervention without occurrence of complications, was lower, with a rate of 40.7% according to Fortin et al.[21] This is because of several complications seen with SEMS use which include stent migration, which could be as high as 20 to 50% of cases.[22] Other complications include granulation tissue formation in 4-33% of cases[2,9] stent fracture with or without tumor infiltration in 10% of cases[2], mucus plug formation in 38% of cases,[7] hemoptysis

in 9–16% of cases[2] and rarely, tracheoesophageal or tracheovascular fistula formation.[23] These complications usually necessitate reintervention to allow proper diagnosis and management of the aforementioned complications.

Stent migration may be defined as any displacement of a previously deployed stent from its intended position. It is one of the most common complications after SEMS placement. This is despite some technological advancement in stent construction, which theoretically eliminate significant stent migration risk. Advancements include adaptation of a nitinol–based stent construction enhance conformity in tortuous airways, construction of partially covered stents with uncovered proximal and distal ends to induce granulation reaction, and the addition of antimigration fins and studs in the edges of the stent.[24] The persistence of stent migration, however, has brought about new research in additional procedures or ways to further decrease the risk for stent migration. One of these procedures was described in a study by Mehta et al in 2017.[25] In this paper, the authors introduced the "hitch stitch" procedure, which involves percutaneously fixating the SEMS via bronchoscopic guidance after it has been deployed in the airway. They reported that in 42 patients who underwent the procedure, only 1 had a recurrence of stent migration. This procedure, however, does not completely eliminate stent migration, and also comes with the risk of surgical site infection. Thus, there would be a need to identify specific groups of patients which may benefit from this additional procedure, despite the additional operative time and possible complications.

Risk factors for stent migration have been discussed in several studies. Generally, it is believed that patients with benign etiologies of CAO have increased incidence of stent migration due to longer survival.[26] According to Huang in 2018,[27] other patient factors which may increase the chance of migration include those with external compression of the trachea (n = 3/56), and patient with bronchomalacia (n = 9/24). A study by Saad in 20033 reported 4 cases of stent migration, which were attributable to the severely funnel–shaped lesions in these patients. Another study by Gildea in 2006[28,29] noted 100% migration risk in post lung transplant patients who underwent tracheal stenting with anastomotic stenosis. Stent factors which may increase the risk for migration include those who used silicone stents, seen in 27 of 167 stent procedures (Hazard Ratio 3.52) in a study by Ost in 2012,[29] and in 69% of patients with benign stenoses (n = 11/16) in a study by Gildea.[28] The use of fully covered metal stents also had increased incidence of migration, with a rate of 83% in a study by Dooms.[30] Operative factors which have shown to increase stent migration include stents placed in the trachea[27,30] in contrast to stents placed in both trachea and mainstem bronchi or main stem bronchi alone.

Other complications of tracheal stenting have been proven to be attributable to some operative and stent factors, which may be worth exploring if correlated with stent migration. The same study by Huang in 2018[27] showed that a procedure length of greater than 110 minutes and stent length of greater 60 mm were associated with increased risk for restenosis and granulation tissue formation. The study however had a low power to correlate these two factors (procedure length and stent length) with stent migration. Correlation of these factors is therefore worth exploring. Additionally, other patient factors such as smoking may be worth investigating due to the fact that smoking significantly increases the risk of pulmonary disease, with significant decline in risk after 10 years of cessation.[31]

There are no local data regarding stent migration in the country. In fact, majority of published studies regarding the topic describe findings in the Caucasian population. Since anatomic differences in the airway between races have been well–established,[32,33] factors which increase the incidence of stent migration may differ in the Filipino population and is worth investigating. Therefore, the aim of this study was to identify any patient, operative and stent factors that were correlated with stent migration. By doing so, patients at increased risk for stent migration may be identified, who may benefit from additional procedures such as the hitch stitch procedure.

This study identified correlates or factors associated with stent migration. These correlates could then be further studied to prove causality with stent migration. Ultimately, interventionalists may be able to identify patients with increased risk for stent migration who may benefit from additional procedures to possibly avoid the aforementioned complication from occurring.

Research Objectives

The study aimed to determine which patient, operative and stent factors correlate with stent migration post operatively; specifically, to estimate the incidence rates for post operative stent migration; estimate the incidence of repeat interventions due to stent migration; determine if age, sex, smoking status, BMI, cause and nature of central airway obstruction, previous tracheobronchial surgery, history of chemotherapy or radiotherapy, procedure duration, stent location or dimension are associated with the development of post operative stent migration within 30 days of its insertion.

Operational Definition of Variables
Outcome Variables

With Stent Migration: physical displacement of a deployed SEMS from its original position which occur up to 30 days after the conduct of operation (SEMS insertion for CAO) documented via chest radiograph or bronchoscopic confirmation, which can be either symptomatic or asymptomatic

Clinically significant stent migration: stent migration with clinical manifestation of dyspnea, stridor, dysphagia, or any symptom of respiratory distress

Non-clinically significant stent migration: stent migration without clinical signs or symptoms, only discovered during surveillance bronchoscopy

Without Stent Migration: absence of the occurrence of the above-mentioned physical displacement of the stent in patients who underwent SEMS insertion for central airway obstruction, assumed when patients have an unremarkable post operative course with no additional interventions done up to 30 days after the conduct of operation (SEMS insertion for CAO) with or without flexible bronchoscopy documentation

Incidence Rate of Stent Migration: computed by the number of patients with stent migration divided by the person-time contribution of subjects who underwent tracheal stenting

Person-Time Contribution of cases: time (in days) to occurrence of stent migration contributed by all subjects included in the study

Incidence Rate of Repeat Intervention due to Stent Migration: computed by the number of patients who underwent more than one repeat intervention due to stent migration divided by the person-time contribution of subjects who underwent tracheal stenting

Exposure Variables

Patient Factors

Age: defined in years and presented as a continuous variable

Sex: male or female

Smoking status: smoker (including current or previous smokers of less than 10 years ago) or non-smoker

Body Mass Index (BMI): computed by dividing weight in kg by (height in meters)2

Cause for CAO: determined via review of the postoperative diagnosis in the operative record (ascertained through clinical correlation of the preoperative computed tomography scan and intraoperative bronchoscopic findings)

- *Benign:* etiology of CAO is due to nonmalignant conditions such as stenosis, tracheomalacia
- *Malignant:* etiology of CAO is due to malignant conditions such as lung carcinoma, thyroid carcinoma, or primary tracheal carcinoma ascertained by the final histopathologic report of each patient

Nature of CAO: determined via review of the intraoperative findings in the operative record

- *Intrinsic:* if CAO involves narrowing of the airway due to intraluminal blockade of the airway
- *Extrinsic:* if CAO involves narrowing of the airway due to extraluminal compression of the airway without invasion of the airway
- *Mixed:* if CAO involves narrowing of the airway due to both intraluminal blockade and extraluminal compression of the airway

Pre-Stent Tracheobronchial Surgery (yes or no): if the patient had any surgery involving the trachea or main stem bronchi prior to stenting determined by review of the patient's clinical history in his/her medical record

Chemotherapy: if the patient had undergone any form of chemotherapy, determined by review of the patient's clinical history in his/her medical record, given time interval:

- *None:* no history of chemotherapy
- *Pre stent:* undergone any form of chemotherapy at any time before stent insertion
- *Post stent:* undergone any form of chemotherapy up to 30 days after stent insertion
- *Both Pre stent and Post stent:* undergone any form of chemotherapy both at any time before stent insertion and up to 30 days after stent insertion

Radiotherapy: if the patient had undergone any form of radiotherapy, determined by review of the patient's clinical history in his/her medical record, given time interval:

- None: no history of radiotherapy
- Pre stent: undergone any form of radiotherapy at any time before stent insertion
- Post stent: undergone any form of radiotherapy up to 30 days after stent insertion
- Both Pre stent and Post stent: undergone any form of radiotherapy both at any time before stent insertion and up to 30 days after stent insertion

Operative Factors

Procedure duration: defined as duration of procedure (from insertion to withdrawal of the rigid bronchoscope) expressed as < 110 minutes or ≥ 110mins[27]

Stent placement: determined via review of the operative record

- Proximal trachea: if stent is placed in the proximal half of the length of the trachea
- Distal trachea: if stent is placed in the distal half of the length of the trachea
- Main bronchus: if stent is placed in the left or right main stem bronchus

Stent Factors

Stent dimensions: recorded on the chart as specified on the manufacturer box expressed in both length (in mm) and diameter (in mm). Determination of the optimal cut off point for stent length and diameter duration shall be done in this study.

METHODOLOGY

Study Design and Population

This was a retrospective cohort study approved by the Technical Review Board (TRB) and Institutional Ethics Review Board (IERB) of the Lung Center of the Philippines, with adherence to the Declaration of Helsinki. Examination of the Operating Room Census of the Division of Thoracic Surgery of the Department of Thoracic Surgery and Anesthesia were done to screen patients eligible for inclusion in this study. All patients who underwent tracheal stenting with SEMS in the Lung Center of the Philippines from January 2012 to July 2022 were included.

Exclusion criteria include patients with the following characteristics:

1. Previous tracheal stenting from a different institution who continued management at the Lung Center of the Philippines
2. SEMS use for other etiologies such as trauma and fistula
3. Occurrence of other post operative complications after stenting, other than stent migration, which include but not limited to: granulation tissue formation, stent fracture, mucus plug formation, hemoptysis and fistula formation

After the patient has been determined to not have the exclusion criteria, the medical chart of each patient was examined to ascertain a final diagnosis of central airway obstruction, and that each patient underwent tracheal stenting for that indication.

Outcome Variables Determination

Each patient was then grouped to have had stent migration or not by reviewing any additional operative techniques. Patients were deemed to have stent migration if additional operative records were found indicating as such. Stent migration was noted to be *clinically significant* if there were symptomatic indications for the repeat procedure such as "stridor" "dyspnea", or "central airway obstruction". Stent migration was noted to be *non-clinically significant* if migration was incidentally noted on follow-up bronchoscopy. On the other hand, patients were deemed to have no stent migration if no additional medical records were seen, or if there were additional operative records but not related to having stent migration. These data were collected to compute the incidence rate of stent migration. The number of additional operative records found due to stent migration corresponded to the number of repeat interventions per patient, and were recorded. Additionally, the time to stent migration and first repeat intervention were also recorded

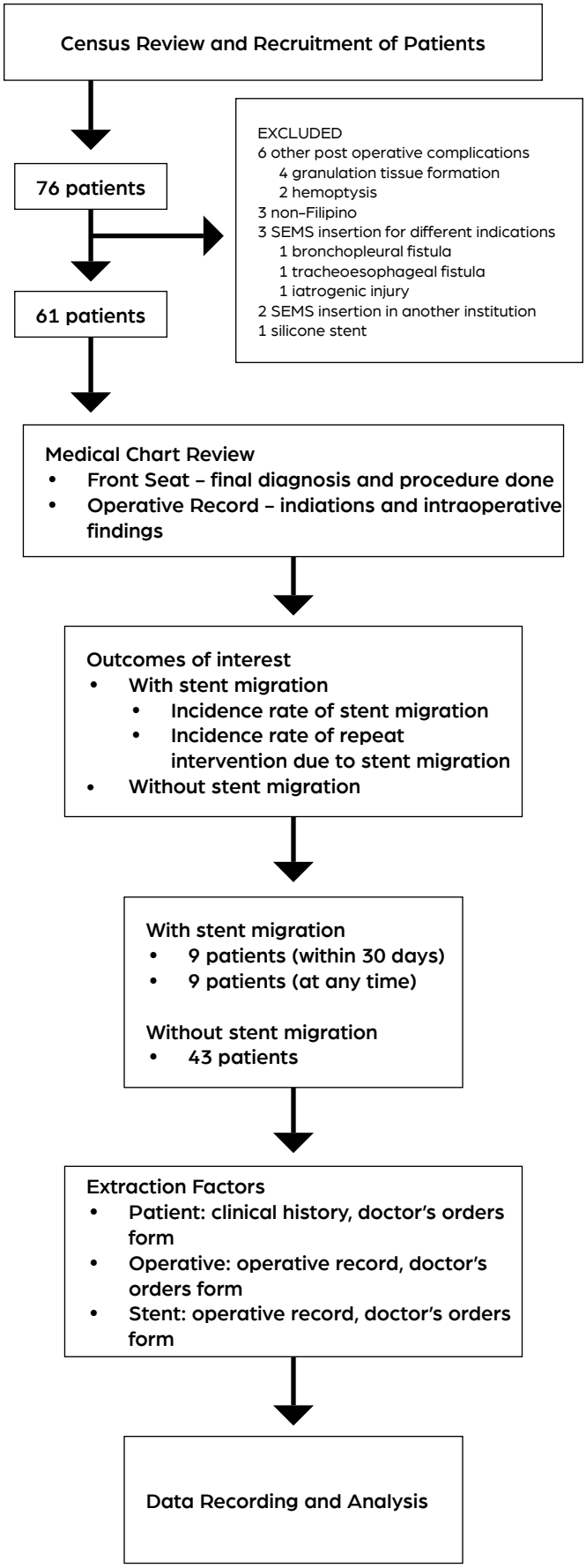

Figure 1. *Flowchart for the study design*

by counting the number of days between stent insertion and the occurrence of these events, if any. All patients were followed up until the last known follow up.

Exposure Variables Determination

Patient factors collected from each patient included age, sex, smoking status, BMI, cause of CAO (whether benign or malignant), nature of CAO (whether intrinsic, extrinsic, or mixed), and presence of absence of the following: present tracheobronchial surgery, pre/post stent chemotherapy, pre/post stent radiotherapy. These were extracted from the clinical history form of the patient.

Operative factor of procedure duration was extracted from the operative record, and recorded as number of minutes. Location of stent placement was noted as to whether the stent was placed in the proximal trachea, distal trachea, or main stem bronchus. For patients with multiple stents inserted, analysis was done based on the number of stents that were deployed.

Stent factors of length (in mm) and diameter (in mm) were noted also from the intraoperative findings portion of the operative record.

In case of missing data, other forms from the medical chart were investigated for the factor in question. These other forms included, but are not limited to, the doctor's order sheet, operative record, anesthesia record, nurse's record, and others. Source document for each of the factors were noted. In case of missing data, these were excluded from the analysis of that specific factor.

Power Analysis Calculation

This study included all patients who underwent SEMS insertion since the time it was first utilized in the management of patients with CAO in the Lung Center of the Philippines. In 11 years since the year 2012, a total of 76 patients underwent tracheal stenting in our institution. However, upon application of the exclusion criteria, 6 patients were excluded due to occurrence of other post operative complications (4 patients with granulation tissue formation and 2 patients with hemoptysis), 3 patients were excluded because they were not Filipino, 3 patients were excluded due to stent insertion for different indications (bronchopleural fistula, tracheo-esophageal fistula and iatrogenic injury), 2 patients were excluded due to stent insertion in another institution, and 1 patient was excluded because silicone stent was used. This brought the total number of patients included in the study at 61. There were no patients who presented with symptoms of stent migration but were actually not found to have the said complication.

Power analysis was performed using R version 4.0.3. The sample size of 61 participants, 30% of which had stent migration, in a univariable Cox proportional hazards regression with 5% significance level, achieved the following:

- 3% power (minimum) in the lowest estimate of hazards ratio of 1.01 for smoker (43% of participants)
- 78% power (maximum) in the highest estimate of hazards ratio of 3.61 for obesity (52% of participants)

Stent Placement Procedure and Management of Complications

All patients included in the study were preoperatively assessed with a chest computed tomography scan of the neck and chest. After identifying that the patients were suitable for tracheal stenting, they were scheduled for an emergency bronchoscopy procedure and wheeled into the operating room. All patients were placed in the supine position, with induction of general anesthesia (total intravenous anesthesia) done thereafter. Due to the emergent nature of patients with CAO, rigid bronchoscopy was performed for all patients in order to secure the airway. Once patency of the airway was assured, jet ventilation and muscle paralysis were administered to be able to ventilate the patients adequately and prevent inadvertent airway injury. After assessment of the nature and extent of the CAO, a SEMS of appropriate size, spanning the length of the obstruction, was deployed. We typically used a Flextent® Nitinol Alloy Thermal-Memory Inner-cavity Medical Stent with diameter 20% larger than the normal diameter of the patient's trachea, and a stent with diameter 20% larger than the normal diameter of the patient's bronchus. Proper deployment of the stent was documented via endoscopic visualization of the restoration of the luminal patency. After the procedure, patients were transferred to the Surgical Intensive Care Unit (SICU) and a chest radiograph was done to document stent placement. Patients were then transferred back to room after 4 hours of monitoring in the SICU. If without surgical complications, patients were discharged on the second or third post operative day and followed up on 1-to-4-week intervals while their stent was still inserted. Surveillance bronchoscopy was advised typically performed at 4-week intervals (or more frequently as indicated) to be able to monitor proper stent placement.

Significant stent migration was usually clinically diagnosed, with patients presenting with dyspnea or stridor. Hence, they were immediately referred to a thoracic surgeon if they were still admitted. In the event of suspected stent migration, a chest radiograph was requested to document any change in the position of the stent prior to transfer to the operating room. In more emergent situations, patients were immediately transferred to the operating room for reintervention and appropriate management.

Statistical Analysis

The patient, operative, and stent profile of patients who had SEMS insertion in the Lung Center of the Philippines, between January 2012 to July 2022 were summarized by descriptive statistics. Initially, the normality of the distribution of continuous numerical variables (age and BMI) were assessed by Shapiro-Wilk test of normality. Normally distributed continuous numerical variables were described as mean and standard deviation. Non-normally distributed continuous numerical variables and discrete numerical variables (time-to-complication) were described as median and interquartile range. Categorical variables (sex, smoker, malignant etiology of CAO, nature of CAO, present tracheobronchial surgery, chemotherapy, radiotherapy, procedure duration, stent placement, SEMS length, and SEMS diameter) were described as frequency and percentages.

Incidence rate of stent migration and mortality were presented as estimate and 95% confidence intervals. The time-at-risk was right-censored to 30-days from SEMS insertion among those who did not have recorded stent migration. Unadjusted hazard ratios and 95% confidence intervals in developing stent migration, while accounting for the time-to-event, i.e., time from SEMS insertion to development of stent migration, of the different patient, operative, and stent factors was estimated by univariable Cox proportional hazards regression. A significant HR was evaluated on a level of significance of 5%.

RESULTS

A total of 61 patients and 65 stent insertion procedures were included in the study. Three patients had 2 stents deployed in the left main bronchus and distal trachea, respectively, and one patient had 2 stents inserted in the proximal and distal trachea, respectively. Two patients expired on the 4th and 7th post operative day for non-operative causes. There were 16 patients (26%) who were lost to follow-up. For these patients, they were appropriately analyzed as right censored to the last known follow up. Being that the type of analysis in this study is a time-to-event analysis, right censoring patients who were lost to follow up was done so as not to lose the information that these patients could have given. Nine patients were noted to have stent migration within 30 days after insertion. Eight of these patients had clinically significant stent migration, while only one patient had non-clinically significant stent migration. However, on further review of all patients until last known follow-up, an additional 9 patients had stent migration beyond 30 days of insertion, all of whom had clinically significant stent migration. Stent migration in these patients ranged from 35 to 315 days post insertion. Two different statistical analyses were therefore done – first, with stent migration occurring within 30 days, and second, at any time after SEMS insertion.

Figure 2 shows the number of stent migration cases in contrast to the number of patients who had SEMS insertion from January 2012 to July 2022. Year 2019 had the highest number of cases of SEMS insertion, with 18 patients, 5 of which had stent migration. On the other hand, the year 2014 had only 2 patients who underwent SEMS insertion, and no cases of stent migration. The year 2015 had no patients who had SEMS insertion.

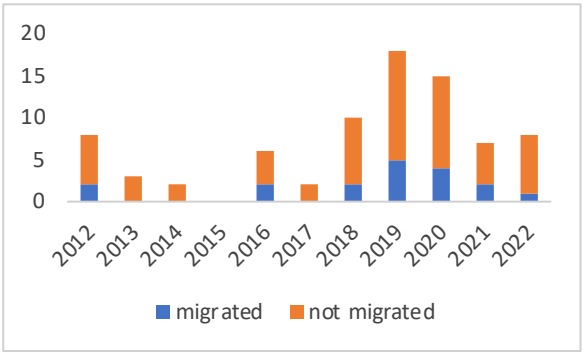

Figure 2. *Comparison of patients who had SEMS insertion in Lung Center of the Philippines, between 2012-2022, divided into those with stent migration versus those without stent migration*

The clinical profile of all patients, with stent migration defined as within 30 days, are shown in Table 1A. On the other hand, the clinical profile of all patients, with stent migration defined as any time after insertion, are shown in Table 1B.

In Table 1A, there was no sufficient evidence to conclude that the investigated patient factors were significantly associated with stent migration within 30 days. However, in Table 1B, obesity was noted to be a significant factor for stent migration, such that those who were obese had a 252% increase in hazards of stent migration in comparison to non-obese patients. There was no sufficient evidence to conclude that the rest of the investigated patient factors were significantly associated with stent migration.

Table 1A. *Clinical profile of patients who had SEMS insertion in Lung Center of the Philippines, between 2012–2022. Stent Migration defined as inserted within 30 days.*

Clinical profile	No Stent Migration N = 52	With Stent Migration N = 9	Unadjusted HRs [95% CI]	P value
Age (years), mean (SD)	57.25 (17.64)	51.00 (14.76)	0.98 [0.95, 1.02]	0.351
Female, n (%)	24 (46.15%)	5 (55.56%)	1.50 [0.40, 5.61]	0.542
Smoker, n (%)	23 (44.23%)	3 (33.33%)	0.62 [0.15, 2.48]	0.498
Obese, n (%) [n=58]	24 (48.98%)	8 (88.89%)	7.05 [0.88, 56.38]	0.066
Malignant etiology of obstruction, n (%)	31 (59.62%)	2 (22.22%)	0.23 [0.05, 1.12]	0.069
Nature of Central Airway Obstruction, n (%)				
Intrinsic	27 (51.92%)	7 (77.78%)	Reference	
Extrinsic	16 (30.77%)	0	–	–
Mixed	9 (17.31%)	2 (22.22%)	0.89 [0.18, 4.26]	0.879
Prestent Tracheobronchial Surgery, n (%)	16 (30.77%)	4 (44.44%)	1.68 [0.45, 6.25]	0.441
Chemotherapy, n (%)				
None	45 (86.54%)	9 (100.00%)	Reference	
Pre-stent	5 (9.62%)	0	–	–
Post-stent	2 (3.85%)	0	–	–
Radiotherapy, n (%)				
None	44 (84.62%)	9 (100.00%)	Reference	
Pre-stent	5 (9.62%)	0	–	–
Post-stent	3 (5.77%)	0	–	–

Note: There were 61 patients included

Table 1B. *Clinical profile of patients who had SEMS insertion in Lung Center of the Philippines, between 2012–2022. Stent Migration defined as any time after insertion.*

Clinical profile	No Stent Migration N = 43	With Stent Migration N = 18	Unadjusted HRs [95% CI]	P value
Age (years), mean (SD)	58.19 (18.30)	51.89 (14.02)	0.99 [0.97, 1.02]	0.704
Female, n (%)	19 (44.19%)	10 (55.56%)	1.81 [0.68, 4.80]	0.234
Smoker, n (%)	19 (44.19%)	7 (38.89%)	1.01 [0.37, 2.72]	0.984
Obese, n (%) [n=58]	20 (50.00%)	12 (66.67%)	3.52 [1.12, 11.11]	0.032
Malignant etiology of obstruction, n (%)	26 (60.47%)	7 (38.89%)	0.52 [0.20, 1.37]	0.186
Nature of Central Airway Obstruction, n (%)				
Intrinsic	22 (51.16%)	12 (66.67%)	Reference	
Extrinsic	14 (32.56%)	2 (11.11%)	0.52 [0.11, 2.41]	0.402
Mixed	7 (16.28%)	4 (22.22%)	0.70 [0.22, 2.30]	0.560
Prestent Tracheobronchial Surgery, n (%)	12 (27.91%)	8 (44.44%)	0.91 [0.34, 2.48]	0.856
Chemotherapy, n (%)				
None	37 (86.05%)	17 (94.44%)	Reference	
Pre-stent	4 (9.30%)	1 (5.56%)	0.42 [0.05, 3.24]	0.404
Post-stent	2 (4.65%)	0	–	–
Radiotherapy, n (%)				
None	39 (90.70%)	14 (77.78%)	Reference	
Pre-stent	2 (4.65%)	3 (16.67%)	0.11 [0.01, 1.01]	0.051
Post-stent	2 (4.65%)	1 (5.56%)	0.09 [0.01, 1.47]	0.091

Note: There were 61 patients included

Table 2A showed comparisons of operative and stent factors of the 65 stent insertion cases. These cases were grouped into those with and without stent migration. For this analysis, stent migration was defined as occurring within 30 days. In Table 2B, the same comparisons were done. The difference being that stent migration was defined as occurring any time after insertion.

In Table 2A, there was no sufficient evidence to conclude that the investigated operative and stent factors were significantly associated with stent migration within 30 days. However, in Table 2B, procedure duration of ≥ 110 mins was found to be a significant factor for stent migration, with an 80% decrease in hazards of stent migration than those who had a procedure duration of < 110 mins.

Table 2A. *Comparison of operative and stent factors between those who had post-operative stent migration (within 30 days) versus those without, among patients who had SEMS insertion in Lung Center of the Philippines, between 2012-2022.*

Factors	No Stent Migration N = 56	With Stent Migration N = 9	Unadjusted HRs [95% CI]	P value
Operative factors				
Procedure Duration ≥ 110mins, n (%)	8 (14.29%)	0	-	-
Stent placement, n (%)				
Proximal trachea	26 (46.43%)	8 (88.89%)	Reference	0.076
Distal trachea	24 (42.86%)	1 (11.11%)	0.15 [0.02, 1.21]	-
Main bronchus	6 (10.71%)	0	-	
Stent factors				
SEMS length ≥ 50 mm, n (%) [n=59]	46 (92.00%)	9 (100.00%)	-	-
SEMS diameter ≥ 20 mm, n (%) [n=59]	32 (64.00%)	5 (55.56%)	0.71 [0.19, 2.63]	0.605

Note: There were 65 stents inserted.

Table 2B. *Comparison of operative and stent factors between those who had post-operative stent migration (at any time after insertion) versus those without, among patients who had SEMS insertion in Lung Center of the Philippines, between 2012-2022.*

Factors	No Stent Migration N = 46	With Stent Migration N = 9	Unadjusted HRs [95% CI]	P value
Operative factors				
Procedure Duration ≥ 110mins, n (%)	5 (10.87%)	2 (15.79%)	0.20 [0.04, 0.97]	0.046
Stent placement, n (%)				
Proximal trachea	19 (41.30%)	15 (21.05%)	Reference	
Distal trachea	21 (45.65%)	4 (21.05%)	0.50 [0.16, 1.56]	0.232
Main bronchus	6 (13.04%)	0	-	-
Stent factors				
SEMS length ≥ 50 mm, n (%) [n=59]	37 (90.24%)	18 (100.00%)	-	-
SEMS diameter ≥ 20 mm, n (%) [n=59]	26 (63.41%)	11 (61.11%)	0.34 [0.11, 1.11]	0.073

Note: There were 65 stents inserted.

Table 3A and 3B showed the incidence rates of stent migration and repeat intervention among patients who had SEMS insertion in Lung Center of the Philippines, with stent migration defined as occurring within 30 days, and at any time after insertion, respectively.

In Table 3A, the incidence rate of stent migration was computed at 0.0074 per person days, if stent migration is within 30 days. In Table 3B, the incidence rate of stent migration was 0.005 per person days, if stent migration occurred any time after insertion. Incidence rate of repeat intervention was noted to be at 33.33% (6 of 18 patients), with a range of 1 to 6 repeat interventions per patient.

Table 3A. *Incidence rate of stent migration (within 30 days) among patients who had SEMS insertion in Lung Center of the Philippines, between 2012–2022.*

Outcome	Estimate	95% Confidence Intervals
Stent migration, *incidence rate**	0.0074	0.0047, 0.012
Repeat intervention due to stent migration, n (%)	6/18 (33.33%)	13.34, 59.01
Number of repeats, *median (IQR)*	2.5 (2)	1, 5.7

**Per person-days*

Table 3B. *Incidence rate of stent migration (at any time after insertion) among patients who had SEMS insertion in Lung Center of the Philippines, between 2012–2022.*

Outcome	Estimate	95% Confidence Intervals
Stent migration, *incidence rate**	0.0050	0.0026, 0.0096
Repeat intervention due to stent migration, n (%)	6/18 (33.33%)	13.34, 59.01
Number of repeats, *median (IQR)*	2.5 (2)	1, 5.7

**Per person-days*

Table 4 tabulates the source document for each patient, operative and stent factor extracted from the medical chart. There was a total of 4 patients without BMI, and 6 patients without SEMS dimensions indicated in the medical chart. Smoking history, etiology and nature of obstruction were mainly extracted from the Clinical History form, but were not consistently noted. In these cases, data were extracted from the Anesthesia Record, and if still not indicated, from the Nurses Record. History of previous surgery, chemotherapy and radiotherapy were consistently extracted from the Clinical History form. Procedure duration and stent placement location were mainly found in the Operative Record. SEMS dimensions were inconsistently recorded in the Operative Record, hence, were extracted from other sources such as the post operative radiographic images of patients.

Table 4. *Sources of data patients who had SEMS insertion in Lung Center of the Philippines, between 2012–2022.*

Variable	Source of Date						
	None	History	Doctors Order Sheet	Operative Record	Anesthesia Record	Nurses Record	Others
Smoker	–	55 (90.16%)	2 (3.28%)	–	2 (3.28%)	2 (3.28%)	–
BMI	4 (6.56%)	42 (68.85%)	1 (1.64%)	1 (1.64%)	7 (11.48%)	–	6 (9.84%)
Malignant etiology of obstruction	–	60 (98.36%)	–	1 (1.64%)	–	–	–
Nature of Central Airway Obstruction	–	2 (3.28%)	–	59 (96.72%)	–	–	–
Prestent Tracheobronchial Surgery	–	61 (100.00%)	–	–	–	–	–
Chemotherapy	–	61 (100.00%)	–	–	–	–	–
Radiotherapy	–	61 (100.00%)	–	–	–	–	–
Procedure duration	–	–	–	60 (98.36%)	1 (1.64%)	–	–
Stent placement	–	1 (1.64%)	–	60 (98.36%)	–	–	–
SEMS dimension	6 (9.84%)	–	–	40 (65.57%)	–	–	15 (24.59%)

DISCUSSSION

Stent migration is one of the most common complications after stent insertion with an incidence rate as high as 20 to 50%. In this study, the incidence rates were computed as person time, with two patients expiring prior to 30 days, and 16 patients having no subsequent follow-up after insertion. Lost to follow-up patients were unavoidable in this study, despite constant reminder for patients to adhere to regular follow up. Causes for lost to follow up are numerous and are beyond the scope of this study. Upon consult with a biostatistician, these patients were statistically analyzed as right censored so as to not lose the information patients could have given. Furthermore, excluding lost to follow up patients would weaken the power of the study, as well as change the results entirely. The incidence rates of stent migration were computed to be at 5 per 1000 persons per day and 7.4 per 1000 persons per day, if stent migration were to be defined as any time after insertion or within 30 days of insertion respectively.

Clinically significant stent migration was found in this study to be high at 94% (17 out of 18 patients). Some etiologies seen for the recurrence of dyspnea include collapse of a segment of the trachea previously expanded by SEMS in patients with bronchomalacia, appearance of granulation tissue in the area previously covered by a SEMS, or proximal migration of the stent causing mechanical irritation of the vocal cord. However, non-clinically significant stent migration was seen in one patient, wherein the migration of the stent was only minimal, seen on surveillance bronchoscopy.

The rate of repeat intervention due to repeated stent migration was noted at 33% (6 of 18 patients) with a range of 1 to 6 interventions done per patient. Among those who had repeat intervention (n = 6), 5 of them had stent migration within 30 days of stent insertion (83%). It is important to note that this only encompassed patients with repeated stent migration, and does not include patients who encountered other post operative complications due to stent insertion. Because of this relatively high incidence rate, the need for surveillance bronchoscopy and removal of airway stents as soon as possible cannot be overemphasized. Currently in our institution, the hitch stitch technique[25] is being done for patients needing maintenance of their stents when stent migration has already occurred.

Previous studies[3,27,29,30] have identified several patient factors which increase the risk for stent migration. These factors include having benign causes of CAO, CAO with external compression, and bronchomalacia. Analysis of the above factors in this study, as well as other clinical factors, yielded no association with stent migration, if migration was confined to within 30 days post insertion. However, there were nine patients who were noted to have stent migration after 30 days. Hence, analysis was also done for stent migration defined as any time after insertion. In this second analysis, two clinical factors were significantly associated with stent migration, namely, obesity and longer procedural time (>110 mins). Obesity was associated with a 252% increase in hazards for stent migration. The authors of this paper believe this to be a novel finding, and has not been seen in other studies. Research on the effect of obesity on the airway has been increasing, and studies have established that obesity increases work of breathing, and may induce airway hyperresponsiveness.[34] These changes could explain why obesity may increase the risk for stent migration. However, this remains to be proven as only association between obesity and stent migration was established in this study. Another clinical factor previously identified in other studies as a risk for stent migration was having severely funnel shaped endotracheal lesions.[3] We were unable to determine if having this type of lesion was a correlate for stent migration in this study due to the lack of uniform definition and grading of severity of funnel-shaped lesions. This may be explored in further studies.

With regards to operative factors, majority of the cases were done by a single surgeon in our institution, who had extensive experience in bronchoscopy and stent insertion prior to the time frame covered in this study. Figure 1 showed that the incidence rate of stent migration versus those without stent migration were comparable to international standard. Because of this, learning curve in SEMS insertion was not thought to be a contributing factor in this study. Furthermore, position of stent placement, which was found to be significant in other studies, was not found to be correlated with stent migration in this study. Results however showed that procedure duration was significantly correlated to stent migration, and had an 80% decrease in hazard for stent migration. This is in contrast to previous studies[27] wherein procedure duration had poor correlation with stent migration. The study only had five patients with stent migration, hence, may explain the disparity with our findings. Explanations as to why this is so is beyond the scope of this research.

No identified stent factors were correlated with stent migration in this study. Despite its recorded disadvantage,[30] nickel titanium alloy (nitinol) stents without anti migration fins or studs were the only kind of stent used for all patients due to limited availability of stents in the local setting. Hence, stent variability was not a factor considered in this study. The size of stent used per patient was also uniformly determined, and was oversized by 20% of the normal diameter of the trachea in all patients. In our institution, modifications in the stent itself have been done as a reaction to the initial occurrences of stent migration.

One of these modifications was the manual removal of the proximal and distal stent covering, to induce granulation tissue formation[24] to decrease the incidence of stent migration. Unfortunately, performance of this modification was not recorded in operative techniques, making identification and analysis not possible. Another modification, as mentioned earlier, was the use of the hitch stitch technique.[25] In our study, only 3 patients underwent the transluminal fixation via the hitch stitch technique after

initial stent migration event. Of these 3 patients, 1 patient did not have recurrence of stent migration until last known follow up. The remaining two patients however still had recurrence of stent migration, occurring 2 days and 32 days after fixation.

Source documents for each clinical factor were presented in Table 4. Missing data were seen during the collection of patients' BMI and stent dimensions. Majority of these missing data were seen in patients who were only referred to our institution for stenting, and transferred back to the referring hospital post operatively for continuity of care. These patients often arrived in emergent or urgent conditions, wherein obtaining their height and weight were not tolerated. Other source documents which may have contained the height and weight of patients were the anesthesia record and nurse record. However, for three patients, all source documents did not contain the needed data. Stent dimension of SEMS used were not indicated in the operative record of six patients. Unfortunately, no other source document would contain this data. Hence, recording of dimensions of stents inserted should be done consistently by the surgeons and nurses for proper documentation and monitoring.

Study Limitations

Due to the retrospective nature of this study, extraction of clinical factors and determination of the presence or absence of stent migration solely relied on review of medical records. Thus, missing data encountered could no longer be retrieved, and consequently was a source of limitation in data analysis. Furthermore, although patients were advised monthly monitoring while their stents were in place, not all patients followed up on time, and some patients did not seek any follow-up at all. These may have caused delay in the diagnosis of stent migration; hence, patients may have been misclassified under patients with migration at any time (instead of within 30 days), or even under without stent migration. Furthermore, the authors of this study dealt with lost to follow-up with right censored statistical analysis. It would have been ideal however, if said patients followed up as they were instructed to do so. Right censored analysis, although appropriate, may have altered the results of this study. Another innate limitation of the study was the inability to establish causality between stent migration and the significant factors of obesity and procedure duration of more than 110. Additionally, possible confounding biases were not controlled in this study due to the inclusion of all patients who underwent SEMS insertion in this study. Finally, as mentioned above, the sample size of this study was limited, hence, were unable to perform matching of variables. The small sample size may have also contributed to the results being not as robust.

CONCLUSION AND RECOMMENDATIONS

Stent migration in Filipino patients with central airway obstruction is correlated to obesity and procedure duration. Further studies are needed to establish causality between stent migration and these factors.

This study may serve as foundation for future studies to explore factors leading to stent migration. Further prospective clinical trials should be done in order to establish a causal relationship between obesity and procedure duration to stent migration. Additionally, studies exploring the mechanisms on how obesity causes stent migration should be done. These studies may focus on complete preoperative airway assessment, since obese Filipino patients may have the tendency to have short necks. Prospective studies regarding how prolonged procedure duration decreases risk for stent duration may also be done. With the establishment of these risk factors for stent migration, future recommendations can be made regarding the addition of procedures such as the hitch stitch as prophylaxis for patients who have a high risk for stent migration. Other studies should also be done to explore clinical factors which affect the other post operative complications of SEMS insertion, with focus on the more common complications such as granulation tissue formation. Finally, check and balance mechanisms should be established to ensure proper documentation in the medical chart, since completeness of data is crucial in performing retrospective studies.

ACKNOWLEDGMENTS

The authors thank Dr. Emilio Villanueva III for his invaluable contribution to the statistical analysis of this research. Dr. Hazel Lee is also acknowledged for her support and editing of this manuscript as well as the staff of the Medical Records of the Lung Center of the Philippines for their help in retrieving the records of the patients included in the study.

FUNDING

None.

CONFLICT OF INTEREST

None declared.

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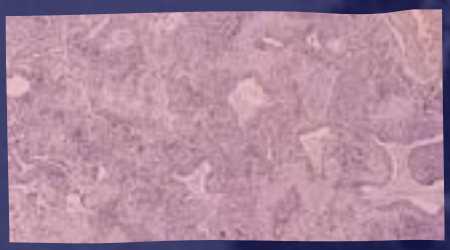

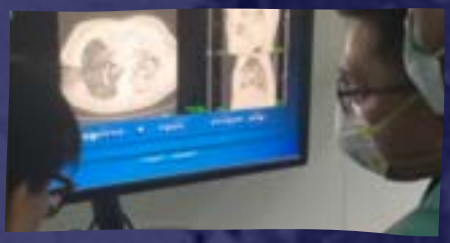

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ORIGINAL ARTICLE

THE UTILITY OF ESTIMATING THE SHUNT FRACTION OF CRITICAL PATIENTS WITH COVID–19 IN DETERMINING THE OUTCOME OF HIGH FLOW NASAL CANNULA AT LUNG CENTER OF THE PHILIPPINES. A PILOT STUDY.

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Lung Center of the Philippines

ABSTRACT

Background. High Flow Nasal Cannula (HFNC) enabled us to treat Acute Respiratory Distress Syndrome (ARDS) successfully among those with COVID–19 but not all patients will benefit and thus eventually ending up being intubated. In ARDS the use of the ratio PaO_2/FiO_2 has been adopted for routine practice however this parameter is dependent on the underlying shunt fraction. As large intrapulmonary shunt fraction develops so is worsening of hypoxemia. However, measuring shunt fraction is not feasible bedside.

Objective. This study investigated the estimated shunt fraction as a parameter in the determination of a specific group of patients that will benefit from HFNC from its outcomes in terms of success, mortality and length of hospital stay.

Methodology. This was a retrospective, cohort study. Total of 205 COVID–19 critical patients initially on HFNC admitted from July 1, 2020 to July 31, 2021 were included in this study.

Results. Forty–seven patients (22.9%) showed improved oxygenation and were successfully withdrawn from HFNC. In the binary logistic regression analysis, factors affecting mortality showed that age was the only variable predictive of in–hospital all–cause mortality. In the factors affecting intubation, logistic regression revealed greater shunt fraction would increase the odds of being intubated. Patients who have 30–40% shunt fraction had 3.8 times higher odds of being intubated and having a shunt fraction of >40% had 3.5 times the odds of being intubated this in comparison with shunt fraction <30%.

Conclusion. HFNC has limited success rate in COVID–19 critical patients but significantly showed benefit in those with shunt fraction <30%. Additionally, this study was not able to show the benefit of HFNC in terms of mortality and length of hospital stay.

Keywords. COVID–19, high flow nasal cannula, shunt fraction, acute respiratory distress syndrome

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Year Completed: 2022
Date Received: 15 October 2023
Date Accepted: 08 January 2024

INTRODUCTION

COVID-19 mainly affects the respiratory system with some patients rapidly progressing to acute respiratory distress syndrome (ARDS). These patients with COVID-19 appear to die from ARDS.[13] High Flow Nasal Cannula (HFNC) enabled us to successfully treat subsets of ARDS patients, including a high proportion of those with COVID-19, without requiring invasive ventilatory support[2,5] and with low mortality.[14] COVID-19 clinical practice guidelines recommended a trial of HFNC prior to intubation.[3,4] However, some experts recommended early intubation to prevent progression of patient self-inflicted lung injury (P-SILI).[8,9] Early intubation within the first 24-hour window of ICU admission lowers the risk of mortality in COVID-19.[11,12]

The PaO_2/FiO_2 ratio has been adopted for routine practice and is used to characterize the severity of ARDS.[6] The use of the PaO_2/FiO_2 ratio is underlined by the necessity to assess hypoxemia independently from FiO_2. Unfortunately, due to the complex mathematical relationship between the Hb level, the Hb-O_2 dissociation curve, and the arterial-mixed venous O2 concentration difference, the relationship between PaO_2/FiO_2 and FiO_2 is nonlinear and depends on the underlying pulmonary shunt fraction.[7,15] In patients with ARDS, hypoxemia is due to large pulmonary shunt fractions.[10] However, measuring shunt fraction is not feasible bedside.[7] In Lung Center of the Philippines, we used HFNC for those with shunt fraction of ≤30% for COVID-19 confirmed critical patients but this was mainly based on physiological concept and without validation. With the onset of COVID-19 pandemic which created a grandiose impact in the healthcare industry with its constant evolving management, we have observed during our practice that HFNC with estimation of shunt fraction had been beneficial to our patients preventing from intubation and affecting its clinical course.

OBJECTIVE

Our aim was to evaluate the use of estimated shunt fraction in the determination of a subset of patients that will benefit from HFNC in terms of its success, mortality and length of hospital stay. The outcome of the study would be helpful in the selection of patients that would have a high success of HFNC and would prevent unnecessary usage of HFNC thus preventing delayed intubations.

METHODOLOGY

Study Design

This was a retrospective, observational cohort study

Study Site

The study was conducted at the Lung Center of the Philippines (LCP), Quezon City. It is a 210-bed capacity hospital which is the center for lung diseases in the Philippines. It was designated as a COVID-19 referral center by the Department of Health for moderate to critical cases in the NCR. LCP allocated 160 bed capacity dedicated for COVID-19 patients.

Study Period

The study was done from September 2021 to December 2021 after the protocol was approved by the technical board review and ethics committee.

Study Population

The participants of the study were admitted Critical COVID-19 patients, 18 years old and above on HFNC not having a $PaCO_2$ ≥45mm Hg, with an absence of clinical history of chronic lung disease, not needing urgent endotracheal intubation with no do-not-intubate order and a hemoglobin of >100 mg/dl from July 1, 2020 to July 31, 2021.

Sample Size and Sampling Design

Total enumeration sampling of all admitted Critical COVID-19 patients from July 1, 2020 to July 31, 2021 were considered in this study. Out of 400 patients, 205 were included in this study having fulfilled the criteria.

Data Collection

Records from the Section of Respiratory Service who were initially on HFNC were obtained and data abstracted from the hospital medical records. Laboratory confirmed (RT-PCR or COVID-19 GeneXpert) COVID-19 patients were selected.[16] Patients' demographics, age, sex, smoking status, presence of co-morbidities, inflammatory markers, and CT scan findings were obtained. The initial ABG findings prior to the use of HFNC was used to obtain the PaO_2 with the corresponding FiO_2 from low-flow oxygen devices (i.e., nasal cannula, face mask, non-rebreather mask) hooked at the emergency room upon initial assessment. Critical COVID-19 defined as patients with ARDS or sepsis with acute organ dysfunction.[4] ARDS criteria used was 1.) Onset: within 1 week of a known clinical insult or new or worsening respiratory symptoms. 2.) Chest imaging (radiograph, CT scan, or lung ultrasound): bilateral opacities, not fully explained by volume overload, lobar or lung collapse, or nodules. 3.) Origin of pulmonary infiltrates: respiratory failure not fully explained by cardiac failure or fluid overload. Objective assessment (e.g. echocardiography) obtained to exclude hydrostatic cause of infiltrates/oedema if no risk factor was present.[3] While sepsis was defined as having signs of organ dysfunction include: altered mental status, difficult or fast breathing, low oxygen saturation, reduced urine output, fast heart rate, weak pulse, cold extremities or low blood pressure, skin mottling, or laboratory evidence of coagulopathy, thrombocytopenia, acidosis, high lactate, or hyperbilirubinemia.[3] The PaO_2/FiO_2 ratio across an administered FiO_2 range was plotted against isoHunt curves from Feiner et al. (Figure 1). On this chart with the PaO_2/FiO_2 ratio (y-axis) and FiO2 level (x-axis), shunt fraction isoHunt curves depict lines of fixed shunt values. By examining

where a patient's paired PaO_2/FiO_2 and FiO_2 data points intersected these curves, the estimated shunt fraction was categorized into ranges: a) < 30%, b) 30–40%, c) > 40%.

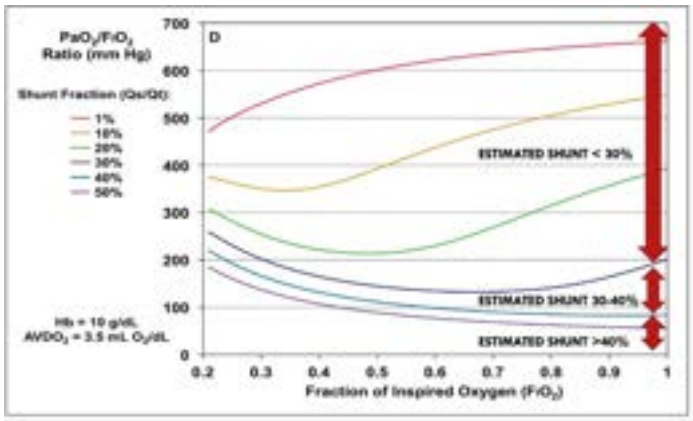

Figure 1. *Shunt Fraction Curves*

PaO_2/FiO_2 ratio as a function of FiO2 from room air (0.21) to 1.0 for simulated constant intrapulmonary shunt (Qs/Qt), from 0.01 to 0.5. The simulation was calculated for a hemoglobin (Hb) concentration of 10 g/dL and arterial–venous oxygen content difference of 3.5 mL O2/dL.[1]

Outcome Measures

I. HFNC success is defined by number of patients who were initially on high flow nasal cannula on the first 24 hours until discontinuation due to resolution of symptoms (absence of fever, improvement of respiratory symptoms, stable vital signs), or until hospital discharge without progression to invasive mechanical ventilation.[17]
II. Length of Hospital Stay refers to the duration of hospital stay (counted as days) beginning from the day of admission to death or discharge.
III. Mortality is the occurrence of in-hospital death regardless of cause.

Statistical Analysis

For this study the following statistical analysis were used:

a. Frequencies and percentages were used for categorical variables while mean and standard deviation or median and interquartile range for numerical variables. Fisher Exact or Chi-square tests were used to determine the association between two categorical variables. Numerical variables were compared using analysis of variance or Kruskal Wallis test.
b. Factors affecting mortality and intubation used summary of binary logistic regression.
c. All statistical analysis was performed at 5% level of significance using SPSS software.

Ethical Considerations

This study was conducted in accordance with the National Ethical Guidelines for Health and Health Related Research 2017, and the Data Privacy Act of 2012. The protocol was approved by the Lung Center of the Philippines Institutional Ethics Review Board (LCP-IERB). Information that was collected from chart were kept confidential. In the event of any publication regarding this study, the identity of the patients will remain confidential.

RESULTS

Patient Recruitment

Between July 2020 to July 2021 there were 400 charts reviewed from Lung Center of the Philippines Medical Records. A total of 195 subjects were excluded in the data analysis, 78 had PaCO2 >45mmHg, 55 had hemoglobin <100mg/dl, and 62 had history of chronic lung disease. A total of 205 study subjects were included in the data analysis (Figure 2).

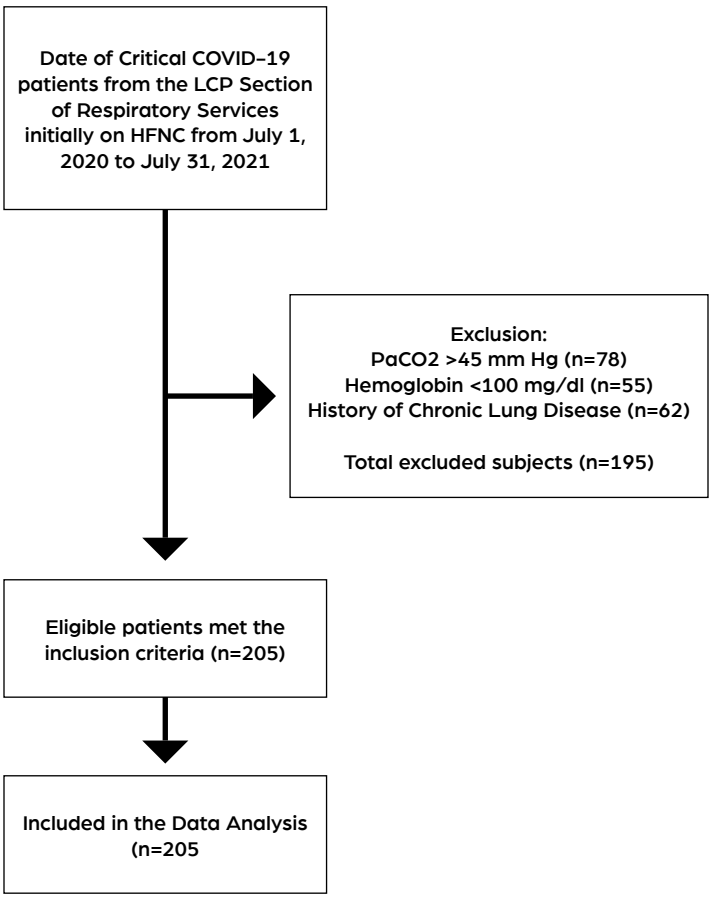

Figure 2. *Flow chart of patients included in the study*

Baseline Characteristics and Demographical Data

Table 1. *Baseline characteristics of patients who were initially on High Flow Nasal Cannula from Covid 19 at Lung center of the Philippines from July 2020 to July 2021*

Characteristics	All (n = 205)	Shunt Fraction			P-value
		<30% (n = 86)	30–40% (n = 68)	>40% (n = 51)	
Age, years	61.7 ± 13.9	61.7 ± 14.0	58.3 ± 14.4	**66.3 ± 12.1**	0.008$
Young Adults (19–39 years old)	16 (7.8)	6 (7.0)	8 (11.8)	2 (3.9)	
Middle-aged adults (40–59 years old)	63 (30.7)	25 (29.1)	26 (38.2)	12 (23.5)	
Old-aged adults (60–99 years old)	126 (61.5)	55 (64.0)	34 (50.0)	37 (72.5)	
Sex					
Female	75 (36.6)	31 (36.0)	17 (25.0)	27 (52.9)	0.008#
Male	130 (63.4)	55 (64.0)	51 (75.0)	24 (47.1)	
Smoker	58 (28.3)	24 (27.9)	26 (38.2)	8 (15.7)	0.025#
Comorbidities					
Hypertension	117 (57.1)	49 (57.0)	35 (51.5)	33 (64.7)	0.363#
Diabetes Mellitus	61 (29.8)	31 (36.0)	11 (16.2)	19 (37.3)	0.009#
Pulmonary Tuberculosis	13 (6.3)	8 (9.3)	3 (4.4)	2 (3.9)	0.436#
Body Mass Index ≥ 25 kg/m2	12 (5.9)	6 (7.0)	4 (5.9)	2 (3.9)	0.869#
Asthma	12 (5.9)	3 (3.5)	4 (5.9)	5 (9.8)	0.306#
Chronic Obstructive Pulmonary Disease	11 (5.4)	6 (7.0)	2 (2.9)	3 (5.9)	0.623#
Chronic Kidney Disease	10 (4.9)	6 (7.0)	3 (4.4)	1 (2.0)	0.422#
Coronary Artery Disease	6 (2.9)	3 (3.5)	3 (4.4)	0 (0.0)	0.386#
Cancer	6 (2.9)	3 (3.5)	0 (0.0)	3 (5.9)	0.118#
Stroke	4 (2.0)	2 (2.3)	1 (1.5)	1 (2.0)	1.000#
Congestive Heart Failure	2 (1.0)	2 (2.3)	0 (0.0)	0 (0.0)	0.511#
CT SCAN					
1. Transient Ground Glass Opacities	4 (2.2)	2 (2.5)	2 (3.3)	0 (0.0)	0.565
2. Bilateral Ground Glass Opacities	62 (33.3)	29 (36.7)	22 (36.7)	11 (23.4)	
3. Consolidation	11 (5.9)	5 (6.3)	3 (5.0)	3 (6.4)	
4. Bilateral Ground Glass Opacities and consolidation	109 (58.6)	43 (54.4)	33 (55.0)	33 (70.2)	
Inflammatory Markers					
LDH (U/L)	481 ,196	435 ,204	494 ,228	547 ,151	**0.001***
Ferritin (ng/ml)	1,200 ,243	1,200 ,268	1,200 ,0	1,200 ,280	0.367*
CRP (mg/L)	221 ,138	200 ,144	241 ,108	210 ,127	**0.080***
D-dimers (ng/ml)	200 ,350	200 ,200	250 ,400	200 ,700	0.289*
Procalcitonin. NORMAL (<0.5) ng/ml	0.34 ,0.63	0.32 ,0.68	0.35 ,0.54	0.39 ,0.64	0.776*

mean ± standard deviation, frequency (%), median, interquartile range
$ANOVA, #Fisher-exact, *Kruskal Wallis

Overall, the mean age of patients included in this study was 62 years old. The mean age group also varied in the different shunt fractions. In shunt fraction > 40%, the mean age was 66 years old, shunt fraction of 30–40% the mean age was 58 years old, and shunt fraction of < 30% the mean age was 66 years old. There was a significant higher proportion of old-aged adults (60–99 years old) for all 3 shunt fraction groups (62%).

There were 130 male (63.4%) and 75 female (36.6%) included in the study. A significant higher proportion of male was seen in the 30–40% shunt fraction (75%) compared to females (37%).

A total of 58 subjects (28.3%) were smokers. In shunt fraction < 30%, 24 were smokers (27.9%); In shunt fraction 30–40%, 26 were smokers (38.2%); and for shunt fraction >40%, 8 were smokers (15.7%).

The most common comorbidities were hypertension 117 (57.1%) followed by diabetes mellitus 61 (29.8%). A significant lower proportion of patients with diabetes mellitus were in the shunt fraction 30–40% (16.2%).

There was no significant difference between all three shunt fraction groups in the chest CTSCAN findings and majority of the findings had ground glass opacities bilateral with consolidation (59%). The inflammatory marker LDH significantly increased in its trend as the shunt fraction increases having a p value 0.001. In the shunt fraction >40% the LDH had a median of 547. CRP at shunt fraction 30–40% was lower compared to the other shunt fraction with a median of 241. No significant difference was observed for the other inflammatory markers (Ferritin, D-dimer and Procalcitonin.)

Table 2. *Outcome measures of patients*

Characteristics	All (n = 205)	Shunt Fraction			P-value
		<30% (n = 86)	30–40% (n = 68)	>40% (n = 51)	
Hospital stays, days	14.5 ± 10.8	13.4 ± 8.8	16.8 ± 14.6	13.3 ± 6.9	0.097
Intubated	147 (71.7)	51 (59.3)	54 (79.4)	42 (82.4)	0.004
Time to intubation					
< =12 h	64 (43.5)	14 (27.5)	22 (40.7)	28 (66.7)	0.001
13 – 47 h	26 (17.7)	8 (15.7)	12 (22.2)	6 (14.3)	
> = 48 h	57 (38.8)	29 (56.9)	20 (37.0)	8 (19.0)	
Success of HFNC	47 (22.9)	28 (32.6)	12 (17.6)	7 (13.7)	0.019
In-Hospital All-Cause Mortality	109 (53.2)	42 (48.8)	39 (57.4)	28 (54.9)	0.559

mean ± standard deviation, frequency (%),
[$]ANOVA, [#]Fisher-exact

Overall, the average length of hospital stay was 14 days. Length of hospital stay was not significant in all groups of shunt fraction. However, a marginal increase in the length of hospital stay (mean of 16.8 days) in the shunt fraction 30–40% was observed.

A total of 147 patients (71.7%) were subsequently intubated. Sixty-four patients (43.5%) were intubated less than 12 hours, 26 patients (17.7%) were intubated 13–47 hours, and 57 patients (38.8%) were intubated after 48 hours of HFNC use. A significant number of patients intubated in the shunt fraction >40% (82%) and shunt fraction 30–40% (79%) compared to <30% group (59%) was seen. A significant higher proportion of patients in >40% group were intubated in less than 12 hours. For shunt fraction 30–40% there was no significant difference in those intubated in less than 12 hours (41%) and intubation occurring more than 48 hours (37%). The shunt fraction <30% group, had a higher proportion of patients intubated more than 48 hours.

The success of HFNC was seen in 47 patients (22.9%). A significantly higher proportion of patients in the shunt fraction <30% had success from HFNC (32.6%). Shunt fraction has statistically significant impact on success of HFNC with a p-value of 0.019.

A total of 109 patients (53%) expired. In-hospital all-cause mortality did not differ among all shunt groups.

Table 3. *Factors affecting mortality*

Candidate Predictors	B	P-value	Adjusted odds Ratio	95% Confidence Interval	
				Lower	Upper
Age Group					
1. Young Adults (19-39 years old)		0.005			
2. Middle-aged adults (40-59 years old)	0.349	.626	1.418	0.348	5.786
3. Old-aged adults (60-99 years old)	1.416	0.042	4.120	1.055	16.088
Shunt fraction					
1 <30%		0.211			
2 30-40%	0.635	0.099	1.886	0.887	4.012
3 >40%	0.027	0.949	1.027	0.454	2.323

Logistic regression of factors affecting mortality showed that age was the only variable predictive of in-hospital all-cause mortality. For old, aged adults (age range 60-99), the odds of mortality are 4.1 times greater than at the young age group (age range 19-39). (Table 3.)

Table 4. *Factors affecting intubation*

Candidate Predictors	B	P-value	Adjusted odds Ratio	95% Confidence Interval	
				Lower	Upper
Shunt fraction					
1 <30%		.005			
2 30-40%	1.332	.004	3.790	1.524	9.425
3 >40%	1.250	.018	3.491	1.240	9.823
LDH	.001	.366	1.001	.999	1.003
D-dimer	.000	.832	1.000	1.000	1.000
Procalcitonin	-.011	.316	.990	.969	1.010

In the factors affecting intubation, logistic regression revealed that greater shunt fraction would increase the odds of being intubated. Patients who have 30-40% shunt fraction had 3.8 times higher odds of being intubated and having a shunt fraction of >40% had 3.5 times the odds of being intubated this in comparison with shunt fraction <30%.

DISCUSSION

Overall findings of this study showed that older age, male sex, smoking history, the presence of co-morbidities, elevated inflammatory markers, presence of bilateral GGO's with consolidation on Chest CT scan, across shunt fraction of >30% did not benefit from trial of HFNC.

High Flow Nasal Canula and Shunt Fraction

In a study by Feiner et al. 2017, the variability of the PaO_2/FiO_2 ratio (P/F) across different FiO_2 levels and its relationship with shunt fractions, particularly 10-30%, highlights a dynamic nature reflecting lung function. In higher shunt fractions >40%, the P/F ratio shows more stability despite FiO_2 changes compared to lower shunt values, where the P/F ratio continues fluctuating significantly with FiO_2 changes.[1] (Figure 1) This understanding is crucial when considering HFNC therapy application, providing up to 60 liters per minute of heated and humidified oxygen/air blend with precise FiO_2 control (21-100%).[18] Our novel method consists of estimating shunt fraction based on visually plotting the given P/F ratios to a particular FiO_2 level the

patient received. Although this method was not validated, our results show HFNC success in lower estimated shunt fractions <30%. By harnessing HFNC's capacity for wide FiO_2 adjustment, substantial P/F ratio improvements occurred in this subgroup. This aligns with analysis of Feinter et al. indicating sizeable P/F ratio fluctuations across rising FiO_2 levels specifically at shunt fractions <30%.

Intubation

In our study, estimated shunt fractions between 30–40% and exceeding 40% had lower HFNC success and eventual intubation. This parallels observations of Feiner et al. showing more P/F ratio stability despite wide FiO_2 adjustments in higher >40% shunt groups, likely from the plateau of oxygenation improvement. Regardless of HFNC's delivered FiO_2, the P/F ratio in these higher estimated shunt ranges does not significantly increase.[1] This resistance to FiO_2 increments indicates a transition point where HFNC limitations give way to the need for invasive ventilation with PEEP as standard ARDS management.[19–21] Since this visual estimation approach remains non-validated, our findings in higher shunt fractions concurred with the study of Delbouve et al. 2021, wherein designating P/F ratios <150 as a threshold predictor of intubation in COVID-19 respiratory failure.[22] Plotting the data from Delbouve et al. on the shunt fraction curves from (Figure 1), P/F ratios <150 intersected shunt fraction above 30%, indicating oxygenation limitations. The plateauing of P/F ratios likely contributed to the recommendation by Delbouve et al. of an intubation threshold of P/F ratio <150, given HFNC's inability to further improve parameters. Moreover, a study by Raimondi et al. in 2021, suggests a single evaluation of the P/F ratio, especially at high FiO_2, could lead to inaccurate judgement of patients' severity for COVID-19.[23] The relationship between the P/F ratio and FiO_2 is not linear, making their interpretation complex.[24,25] It depends on factors like ventilation, perfusion, O2 arterio-venous difference, and hemoglobin concentration.[1] Therefore, a higher shunt fraction would warrant an invasive form of ventilation for adequate oxygenation, due to the inaccuracy of basing decisions solely on P/F ratio.

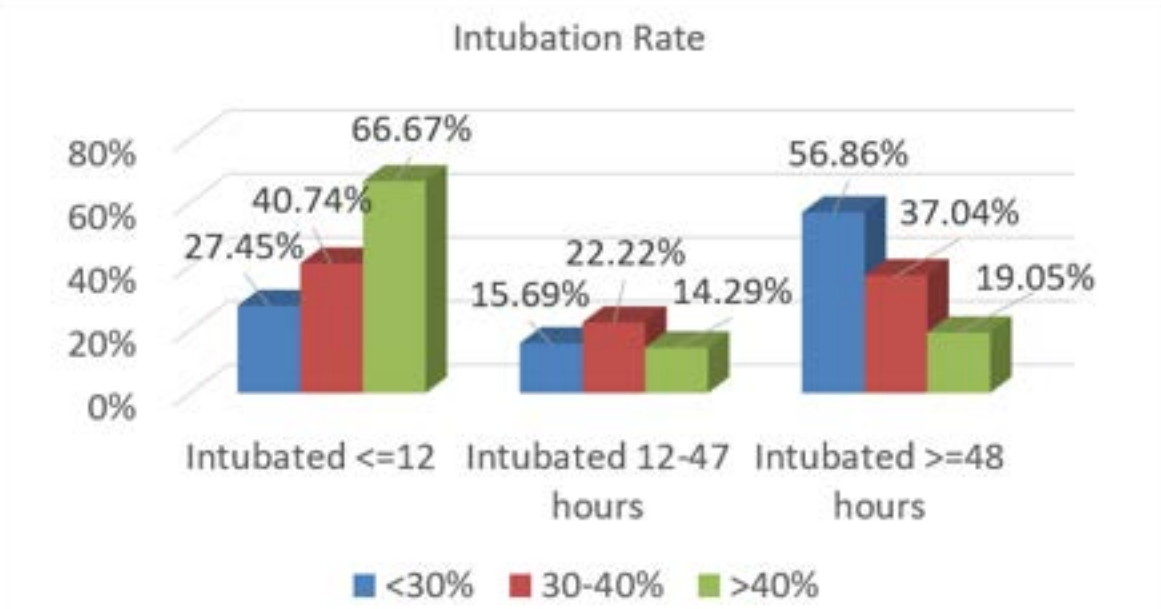

Figure 3. Intubation Rate in Different Shunt Fractions

In our study, the intubation rate was further categorized according to the time of intubation (12 hours, 13–47 hours, 48 hours). Our results showed that a trial of HFNC with an estimated shunt fraction of 30–40% and more than 40% would eventually lead to intubation within 12 hours (41% and 67%, respectively). A higher estimated shunt fraction would lead to intubation within 12 hours due to persistent respiratory failure. However, there was a significantly lower intubation rate for a shunt fraction <30% (27%), indicating a better tolerance for HFNC. Notably, those in the shunt fraction <30% group had a significant rate of intubation after more than 48 hours (57%), mainly due to the development of nosocomial infections secondary to COVID-19, leading to new onset respiratory failure (Figure 3). Further investigation regarding the development of nosocomial pneumonia in the <30% shunt fraction group was not conducted. However, the most likely cause would be failure in infection control practices during the pandemic peak. This aligns with Wolfensberger et al. 2018 study, which found frequent pathogen transfer in healthcare settings due to moist surfaces, manipulation of invasive devices, and prolonged care activity.[26]

Length of Hospital Stay

In our study it was noted that length of hospital stay was marginally increased in the 30–40% shunt fraction. In

comparison with the study of Chen et al. 2021 potential risk factors that may increase the length of hospital stay were advance age, higher levels of neutrophil counts, D-Dimer and CRP.[27] This was not reproduced in our study because of limitations in the cut off values in our laboratory setting such as D-Dimer and CRP. Advance age served as the predicting factor for our mortality which overall was 53.2% and in our overall data most patients did not increase the length of their hospital stay because majority had complications such as nosocomial pneumonia and majority expired.

Mortality

In this study, COVID-19 in hospital all-cause mortality remains high in all shunt fraction groups. This is comparable with the descriptive study in 2021 by Ubaldo et al. which also showed increase in all-cause mortality among admitted patients in the Philippine setting.[28] Our study showed that in-hospital all-cause mortality remains above 50% and that there was no significant difference across the shunt fraction groups. This is consistent with the study by Dessie et al. 2021 in which having factors such as acute kidney injury, COPD, diabetes, hypertension, cancer, increased D-dimer, male gender, older age, current smoker, and obesity increased the risk of the fatal outcome of COVID-19.[29] Further, in our study, older age is a significant predictor of mortality specifically at aged 60-99 adults. The co-morbidities were not seen to be significant which may be probably due to a lower sample population with existing comorbidities. Inflammatory markers were not significant in our study due to limitations and cut-off values in our laboratory which could underestimate the results.

Study limitations

Since this is a retrospective chart review, factors that we were not able to extrapolate because of missing information/s, were considered by imputation. Identified inflammatory markers have different units requiring different reagents and techniques which might have affected the results. Because of the overwhelming number of COVID-19 patients during the peak of the pandemic those patients who may benefit from HFNC were immediately intubated because of the scarcity of HFNC machines. Additionally, with the limited staff and high patient volume, some patients did not receive HFNC immediately, potentially affecting the clinical outcomes. Furthermore, the study did not account for potential confounding variables in medical management that might have influenced the success of HFNC. Such treatments, including Hemoperfusion, Tocilizumab, Remdesivir, and Dexamethasone, which were integral therapeutic options at the Lung Center of the Philippines during this period. Their exclusion from the study's analysis leaves opens the possibility that these treatments could be confounding factors, potentially impacting patient outcomes in conjunction with HFNC therapy, though their exact influence remains uncertain.

Additionally, this study did not investigate the various stages of ARDS in patients. The failure to differentiate between the early and fibrotic stages of ARDS is a significant limitation, as these stages can have different impacts on the efficacy of HFNC therapy and potentially prolong the length of hospital stay. This oversight might have contributed to an incomplete understanding of the factors influencing patient outcomes and the overall effectiveness of HFNC in this patient population.

CONCLUSION

In this study, when evaluating the effectiveness of HFNC as a therapeutic intervention for critical COVID-19 patients, it was observed that HFNC demonstrates a limited success rate in improving overall patient outcomes. However, it notably provided significant benefits in patients with a shunt fraction less than 30%. Despite these findings, the study did not conclusively demonstrate that HFNC therapy leads to reduced mortality or shorter hospital stays in the broader population of critically ill COVID-19 patients. While shunt fraction proves to be a valuable parameter in assessing patient suitability for HFNC therapy, it should not be the sole criterion. Instead, it is recommended that shunt fraction measurements be integrated with clinical judgment and supplemented with other parameters, such as the validated ROX index, to make more informed decisions about the use of HFNC in managing critical COVID-19 patients. This approach underscores the necessity of a multifaceted assessment strategy in the treatment of severe COVID-19 cases, where HFNC's role is one of several considerations in a comprehensive therapeutic plan.

RECOMMENDATION

For Clinical Practice

We recommend the use of APACHE and SOFA, a scoring tool in the prognostication of mortality of patients as an initial tool in evaluating patients who may benefit from HFNC. These may have a clinical effect on the shunt fraction as well. The use of ROX index, a validated tool to predict failure of HFNC can be use as comparison for the estimation of shunt fraction.

For Future Research

In areas of future research, we recommend looking into the utility of shunt fraction in patients with chronic lung disease, in those with PaCO2>45 mmHg since they comprise most of the populations that visit the emergency room. Additionally, further research could also consider including and analyze patients with hemoglobin of less than <10, as this parameter would have a significant impact in estimation of shunt fraction curves, which may result in different clinical outcomes.

FUNDING

None.

CONFLICT OF INTEREST

None declared.

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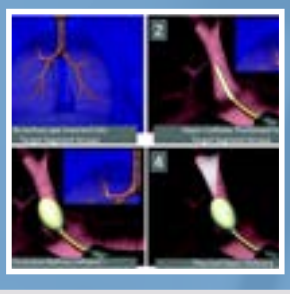

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Scientific Proceedings

ORIGINAL ARTICLE

POST–COVID–19 OUTCOMES: PERSISTENT SYMPTOMS, FUNCTIONAL CAPACITY AND SURVIVAL STATUS ONE YEAR AFTER RECOVERY FROM COVID–19 INFECTION IN THE LUNG CENTER OF THE PHILIPPINES

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Lung Center of the Philippines

ABSTRACT

Introduction. Almost 90% of patients who recovered from COVID–19 had at least one persistent symptom two months later and around 2% of people infected have long COVID symptoms even after 3 months. The most common persistent symptoms identified include fatigue, dyspnea, joint pain, chest pain and cough. This study aimed to identify persistent symptoms, functional capacity, proportion of survivors after one year of COVID–19 infection and determine if there is an association between these outcomes and the severity of their COVID–19 disease

Objective. This study aimed to determine the clinical outcomes of patients 1 year after recovery from COVID–19, in terms of persistent post COVID–19 symptoms, functional capacity, and survival status and to determine the association of these outcomes with their COVID–19 disease severity.

Methodology. This was an ambispective cohort study done in a tertiary hospital in the Philippines. The COVID–19 patients who were discharged at the Lung Center of the Philippines from April 1 to August 31, 2020 were recruited. Self–reported persistent symptoms, functional capacity using the European Respiratory Society (ERS) Functional Scale, and survival status were determined via phone interviews.

Results. A total of 100 patients were included in this study. Three subjects (3/100, 3%) were reported as mortality based on the report from relatives who received the call. Of the 97 remaining patients, 44% (43/97) had self–reported persistent symptoms described as fatigue (28/97, 29%), depression (13/97, 13%), impaired concentration or "brain fog" (11/97, 11%), and difficulty of breathing (9/97, 9%). Ninety–two (92/97, 95%) patients had none to negligible functional capacity limitations. Persistent difficulty of breathing was nine times more likely to be found in severe cases than in moderate cases [OR 9.3 (95%CI 1.088 to 78.910)] while persistent fatigue was eight times more likely to be found in severe cases [OR 8.2 (95%CI 2.5 to 27.1)] and 12 times more likely to be found in critical cases [OR 12.6 (95%CI 2.6 to 60.5)].

Conclusions. Patients after 1 year of COVID–19 infection revealed high proportion of survivors, some with persistent symptoms, and few with significant functional capacity limitations. Persistent symptoms of fatigue and difficulty of breathing were found to be associated with severe COVID–19. Comprehensive care of COVID–19 patients addressing these post–COVID–19 outcomes after recovery must be instituted.

Keywords. COVID–19, functional capacity, post–COVID–19 symptoms, mortality

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Year Completed: 2022
Date Received: October 26, 2023
Date Accepted: January 25, 2024

This paper was recognized by the following societies: 1. American Thoracic Society, Poster presentation, in the Annual Chest Conference held in San Francisco, California, 15–18 May 2022; 2. Philippine College of Physicians (PCP), 2nd place in the PCP Young Investigator's Award, PCP Annual Research Contest, 04 May 2022. 3. Philippine College of Chest Physicians (PCCP), Finalist, PCCP Annual Research Contest, 17 February 2022. 4. Lung Center of the Philippines (LCP), 1st place, LCP Annual Research Forum, 28 February 2022.

INTRODUCTION

The Philippines had tallied more than 3 million COVID-19 cases with a mortality rate of 1.72 % and recovery rate of 91.5% (Department of Health, Philippines). COVID-19 infection doesn't end after hospital discharge. Some patients who recovered from COVID-19 are left struggling with symptoms which persist through weeks, months and even a year. Almost 90% of patients who recovered from COVID-19 had at least one persistent symptom two months later1 and around 2% of people infected have long COVID symptoms even after 3 months. The most common persistent symptoms identified include fatigue, dyspnea, joint pain, chest pain and cough.2 Most follow-up study of recovered patients ranges from 2 months to 8 months as the longest. These studies show data regarding the immediate and short-term outcome of COVID-19 but the full spectrum of post-discharge characteristics is still unknown.

OBJECTIVE

This study aimed to identify persistent symptoms, functional capacity, proportion of survivors after one year of COVID-19 infection and determine if there is an association between these outcomes and the severity of their COVID-19 disease. The findings of this study shall contribute to the dearth of knowledge on the long-term effects of COVID-19 and shall guide COVID-19 outpatient clinics on the patient's post-COVID-19 course.

METHODOLOGY

This study is an ambispective cohort study design done in the Lung Center of the Philippines (LCP). LCP is a COVID-19 referral center for moderate to critical COVID-19 cases and dedicated 160 bed capacity for COVID-19 patients. The study duration is from June 2021 to December 2021.

The participants of the study were patients 18 years old and above who were discharged at the Lung Center of the Philippines with diagnosis of COVID-19 Recovered Moderate, Severe, or Critical from April 1 to August 31, 2020. A minimum sample size of 79 was computed to achieve 80% power considering small effect size (w = 0.35) for a chi-square test at 5% level of significance.

A list of eligible patients was taken from the LCP medical records section. The patients were initially called via phone for a brief introduction of the study and were asked to read and accomplish an online informed consent which was sent via email. All patients who gave their informed consent online were interviewed and asked for their baseline characteristics, persistent symptoms, and ERS functional capacity scale. A data collection form was used to collect all these data (Appendix A and B).

Qualitative sociodemographic and clinical characteristics used frequency and percentage to summarize data. Quantitative variables were summarized using mean and standard deviations. Long term clinical sequelae, persistent symptoms and proportion of survivors used frequency and percentage distribution. Fisher exact test and logistic regression were used to determine association of the above outcomes with disease severity. Functional capacity using the ERS scale, used mean and standard deviation and interquartile range. All hypothesis testing was performed at 5% level of significance.

Ethical Considerations

The study protocol was approved by the Lung Center of the Philippines-Institutional Ethics and Review Board (LCPIERB) and was conducted in accordance with the National Ethical Guidelines for Health and Health Related Research 2017 and the Data Privacy Act of 2012. Online informed consent was obtained from all patients.

RESULTS

Patient Recruitment

There were 502 patients who were discharged as COVID-19 recovered between April 1 to August 21, 2020. Out of the 502 subjects, 100 were included in the study. A total of 402 were excluded due to classification as COVID confirmed mild (15), COVID probable (98), and cannot be contacted due to wrong contact number information, cannot be reached, unattended, and no response (289). Refer to Figure 1 for the study flowchart.

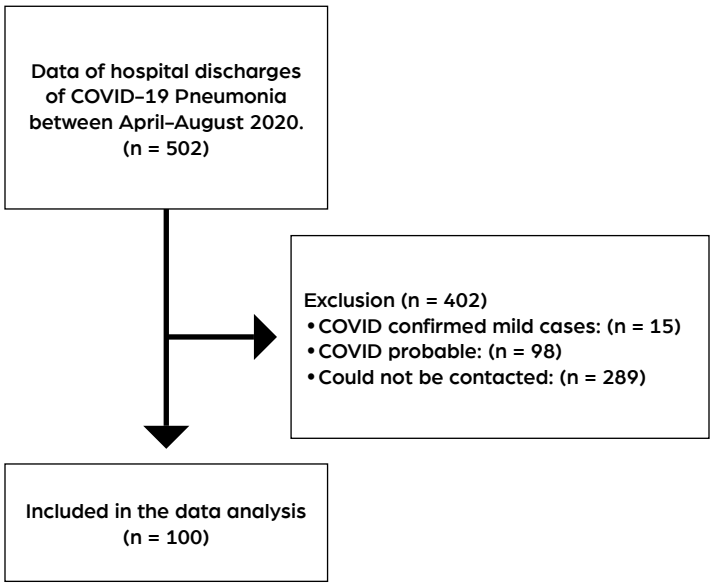

Figure 1. *Flow chart of patients included in the study.*

Baseline Characteristics

The median age of patients was 51 years old. Majority were male (52%), non-smokers (78%), and had comorbid conditions (66%). Comorbid conditions include hypertension (38%), diabetes mellitus (28%), asthma (9%), coronary artery disease (7%), chronic obstructive pulmonary disease (5%), pulmonary tuberculosis (4%), chronic kidney disease (4%), cerebrovascular disease (4%), and Alzheimer's disease (2%). Included patients had moderate (46%), severe (42%), and critical (12%) COVID-19 (Table 1).

Table 1. Baseline sociodemographic and clinical characteristics of patients who recovered from COVID-19 admitted at the Lung Center of the Philippines from March to August 2020

Characteristics	Results
Age, years	51.3 ± 16.2
Sex, Male	52 (52.0)
Smoking History	
Smokers	22 (22.0)
Number of smoking Pack Years	14.0 ± 12.4
No Comorbidity	34 (34.0)
With Comorbidity	66 (66.0)
Hypertension	38 (38.0)
Diabetes Mellitus	28 (28.0)
Asthma	9 (9.0)
Coronary Artery Disease	7 (7.0)
Chronic Obstructive Pulmonary Disease	5 (5.0)
Others:	26 (26.0)
Pulmonary Tuberculosis	4 (4.0)
Chronic Kidney Disease	4 (4.0)
Cerebrovascular Disease	4 (4.0)
Alzheimer's Disease	2 (2.0)
Moderate	46 (46.0)
Severe	42 (42.0)
Critical	12 (12.0)

Clinical outcomes after 1 year

Persistent Symptoms

There were 55 out of 97 patients (57%) who did not present with any persistent symptom after 1 year of recovering from COVID-19. The other 43 (44%) patients had persistent symptoms, who presented with just 1 symptom (22/97, 23%), 2 symptoms (13/97, 13%), 3 or more symptoms (8/97, 8%). Fatigue (28/97, 29%), depression (13/97, 13%), impaired concentration or "brain fog" (11/97, 11%), and difficulty of breathing (9/97, 9%) were the more common persistent symptoms reported. Other reported symptoms were as follows: cough (6%), joint pains (5%), muscle pain (3%), and chest pain (1%). There were no noted reports of loss of smell, loss of taste, fever, and headache after 1 year of recovery from COVID-19 among the 100 patients discharged from Lung Center of the Philippines (Table 2).

Functional Capacity

There were 60 patients (60.6%) had no residual functional limitations, 32 patients (32.3%) had negligible functional limitations, 4 patients (4%) had slight functional limitations, and 1 patient (1%) had severe functional limitation using the ERS functional scale (Table 3).

Table 2. Persistent symptoms after 1-year of patients who recovered from COVID-19 admitted at the Lung Center of the Philippines from March to August 2020.

Persistent Symptoms	Frequency, % N = 97
Without symptoms after 1 year	55 (57)
With symptoms after 1 year	43 (44)
1	22 (23)
2	13 (13)
>3	8 (8)
Fatigue	28 (29)
Depression	13 (13)
Brain fog/Cognitive Impairment	11 (12)
Difficulty of breathing	9 (9)
Cough	6 (6)
Joint Pains	5 (5)
Muscle Pain	3 (3)
Chest Pain	1 (1)

Table 3. Functional capacity of patients who recovered from COVID-19 admitted at the Lung Center of the Philippines from March to August 2020.

Post COVID-19 Functional Capacity Scale	Frequency, % N = 100
0 – No functional limitation	60 (60.6)
1 – Negligible functional limitation	32 (32.3)
2 – Slight functional limitation	4 (4.0)
3 – Moderate functional limitation	0 (0.0)
4 – Severe functional limitation	1 (1.0)
Death/Mortality	3 (3.0)

Survival Status

Ninety-seven patients out of 100 were reported to survive after 1 year (Table 3). The three mortalities had the following cause of deaths as reported by family members: acute respiratory failure secondary to chronic obstructive pulmonary disease who died after a year of recovery, acute coronary syndrome, and end stage renal disease both died few months after recovery. However, the relation of the cause of death to previous COVID-19 infection cannot be ascertained.

Association of Persistent Symptoms and Functional Capacity with COVID-19 Disease Severity

This study revealed favorable clinical outcomes after 1 year were evident in less severe disease. Trends noted were: a higher proportion of patients with persistent fatigue and difficulty of breathing were noted as the severity increased, and higher proportion of patients with functional scale of 0-1 (no to negligible functional limitation) were noted in moderate severity group as compared to the severe and critical severity group (Table 4).

On further analysis of the association with severity of disease, persistent difficulty of breathing was nine times more likely finding in severe cases than in moderate cases [OR 9.3 (95%CI 1.088 to 78.910)] while persistent fatigue was eight times more likely finding in severe cases [OR 8.2 (95%CI 2.5 to 27.1)] and 12 times more likely finding in critical cases [OR 12.6 (95%CI 2.6 to 60.5)] (Table 5).

Table 4. *Disease severity and clinical outcome of patients who recovered from COVID-19 admitted at the Lung Center of the Philippines from March to August 2020.*

Clinical Outcomes	Moderate N = 46	Severe N = 42	Critical N = 12	P-value
Persistent symptoms				
Fatigue	4 (8.7)	18 (43.9)	6 (54.5)	0.001
Depression	3 (6.5)	7 (17.1)	3 (27.3)	0.100
Brain fog	3 (6.5)	5 (12.2)	3 (27.3)	0.122
Difficulty of breathing	1 (2.2)	7 (17.1)	1 (9.1)	0.050
Cough	4 (8.7)	2 (4.9)	0 (0.0)	0.716
Joint Pain	0 (0.0)	4 (9.8)	1 (9.1)	0.058
Muscle Pain	0 (0.0)	2 (4.9)	1 (9.1)	0.092
Chest Pain	0 (0.0)	1 (2.4)	0 (0.0)	0.531
Functional Capacity				
0 – No functional limitation	42 (91.3)	16 (38.1)	2 (16.7)	0.001
1 – Negligible functional limitation	4 (8.7)	21 (50.0)	7 (58.3)	
2 – Slight functional limitation	0 (0.0)	3 (7.1)	1 (8.3)	
3 – Moderate functional limitation	0 (0.0)	0 (0.0)	0 (0.0)	
4 – Severe functional limitation	0 (0.0)	0 (0.0)	1 (8.3)	
Mortality	0 (0.0)	2 (4.8)	1 (8.3)	0.101

Table 5. *Association of disease severity with clinical outcome of patients who recovered from COVID.*

	Difficulty Breating		Fatigue		Functional Capacity	
	P-value	Odds Ratio	P-value	Odds Ratio	P-value	Odds Ratio
Moderate (Reference)	0.118		0.001		0.426	
Severe	0.042	9.265	0.001	8.217	0.998	Too wide
Critical	0.302	4.500	0.002	12.600	0.997	Too wide

DISCUSSION

This study revealed that in this cohort of COVID-19 recovered patients that were included, majority of the patients survived, some presented with persistent symptoms, and a large number had no significant limitation in functional capacity. Among those who presented with persistent symptoms, more common symptoms reported were fatigue, depression, impaired concentration or "brain fog," and difficulty of breathing. Persistent symptoms of fatigue and difficulty of breathing were found to be associated with severe COVID-19.

Persistent Symptoms

In comparison with other studies, this study's percentage of patients who had persistent symptoms after COVID-19 infection was 43%, varying from those reported in other studies which ranged from 30%,[3] 80%,[4] and 87.4%.[2] Similar persistent symptoms were reported which include fatigue as the most common symptom, followed by, in no particular order, depression, loss of concentration or "brain fog," dyspnea, joint pains, and chest pain.[2-6]

The National Institute for Health and Care Excellence[7] guidelines defined post-COVID-19 syndrome as signs and symptoms developing during or after COVID-19 and continuing for more than 12 weeks [NICE]. However, various terms have been used globally, reporting a wide range of physical, cognitive, and psychological symptoms, and vary in follow-up intervals from as short as 3 months to 9 months.[2-6] This study reported the longest interval from the COVID-19 infection, which is beyond 1 year from recovery.

Functional Capacity

Two studies used the Europol visual analog scale to assess the quality-of-life post-COIVD-19 infection. Patients were asking to score their quality of life from 0 (worst imaginable health) to 100 (best imaginable health) before COVID-19 and at the time of the visit. A difference of 10 points defined worsened quality of life. The first study reported 63 out of 143 patients (44%) had worsened quality of life after 2 months of recovery.[2] In the second study, 51 out of 177 patients (29%) had experienced worsened quality of life after 6 months of recovery compared with baseline.[3]

In terms of activity of daily living (ADL), one study used a questionnaire to assess its effect on the different ADL and reported 14 patients (7.9%) had negative impact on at least 1 activity of daily living, after 6 months of recovery.[3]

Correlation of the persistent symptoms with their functional capacity or quality of life cannot be ascertained as current studies lack evidence for this claim.

Survival Status

This one-year follow-up study of COVID-19 recovered patients revealed high proportion of survivors. There is still lack of data from other studies regarding survival status of patients as well as the causes of deaths post-COVID-19 if related to the previous COVID-19 infection.

Association of Persistent Symptoms and Functional Capacity with COVID-19 Disease Severity

Studies available employed the use of objective measures such as the 6-minute-walk test (6MWT) reported as 6-minute-walk distance (6MWD) and pulmonary function test in measuring functional capacity.[8,9]

Three hundred ninety-two patients underwent 6-MWT and pulmonary function test to measure functional capacity. Patients with severe to critical disease presented with an average of 16 meters shorter walking distance compared with moderate disease. Patients with severe to critical disease have 3.0 and 4.6 times more likely to present with a lower total lung capacity and reduced DLCO respectively compared with moderate disease.[8]

In another study, patients with severe to critical COVID-19 were older and had higher BMI compared to mild to moderate disease. Overall findings showed normal pulmonary function test in patients after mild to moderate disease. Patients with severe to critical disease showed lower lung volumes, reduced diffusion capacity (DLCO), 120 meters lower 6MWD, and 5.6% average decrease of 02 saturation even after adjustment of variables (age, sex, BMI) after 4 months of follow-up.[9]

However, there were no studies available regarding association with persistent symptoms and with disease severity.

Limitations of the study

Several limitations in the study were recognized. The small sample size limited precise detection of association of the outcomes with disease severity. There was a high rate of unreachable patients leading to lower number of eligible subjects and at risk for selection bias. Outcomes gathered were subjective and self-reported during phone interviews which may increase the risk for recall bias and ascertainment of outcome bias.

CONCLUSION AND RECOMMENDATIONS

Patients after 1 year of COVID-19 infection revealed high proportion of survivors, some with persistent symptoms, and few with significant functional capacity limitations. Persistent symptoms of fatigue and difficulty of breathing were found to be associated with severe COVID-19.

Comprehensive care of COVID-19 patients after recovery must be instituted. Routine inquiry on post-COVID-19 symptoms and functional capacity or quality of life should be done during follow up in outpatient clinics. Readily available objective measures such as 6MWT or structured questionnaires on functional capacity and quality of life may be used in the clinic.

Further research with adequate sample size to detect association with severity or interaction of the outcomes with each other and employing objective measures via chest CT scan, 6MWT, pulmonary function tests, and latest validated questionnaires on functional capacity and quality of life may provide robust evidence on post-COVID-19 patients sequelae. Also, impact of pulmonary rehabilitation or exercise programs in improving their long-term clinical outcome may also be investigated. Interestingly, impaired concentration or "brain-fog" may also be studied as one of the neurological sequelae of COVID-19.

FUNDING

This study is a self-funded study.

CONFLICT OF INTEREST

None.

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APPENDICES

APPENDIX A. Data Collection Form (English Version)

I. Investigator: May I know who is on the line? _____ (Interviewer to verify the name of participant, if other person is on the line ask for the participant or the legally authorized representative).

II. Review the Informed consent form, allow participant or legally authorized representative to ask questions.

III. Interviewer to ask for verbal confirmation that they voluntarily agreed to proceed with interview, objectives of the study were clear, questions have been answered and have signed and dated the informed consent on their possession.

IV. Interview Questions:

DEMOGRAPHIC DATA	
Name:	
Age:	
Sex:	
Occupation: (Medical or Non-Medical)	
CLINICAL HISTORY	
COVID-19 Classification (Moderate/Severe/Critical):	
Date of Discharge:	
Past Medical History:	Bronchial Asthma
	Cardiovascular Disease
	Cerebrovascular Disease
	Chronic Obstructive Pulmonary Disease
	Diabetes Mellitus
	Kidney Disease
	Liver Disease
	Malignancy
	Others
Smoking History:	

POST COVID FUNCTIONAL CAPACITY SCALE	
How much are you currently affected in your everyday life by COVID–19?	0: I have no limitations in my everyday life and no symptoms, pain, depression or anxiety related to the infection. 1: I have negligible limitations in my everyday life as I can perform all usual duties/ activities, although I still have persistent symptoms, pain, depression or anxiety. 2: I suffer from limitations in my everyday life as I occasionally need to avoid or reduce usual duties/activities or need to spread these over time due to symptoms, pain, depression or anxiety. I am, however, able to perform all activities without any assistance. 3: I suffer from limitations in my everyday life as I am not able to perform all usual duties/activities due to symptoms, pain, depression or anxiety. I am, however, able to take care of myself without any assistance. 4: I suffer from severe limitations in my everyday life: I am not able to take care of myself and therefore I am dependent on nursing care and/or assistance from another person due to symptoms, pain, depression or anxiety. D: Patient Expired

PERSISTENT SYMPTOMS
Are you still experiencing the following symptoms?

Fatigue	YES	NO	* If NO, month of symptom resolution
Difficulty of breathing	YES	NO	* If NO, month of symptom resolution
Joint pains	YES	NO	* If NO, month of symptom resolution
Chest pain	YES	NO	* If NO, month of symptom resolution
Cough	YES	NO	* If NO, month of symptom resolution
Loss of smell	YES	NO	* If NO, month of symptom resolution
Loss of taste	YES	NO	* If NO, month of symptom resolution
Fever	YES	NO	* If NO, month of symptom resolution
Muscle pain	YES	NO	* If NO, month of symptom resolution
Headache	YES	NO	* If NO, month of symptom resolution
Confusion/Brain Fog	YES	NO	* If NO, month of symptom resolution
Depression	YES	NO	* If NO, month of symptom resolution

IF Patient Answers Yes in the Depression symptoms, please answer these questions:

DEPRESSION SCALE				
Over the last 2 weeks, how often have you been bothered by any of the following problems?	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself – or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed? Or the opposite – being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3

APPENDIX B. Data Collection Form (Tagalog Version)

I. Tagapagsaliksik: Ano ang inyong pangalan? _____ (Tagapagsaliksik ay dapat mapatunayan na ang nasa linya ay ang kalahok o legal na awtorisadong kinatawan para sa pagaaral na ito.)

II. Muling bangitin sa kalahok ang consent form at bigyan ng oportunidad ang kalahok na linawin ang kanilang mga katanungan.

III. Kumpirmahin ng tagapagsaliksik na ang kalahok ay boluntaryong sumasangayon na sumali sa pag-aaral, lubos na naintindihan ang layuinin ng pag-aaral, nalinaw ang kanilang mga katanungan, at napirmahan ang document ng malayang pagsang-ayon na ibinigay sa kanila.

IV. Mga katanungan sa pag-aaral:

DEMOGRAPIKONG DATOS	
Pangalan:	
Edad:	
Kasarian:	
Trabaho:	
MEDIKAL NA TALA NG KALUSUGAN	
Klasipikasyon ng COVID-19:	
(Katamtaman/Malala/Kritikal)	
Medikal na Tala ng Kalusugan	Hika
	Sakit sa puso at mga daluyan ng dugo na para sa puso
	Sakit sa mga daluyan ng dugo na para sa utak
	Sakit sa baga
	Diyabetes
	Sakit sa bato
	Sakit sa atay
	Tumor/Kanser
	Iba pa
Paninigarilyo:	
SUKATAN NG KAKAYAHANG KUMILOS	
Sa kasalukuyan, gaano naaapektuhan ng COVID-19 ang iyong araw-araw na pamumuhay? How much are you currently affected in your everyday life by COVID-19?	0: Wala akong limitasyon sa araw-araw na mga gawain. Wala ring mga sintomas, pananakit, depresyon o pagkabalisa na may kaugnayan sa impeksyon. 1: May iilang limitasyon sa araw-araw na pamumuhay ngunit hindi naman kapansin-pansin ang mga ito dahil nagagawa ko pa rin ang mga karaniwang trabaho/gawain kahit pa patuloy na nararamdaman ang mga sintomas, pananakit, depresyon o pagkabalisa. 2: Nakakaranas ako ng mga limitasyon sa araw-araw na pamumuhay dahil paminsan-minsan kailangan kong iwasan o bawasan ang mga karaniwan kong trabaho/gawain o kaya naman kailangan ko ng mas mahabang oras para gawin ang mga ito dahil sa mga sintomas, pananakit, depresyon o pagkabalisa. Gayunpaman, kaya ko pa ring gawin ang mga gawain nang walang tulong ng iba. 3: Nakakaranas ako ng limitasyon sa araw-araw na pamumuhay. Hindi ko magawa ang aking mga trabaho/gawain dahil sa mga sintomas, pananakit, depresyon o pagkabalisa. Gayunpaman, kaya ko pa ring alagaan ang aking sarili nang walang tulong ng iba. 4: Lubhang nalilimitahan ang aking araw-araw na pamumuhay. Hindi ko kayang alagaan ang aking sarili at nakadepende ako sa pag-aalaga at/o tulong ng iba dahil sa mga sintomas, pananakit, depresyon o pagkabalisa. D: Pumanaw na ang pasyente
PABALIK-BALIK NA SINTOMAS	
Nararanasan mo pa rin ba ang mga sumusunod na sintomas?	

Lubhang pagkapagod	Oo	Hindi	*Kung hindi, bilang ng buwan bago nawala ang sintomas
Hirap sa paghinga	Oo	Hindi	*Kung hindi, bilang ng buwan bago nawala ang sintomas
Pananakit ng kasu-kasuan	Oo	Hindi	*Kung hindi, bilang ng buwan bago nawala ang sintomas
Pananakit ng dibdib	Oo	Hindi	*Kung hindi, bilang ng buwan bago nawala ang sintomas
Ubo	Oo	Hindi	*Kung hindi, bilang ng buwan bago nawala ang sintomas
Pagkawala ng pang-amoy	Oo	Hindi	*Kung hindi, bilang ng buwan bago nawala ang sintomas
Pagkawala ng panlasa	Oo	Hindi	*Kung hindi, bilang ng buwan bago nawala ang sintomas
Lagnat	Oo	Hindi	*Kung hindi, bilang ng buwan bago nawala ang sintomas
Pananakit ng kalamnan	Oo	Hindi	*Kung hindi, bilang ng buwan bago nawala ang sintomas
Sakit ng Ulo	Oo	Hindi	*Kung hindi, bilang ng buwan bago nawala ang sintomas
Pagkalito/hirap sa pagpokus	Oo	Hindi	*Kung hindi, bilang ng buwan bago nawala ang sintomas
Depresyon/Panlulumo	Oo	Hindi	*Kung hindi, bilang ng buwan bago nawala ang sintomas
Iba pa (tukuyin ang mga ito)	Oo	Hindi	*Kung hindi, bilang ng buwan bago nawala ang sintomas

KUNG ang sagot sa Depresyon o Panlulumo ay oo, pakisagutan ang bahaging ito:

SUKAT NG DEPRESYON				
Nitong nakaraang 14 na araw, gaano ka kadalas binagabag ng alinman sa mga sumusunod na mga problema?	Hindi kailanman	Maraming Araw	Lagpas sa kalahati ng bilang ng mga araw	Halos araw-araw
1. Di gaanong interesado o nasisiyahan sa paggawa ng mga bagay	0	1	2	3
2. Pakiramdam na nalulungkot, nadidipress o nawawalan ng pag-asa	0	1	2	3
3. Hirap na makatulog o manatiling tulog, o labis na pagtulog	0	1	2	3
4. Pagkaramdam ng pagod o walang lakas	0	1	2	3
5. Kawalan ng ganang kumain o labis na pagkain	0	1	2	3
6. Pagkaramdam ng masama tungkol sa iyong sarili – o na bigo ka o nabigo mo ang iyong sarili o ang iyong pamilya	0	1	2	3
7. Hirap magtuon ng pansin sa mga bagay, tulad ng pagbabasa ng dyaryo or panonood ng telebisyon	0	1	2	3
8. Pagkilos o pagsasalita ng mabagal na maaring napansin ng ibang tao? O ang kabaligtaran – pagiging alumpihit o di mapakali kaya ikot nang ikot nang higit sa karaniwan	0	1	2	3
9. Nag-iisip na mas mabuting mamatay ka na lang o saktan mo ang iyong sarili sa ilang paraan	0	1	2	3

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ORIGINAL ARTICLE

CLINICAL PROFILE AND OUTCOMES OF COVID–19 CONFIRMED CASES WITH ACUTE RESPIRATORY DISTRESS SYNDROME UNDERGOING PROTOCOL–DIRECTED ASSISTED PRONE POSITIONING AT THE LUNG CENTER OF THE PHILIPPINES (LCP) FROM MAY 1, 2020 TO APRIL 30, 2021

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ABSTRACT

Background. Prone positioning is an emerging tool in the care provided to patients infected with COVID–19 with Acute Respiratory Distress Syndrome (ARDS) at Lung Center of the Philippines (LCP).

Objective. This study aimed to characterize the clinical profile and outcomes of COVID–19 confirmed cases undergoing protocol directed assisted prone positioning.

Methodology. This retrospective single–arm cohort study involved 87 eligible patients seen from May 1, 2020 to April 30, 2021 by reviewing their medical records.

Results. Patients were predominantly middle–aged (49.4%) males (69.0%) with normal BMI (56.3%). Hypertension (59.8%) was the most prevalent comorbidity. Patients were admitted because of acute hypoxemic respiratory failure that required respiratory support. Biochemical markers of inflammation and disease severity, such as LDH, D–dimers and ferritin were consistently high in our study population. On average, the duration of symptoms before intubation was 7.7 days (SD=3.7) while the number of days of illness prior to prone positioning was 10.1 (SD=4.9). In terms of clinical outcomes, 94.3% of the patients had no accidental extubating. However, the all–cause mortality accounted for 29.9%. The mean number of days intubated was 14.1 days (SD=9.3) while the average length of hospital stay was 18.1 days (SD=11.4).

Conclusion. This study revealed a broad picture and proportion of COVID–19 with ARDS undergoing protocol directed assisted prone positioning. Prone position was safe and impacts the clinical outcome of patients.

Keywords: Prone positioning, clinical profile, COVID–19, acute respiratory distress syndrome

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Year Completed: 2022
Date Submitted: 26 December 2023
Date Accepted: 26 January 2024

INTRODUCTION

Coronavirus disease 2019 (COVID-19) which is caused by infection with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), is a global health crisis. In the Philippines, the burden of disease is still on a rising trajectory. The progression to respiratory failure and the requirement for mechanical ventilation in some patients has pushed health care systems worldwide to or beyond their limits.[1] It has been shown that the prone position during mechanical ventilation in patients with acute respiratory distress syndrome was able to improve oxygenation and thus reduce mortality.[2] Emerging evidence indicates that the respiratory system mechanics of patients with ARDS, with or without COVID-19, are broadly similar. As part of the management of COVID-19 related severe ARDS, the World Health Organization (WHO) recommends prone positioned mechanical ventilation.[3]

The management of ARDS secondary to the COVID-19 proves to be challenging and controversial. In fact, a series of editorials and case reports currently proposed that principles of mechanical ventilation in early COVID-19 should deviate from classic ARDS.[4] This suggestion was based on the notion that some COVID-19 ARDS patients ("L-type") are characterized by low lung elastance, low lung weight, and low lung recruitability; and the "H-type" are characterized by high lung elastance, high intrapulmonary right-to-left shunt, high lung weight, and high lung recruitability, typical for classic ARDS.[5] Furthermore, the utility of prone positioning in early COVID-19 ARDS has been questioned.

In the Philippines, prone position ventilation was usually used as a salvage treatment for COVID-19 in critical cases. Although the benefits remain controversial, there was paucity of data on the demographic and clinical outcomes of Filipino COVID-19 patients who underwent prone positioning. Hence, the objective of this study will characterize the clinical profile and outcomes of COVID-19 confirmed cases with ARDS undergoing protocol directed assisted prone positioning and their clinical outcomes thereby providing important data on demographic and patient's characteristics to help in planning resource allocation and identify areas for future research.

METHODOLOGY

Research Design

This observational study utilized a retrospective single-arm cohort approach which described and characterized the clinical profile and outcome of COVID-19 confirmed-cases with ARDS undergoing prone positioning from May 1, 2020 to April 30, 2021 using information and data from chart review.

Study Site

This study was conducted at the COVID ward of the Lung Center of the Philippines. LCP is a tertiary government hospital located along Quezon Avenue, Quezon City which specializes in the treatment, care, rehabilitation and/or relief of lungs and allied diseases and designated referral center for severe to critical COVID. It is a center of excellence in healthcare, training and research.

Study Subjects

1. *Inclusion Criteria*
   a. Adult patients above 18 years old and less than 75 years old who underwent prone positioning admitted from May 1, 2020 to April 30, 2021 at LCP.
   b. Patients diagnosed with COVID-19 infection as confirmed by positive nasopharyngeal/ oropharyngeal reverse transcription – polymerase chain reaction (RT-PCR) conducted at the national reference laboratory, a subnational reference laboratory, and/or officially accredited laboratory testing facility.
   c. COVID-19 patients whose severity classification is critical requiring invasive ventilation with acute respiratory distress syndrome
   d. Admitted to the COVID ward of Lung Center of the Philippines from May 1, 2020 to April 30, 2021

2. *Exclusion Criteria*
   a. Patients who were transferred to another intensive care facility and thus lost to follow-up
   b. Those with ICU discharge within 24-h after admittance
   c. Patients with cardiac dysrhythmia
   d. Pregnant patients
   e. Patients with chest tube placement
   f. Hemodynamic instability with mean arterial pressure < 60 mmHg
   g. Patients with Chest wall deformities
   h. Patients with COPD in exacerbation
   i. Established diagnosis of interstitial lung disease
   j. Patients with New York Heart Association (NYHA) class> II
   k. Vertebral column deformities that would preclude prone positioning
   l. Prior single or double lung transplant
   m. Thoracic or cardiac surgery in the last 30 days
   n. Head injury – raised intracranial pressure (ICP)
   o. Those with one or more incomplete data vis-à-vis variables of the study in the clinical history, laboratory results, imaging studies and clinical outcomes in the chart

Selection of Subjects (Sampling design)

Consecutive sampling was utilized to determine the subjects who will be included in this study.

Study Procedures

The medical records/charts of adult in-patients admitted at the Lung Center of the Philippines who fulfilled the inclusion and exclusion were reviewed. When conducting retrospective chart review, the abstraction form was used to ensure consistency, accuracy and reliability while helping to reduce error in data collection.

For the diagnosis of SARS-CoV-2 infection, this was confirmed by scrutinizing the result of RT-PCR in the chart. Consequently, a positive RT-PCR result for COVID-19 was indicative for COVID-19 confirmed case.

In the medical chart of the patient, documentation that patient underwent prone positioning were reviewed as stated in the doctor's order. Prone positioning of COVID-19 confirmed cases was performed in accordance to the LCP protocol on prone positioning in moderate to severe ARDS who had PF ratio of <150 and/or on chest CT scan with ground glass opacity located on the ventral portion of lungs, and/or impossibility of maintaining plateau pressure of <30 cmH2O and alveolar distention pressure of <15 cmH2O, and/or presence of right ventricular dysfunction. Patients were maintained in prone position for 1 hour after which Arterial Blood Gas (ABG) was checked. Patients who responded to prone, were maintained in prone position for 16 to 20 hours and proning schedule was continued. 10–20 min after prone positioning, respiratory variables were recorded while patients were in the supine position. Prone positioning was discontinued if patient had PF ratio of >150 or patient had developed contraindications (e.g. hypotension, arrythmia, unstable cardiac status).

Charts of the patients who were eligible for inclusion as study participants were likewise reviewed to obtain demographic variables (age and gender); clinical characteristics (Body Mass Index, co-existing condition; mean duration of symptoms before intubation, baseline SOFA score, Acute Physiologic Assessment and Chronic Health (APACHE) II score and baseline respiratory parameters); therapeutic profile; and, clinical outcomes (duration of mechanical ventilation, accidental extubating, length of ICU stay, all-cause mortality).

Sequential Organ Failure Assessment (SOFA) score calculated on admission was reviewed from the chart. The SOFA score was made of 6 variables, each representing an organ system. Each organ system was assigned a point value from 0 (normal) to 4 (high degree of dysfunction/ failure).

The interpretation of maximum SOFA score in relation to mortality were as follows: (1) Mortality <10%: SOFA Score 0 to 6; (2) Mortality 15–20%: SOFA Score 7 to 9; (3) Mortality

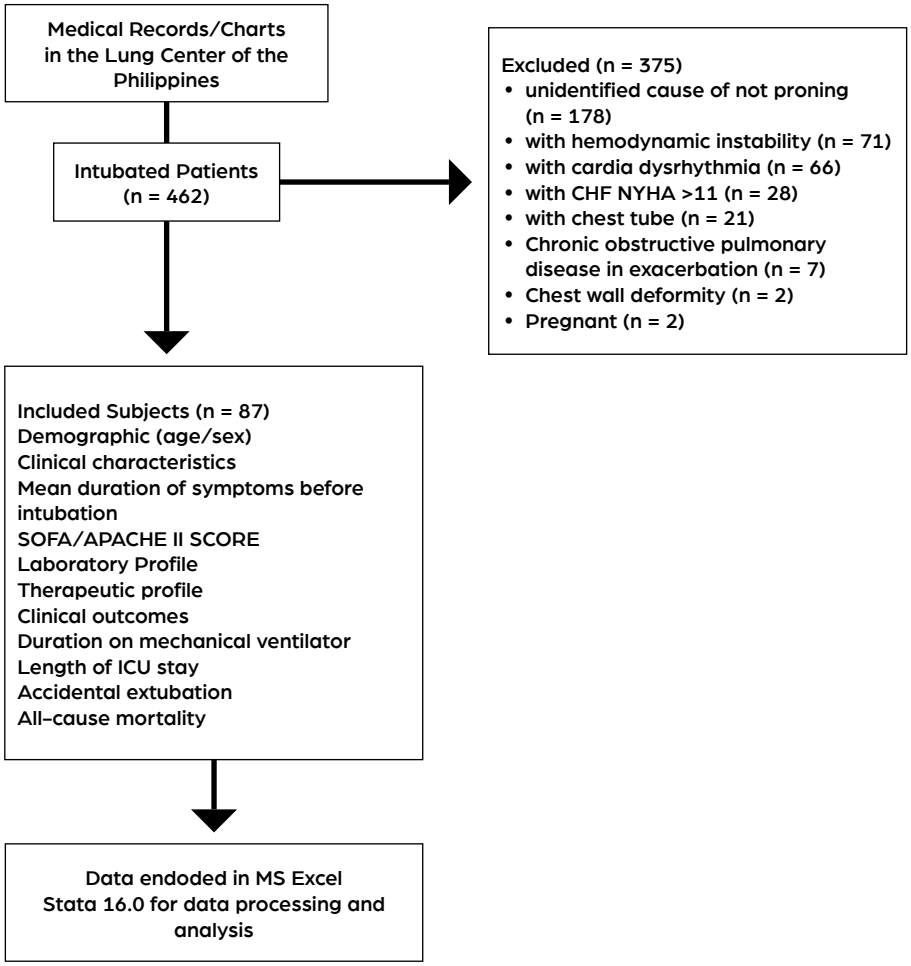

Figure 1. *Patient Recruitment*

40–50%: SOFA Score 10 to 12; (4) Mortality 50–60%: SOFA Score 13 to 14; (5) Mortality >80%: SOFA Score 15; (6) Mortality >90%: SOFA Score 15 to 24.

Finally, drug utilization was evaluated in the charts for the following therapeutic interventions by the attending physician: (1) Dexamethasone, (2) Remdesivir, (3) Hemoperfusion and (4) convalescent Plasma.

Data Analysis

The data were encoded in MS Excel by the researcher. Stata version 16.0 (StataCorp LP, College Station, Texas, USA) was used for data processing and analysis. The epidemiological data such demographic and clinical variables were analyzed using descriptive statistics. Continuous data were presented as mean and Standard Deviation (SD). On the other hand, categorical data were presented as frequency and percentages. Only valid data were utilized in the analysis and those missing information were not replaced or estimated.

Ethical Consideration

This study was done in accordance with ICH-GCP Guidelines and principles and was approved by the Lung Center of the Philippines – Institutional Ethics Review Board (LCPIERB). The results generated from the study will remain confidential and will be used for academic purposes only.

RESULTS

During the study period, 462 individuals were intubated and placed on mechanical ventilation. A total of eighty-seven (87) COVID-19 patients with ARDS who underwent prone positioning admitted at the Lung Center of the Philippines from May 1, 2020, to April 30, 2021 were included in this study and 375 were excluded and did not undergo prone positioning (figure 1). Table 1 presents the age, sex, and BMI profiles of the patients. Most of them were male (69.0%) and in their late middle age (49.4%) and late adulthood (29.9%). On the other hand, majority have normal BMI (56.3%).

Table 1. *Baseline Characteristics*

Profile	N	%
All patients	87	100.0
Age		
Early Adulthood (ages 21–34)	5	5.75
Early Middle Age (ages 35–44)	13	14.9
Late Middle Age (ages 45–64)	43	49.4
Late Adulthood (ages >=65)	26	29.9
Sex		
Female	27	31.0
Male	60	69.0
BMI		
Underweight (<18.5 kg/m2)	6	6.9
Normal weight (18.5–24.9 kg/m2)	49	56.3
Overweight (25.0–29.9 kg/m2)	27	31.0
Obesity (>30.0 kg/m2)	5	5.8

Table 2 below shows the clinical data of the patients. According to the data, hypertension (59.8%) and diabetes mellitus (26.4%) were the prevalent comorbidities. On average, the duration of symptoms before intubation was 7.7 days (SD=3.7) while the number of days of illness prior to prone positioning was 10.1 (SD=4.9). The SOFA score at entry and APACHE II score averages at 3.7 (SD=2.1) and 12.0 (SD=4.9), respectively. Meanwhile, the average respiratory rate was 31.6 (SD=8.7). The ratio of arterial oxygen partial pressure to fractional inspired oxygen was 96.8 (SD=36.5); positive end-expiratory pressure was 9.7 (SD=2.7); and fraction inspired oxygen was 88.3 (SD=20.7) on average. As for the laboratory parameters, LDH, on average, was 617.7 (SD=257.9). In addition, the patients D-dimer was mostly below 200 (61.6%) whereas ferritin was above 1,000 (83.1%). On the other hand, dexamethasone, remdesivir, and hemoperfusion were the most prevalent drug combinations administered to the patients (65.5%). The proning profile reveals that, on average, the proning frequency and duration were 2.3 times (SD=1.3) and 15.8 hours (SD=1.8), respectively.

Table 2. *Proning Profile*

Characteristic	N	%	Mean	SD[1]
All patients	87	100.0		
Coexisting Conditions				
Asthma	2	2.3		
Diabetes mellitus	23	26.4		
Other lung disease	2	2.3		
Chronic kidney disease	3	3.4		
Malignancy	1	1.1		
Coronary heart disease	3	3.4		
hypertension	52	59.8		
HIV[2], transplantation or immuno-suppressive medications	0	0.0		
Duration of symptoms before intubation (days)			7.7	3.7
Day of illness prior to proning			10.1	4.9
SOFA Score at entry[3]			3.7	2.1
APACHE II score			12.0	4.9
Respiratory Parameters				
Respiratory rate			31.6	8.7
PaO_2:FIO_2 ratio[4]			96.8	36.5
PEEP (cm H_2O)[5]			9.7	2.7
FIO_2[6]			88.3	20.7
Tidal volume per ideal body weight (mL/kg[d])			6.2	0.4
Laboratory Parameters				
LDH			617.7	257.9
D-dimer				
<=200	45			
>200	28			
Ferritin				
<=500	6			
501-1,000	8			
>1,000	69			
Therapeutics				
Dexamethasone + Hemoperfusion	20			
Dexamethasone + Remdesivir + Hemoperfusion	57			
Dexamethasone + Remdesivir + Hemoperfusion + Convalescent Plasma	10			
Proning Profile				
Number of the times the patient was prone			2.3	1.3
Duration of proning (hours)			15.8	1.8

1-Standard deviation; 2-Human Immunodeficiency Virus; 3-Sequential Organ Failure Assessment (SOFA) Score; 4-Ratio of arterial oxygen partial pressure to fractional inspired oxygen; 5-Positive end-expiratory pressure (cm H2O); 6-Fraction of inspired oxygen

Table 3. *Clinical outcomes*

Variables	N	%	Mean	SD[1]
All patients	87	100.0		
Accidental extubating				
Yes	5	5.8		
No	82	94.3		
All-cause mortality				
Yes	26	29.9		
No	61	70.1		
Duration of mechanical ventilation (days)			14.1	9.3
Length of hospital stay (days)			18.1	11.4

1-Standard deviation

For the clinical outcomes, the results in table 3 reveals that 94.3%of the patients had no accidental extubation. However, the all-cause mortality accounted for 29.9%. The mean number of days intubated was 14.1 days (SD=9.3) while the average length of hospital stay was 18.1 days (SD=11.4).

DISCUSSION

The researchers comprehensively evaluated the clinical profile of 87 COVID-19 confirmed cases with ARDS undergoing protocol directed assisted prone positioning in our institution from May 1, 2020 to April 30, 2021. It was noted that majority of the patients seek consult within 8 days from the symptom onset and already with elevated inflammatory markers. Patients were admitted due to acute hypoxemic respiratory failure, which requires invasive ventilation, from severe ARDS with hospital mortality of 10-15%. Recommendation for ventilator management such as high PEEP and low tidal volume were also observe. Remdesivir, hemoperfusion and dexamethasone were utilized which was consistent with the hospital protocol. Most of our patients were placed in prone position at least twice during their stay in LCP with an average duration of 15 hours. There were 5 documented accidental extubation and 26 cases of in-hospital mortality.

Majority of patients were male in their middle age (45-64 years old) with normal to overweight BMI, and majority had Hypertension followed by Diabetes mellitus which was the same with the study of Binda et.al, wherein the mean age was 57.6 and predominantly obese males at 66.7% with common comorbidities that Cardiovascular and Diabetes.[19] To date, older age alone was not a risk factor for ARDS.[6] Accordingly, male gender and patients with BMI > 25 were recognized risk factors for developing ARDS7 wherein prone positioning may confer a lung-protective benefit.8 The use of prone positioning in obese patients with COVID-19 was a safe and feasible treatment; however, obese patients might deserve more surveillance and active prevention by intensive care unit staff because of the higher rates of pressure ulcers compared to patients with normal weight.[9] As seen in the study of Binda et al. patients who were obese, had an increase incidence of developing pressure ulcers with correlation to duration of time (24 to 48 hours) the patient was on prone position. Majority of pressure ulcers occurred on sacrum followed by chin and cheekbone. In table 2 baseline SOFA score was 3.7 and 12 for APACHE II score. Patients included in the study of Binda et al. had a SOFA score of 7.0 indicating that high SOFA score provides high mortality rate.

Biochemical markers of inflammation and disease severity, such as LDH, D-dimers and ferritin, were consistently high in our study population. This explains that majority of the patients were already in cytokine storm and with severe ARDS requiring invasive ventilation. Early prone positioning was crucial since based from the study of Shelhamer et al. early proning may play a role in reducing systemic inflammation by increasing alveolar fluid drainage. According to Cherian et al. these inflammatory markers along with respiratory parameters were predictive factors for success of proning in hypoxemic respiratory failure secondary to COVID-19.

Most of our patients received the standard of care such as: dexamethasone, remdesivir and hemoperfusion. Dexamethasone used was demonstrated to decrease the mortality rate of COVID-19 patients, whereas remdesivir was proven in shortening the time to recovery. The optimal timing of remdesivir initiation in hospitalized patients with COVID-19 administered with dexamethasone 29 and the increased adoption of non-invasive supplemental treatments including early prone positioning was associated with significantly shorter time to clinical improvement and positive IgG antibody, lower risk of in-hospital death, in addition to shorter length of hospital stay.19 In ARDS patients with severe hypoxemia, arterial oxygenation

can be improved by combining the prone position with pharmacologic treatment without deleterious effects. But there are no studies to quantify the additive beneficial effects to COVID-19 patients. There are still ongoing debates regarding the use of the hemoperfusion among COVID-19 patients. However, from the study of Soleimani et al. hemoperfusion can significantly increase spO2 level and decrease CRP levels.[20]

During the COVID-19 pandemic, prone position was part of the standard of care, which was widely used in our hospital, to treat mechanically ventilated patients with moderate to severe ARDS. Most patients improved their oxygenation during prone position, most likely due to a better ventilation perfusion matching. Conceptually, prone position may result to a more uniform distribution of lung stress and strain, leading to improved ventilation-perfusion matching and regional improvement in lung and chest wall mechanics. However, there was poor adherence to protocol. In the study of Langer et al. 61% of patients were placed in prone position at least once during their stay in the ICU. The frequency of use of prone positioning increased with ARDS severity. Prone positioning was first applied 2 days after ICU admission, and a median of 3 pronation sessions per patient was performed.[14] Prior clinical trials showed that prone positioning improves oxygenation in patients with ARDS, without benefits in terms of survival.[10] Aside from prone position initiation leading to improved oxygenation parameters,[11] blood pressure does not change significantly in the prone position[12] as in the case of our hypertensive patients.

Based on literatures, decreased hypoxemia and mortality rates were the main outcomes of prone positioning reported.15 The all cause-mortality rate of our study population was 29.9% with an average of 18 days hospital stay among survivors. Although the positive outcomes outweighed complications, the impact of the prone positioning may be improved in the setting of advanced interventions with the added attention and care of a multidisciplinary team to improve patient's outcome trajectories. Contrary to this, it has been demonstrated that prone positioning has no demonstrable impact on mortality rates based on studies performed over the past few years.[17] However, in the study of Park et al. prone positioning tends to reduce the mortality rates in ARDS patients, especially when used in conjunction with a lung protective strategy and longer prone position durations.[18] In terms of complications, the most prevalent were: accidental extubation, pressure ulcer, and facial edema. Accidental tracheal extubation in this setting could be a catastrophic event often treated by turning the patient supine for ventilation and re-intubation. The rate of accidental extubation varies in the literature, but has been reported to be as high as 78%.[15]

Some limitations of this study should be noted. First, this was a single center retrospective observational study in a resource constrained environment under crisis operations. As a result, although patients had critical care needs, they were frequently cared for in ad-hoc intensive care units by non-critical care personnel. There was no standard monitoring form for proning with limited charts reviewed. Our sample size was small which reduces the power of the study. Regarding outcome, we were unable to include patients who would have been eligible as controls creating a sound counterfactual for a contemporaneous comparison of both exposed and unexposed. Finally, compared to existing literature for patients with COVID-19, this study provides results for a large intervention group.

The result of this study may not be readily generalizable to all populations, in particular those with milder disease. The institutional mortality proportion was high and therefore the impact of the intervention may be attenuated in the setting of advanced interventions. There may also be channeling bias due to disease severity or survivor bias.

There were also some notable strengths of this study. We were able to collect detailed data on clinical profile and outcome of our study subjects in a structured manner. Also, our population has been gravely understudied in the COVID-19 pandemic and we've been able to contribute significantly to both describing the clinical profile as well as their outcome for socioeconomically marginalized minority populations.

CONCLUSION AND RECOMMENDATIONS

In terms of the clinical profile, our patients were predominantly middle-aged males with normal BMI. Hypertension was the most prevalent co-morbid condition. Patients were admitted because of acute hypoxemic respiratory failure that required respiratory support. On average, the duration of symptoms before intubation was 7.7 days while the number of days of illness prior to prone positioning was 10.1. Biochemical markers of inflammation and disease severity, such as LDH, D-dimers and ferritin were consistently high in our study population. In terms of clinical outcomes, majority of our patients had no accidental extubation with all-cause mortality accounting only to 29.9%. The mean number of days intubated was 14.1 days while the average length of hospital stay was 18.1 days. This study revealed a broad picture and proportion of COVID-19 with ARDS undergoing protocol directed assisted prone positioning. Prone position was safe and impacts the clinical outcome of patients.

The findings should be replicated across institutions, but prone positioning may be an important consideration for health systems, particularly in the setting of an evolving suite of complementary interventions in the care of COVID-19 patients. Prone positioning for ARDS patients should be prioritized over other invasive procedures because related life-threatening complications were rare. We acknowledge that prone positioning in mechanically

ventilated patients was a resource-intensive intervention, particularly in overwhelmed healthcare systems during pandemic conditions. Before adopting prone positioning techniques, staff education and commitment is paramount. If justified by hospitalized patient volume, we recommend identifying personnel and assigning them to a dedicated prone team and tailoring readily available checklists to institutional needs and constraints.

However, further additional randomized controlled design to study is required for confirm benefit of prone position in ARDS with proning monitoring form (Appendix). Prospective study with larger sample size and control group is recommended to monitor adherence and safety to protocol.

CONFLICT OF INTEREST

None declared.

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APPENDIX

Suggested Proning Safety Checklist

Proning Safety Checklist		
	DONE	NOT DONE
Identify physician to authorize and supervise procedure (attending or fellow)		
Order for prone positioning should be entered into the patient's chart		
Review inclusion & contraindications		
Discuss risk/benefits of the procedure with the patient's decision maker		
Gather staff that will be available for the 15–20 minutes to perform the proning.		
Physician		
4 nurses (2 each side)		
Respiratory therapist		
Equipment		
Proning pillow		
Flat sheets (2)		
Dry flow pads (2–3)		
ECG leads/patches		
Ensure oral suction and ETT suction available (either inline or catheter)		
emergency airway cart and appropriately sized ETT immediately available		
Pre–proning preparation		
Verify ETT is well secured		
Optimize ventilator settings and pre–oxygenate patient		
Suction ETT and oral cavity		
Remove and cap unnecessary lines tubes (e.g., blood pressure cuff, CVP monitoring, tube feedings, maintenance fluids)		
Clean patient		
Ensure patient is well sedated, with adequate analgesia and neuromuscular blockade		
Remove ECG patches and leads from limbs and anterior chest		
The Turn Checklist		
MD responsible for the head turning/support		
Identify turn leader (usually the patient's primary nurse)		
Respiratory therapist at head of bed. Responsible for ETT support and ventilator		
Minimum 2 staff each side of bed		
Tuck arm under patient (arm closest to the ventilator)		
Place oximeter probe on limb not being turned under patient		
Place flat sheet on top of pillows/patient		
Slide patient to edge of bed (away from ventilator)		
Check ETT, lines, tubes		
Rotate patient and slowly turn toward vent until in prone position		

Proning Safety Checklist		
	DONE	NOT DONE
Check ETT, lines, tubes. Assess lines and tubes for dislodgement/kinks/ air entry		
Position arms in modified swimmers' crawl. Face is in the direction of the raised arm. Shoulder dropped and elbow below axilla and other arm at side, palm facing up		
Ensure pillows are under shins and toes are off the bed		
Reattach disconnect lines/cables		
Place bed in reverse Trendelenburg		
Reassess ETT cuff pressures, tidal volumes, sats, BP, HR		
Supination checklist		
Airway trained doctor / adequate staff available		
Endotracheal tube and venous lines secure		
Discontinue non-essential infusions / monitoring		
Adequate sedation +/- muscle relaxation		
Patient wrapping		
Horizontal move away from the ventilator so that the patient can be turned towards the ventilator.		
Check ETT, lines, tubes		
Rotate patient and slowly turn toward vent until in prone position		
Check ETT, lines, tubes. Assess lines and tubes for dislodgement/kinks/ air entry		
Reattach disconnect lines/cables		
Reassess ETT cuff pressures, tidal volumes, sats, BP, HR		

	Before Proning	After Proning
PFR		
Length of ETT		
Length of NGT		
Vital signs		
Blood Pressure		
Heart rate		
Oxygen saturation		

	Before Supination	After Supination
PFR		
Length of ETT		
Length of NGT		
Vital signs		
Blood Pressure		
Heart rate		
Oxygen saturation		

LUNG CENTER OF THE PHILIPPINES

PULMONARY REHABILITATION

WARM-UP & COOL DOWN

BREATHING EXERCISES

CARDIOPULMONARY EXERCISES

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

Materials for Virtual Sessions

Digital Platforms Requirements
- -Zoom Account
- -Viber Account

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

CONDITIONS RECOMMENDED FOR THE PROGRAM

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

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ORIGINAL ARTICLE

COMPARATIVE STUDY OF CLINICAL OUTCOMES OF SEVERE AND CRITICAL COVID-19 PATIENTS WITH AND WITHOUT HEMOPERFUSION ADMITTED IN A REFERRAL HOSPITAL

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ABSTRACT

Background. Coronavirus disease (COVID-19) has been a global problem since 2020, and is challenging to manage, leading to countless deaths worldwide. Severe cases are due to overwhelming hyperinflammatory response termed cytokine release syndrome. Hemoperfusion has been proposed as a means of removing cytokines from the circulation, theoretically improving survival. This study compared the clinical outcomes of hemoperfusion among severe and critical COVID-19 patients admitted in a COVID-19 referral hospital.

M**ethodology.** This is a retrospective cohort study involving hospital records of severe and critical COVID-19 adult patients. Patients were grouped according to severity and hemoperfusion status.

Results. There were 435 patients included in the study, of which 155 were patients without hemoperfusion, and 280 with hemoperfusion. Baseline inflammatory markers of critical patients were significantly higher than severe patients in both the HP group (LDH p=0.01, Procalcitonin p=0.01) and non-HP group (LDH p=0.02, ferritin p=<0.01, D-dimer p=<0.01, IL-6 p=<0.01). There was significant reduction in inflammatory markers post-hemoperfusion for both severe (CRP p=<0.01, LDH p=0.02, ferritin p=<0.01, D-dimer p=<0.01) and critical (CRP p=<0.01) groups. There was a higher probability of survival among severe COVID-19 patients with HP (p=<0.001).

Conclusion. There is an association between hemoperfusion and improved survival among severe COVID patients, but not among critical COVID patients. Hemoperfusion was also associated with better survival among severe patients who were intubated during admission. Future studies should be done in institutions where hemoperfusion is not part of their standard of care.

Keywords: COVID-19, hemoperfusion, cytokine storm, cytokine release syndrome

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Year Completed:
Date Received: 09 January 2024
Date Accepted: 14 February 2024

Presented at the Philippine College of Chest Physicians Research Contest, 41st Annual Chest Convention, 2022 Lung Center of the Philippines Annual Research Forum 2022; European Respiratory Society (ERS) International Congress 2022, Barcelona, Spain; 26th Congress of the Asian Pacific Society of Respirology, 2022, Seoul, Republic of Korea; American Thoracic Society 2023 International Conference, Washington, DC, USA; and CHEST 2023 Annual Meeting, American College of Chest Physicians, Honolulu, USA

INTRODUCTION

Coronaviruses are a large family of viruses that can lead to a wide range of diseases – from a simple cold to severe life-threatening illnesses such as Middle East Respiratory Syndrome (MERS-CoV) and Severe Acute Respiratory Syndrome (SARS).[1] SARS-CoV2, the causative agent for coronavirus disease (COVID-19) is a novel strain of this virus that was first discovered in China in 2019, where it was seen affecting the human population for the first time.2,3 On January 30, 2020, an adult female patient who complained of cough and sore throat was evaluated, and SARS-CoV2 viral RNA was detected by polymerase chain reaction. She was identified as the first confirmed COVID-19 case in the Philippines. As of January 1, 2022, the Department of Health of the Philippines tallied an average of 1,301 daily COVID-19 cases bringing the Philippines total cases to 2,847,486, with a total of 51,545 deaths. The Lung Center of the Philippines was identified as a referral center for COVID last March 2020, and as of January 2022, there have been a total of 4,024 COVID-19 admissions, of which a majority have been severe and critical cases. Different clinical features have been reported in COVID-19, from an asymptomatic form to severe disease leading to respiratory failure, and multiple organ failure requiring intensive-care treatment and mechanical ventilation. Common manifestations of confirmed cases have been listed as fever, fatigue, dry cough, nasal congestion, shortness of breath, myalgia, and arthralgia, while common laboratory findings include lymphopenia, high plasma levels of c-reactive protein (CRP), and elevated lactate dehydrogenase (LDH). About 7-10% of patients progress to critical disease, while 1-2% of patients succumb to the illness. The reported mortality rate of patients varies according to their geographic location.[3] The Center for Disease Control and World Health Organization group the severity of COVID-19 infection into 1) asymptomatic: individuals who do not display symptoms but who test positive for SARS-COV2, 2) mild: patients who have signs and symptoms of COVID-19 without dyspnea and pneumonia on chest roentgenogram, 3) moderate: patients with signs and symptoms of COVID-19, pneumonia on chest imaging and oxygen saturation of 94% and above at room air, 4) severe: patients with oxygenation of less than 94% at room air, PF ratio of <300 mmHg, and respiratory rate of >30, and 5) critical: patients in respiratory failure, septic shock, and/or multiorgan failure. Severe and critical COVID-19 patients have a higher chance of mortality, so far causing more than 5 million deaths worldwide.[1]

In some patients afflicted with the virus, an overwhelming hyperinflammatory response termed as cytokine storm, or cytokine release syndrome (CRS), may be observed. CRS is characterized by high levels of circulating pro-inflammatory cytokines (e.g. IL-1ß, IL-6, and tumor necrosis factor), and is associated with worsening of acute respiratory distress syndrome (ARDS). An increase in levels of pro-inflammatory cytokines may be an appropriate response to severe infection, however, an exaggerated response in COVID-19 patients is likely responsible for multiple organ dysfunction. High levels of pro-inflammatory cytokines directly correlate with the severity of lung injury in patients with severe COVID-19. CRS results in organ dysfunction (e.g. acute kidney injury) and tissue damage by promoting endothelial dysfunction as well as microvascular and macrovascular thrombosis, which is a widely reported phenomenon in patients with COVID-19.[4] Local guidelines, published by the Philippine Society for Microbiology and Infectious Disease, recommend the use of IL-6 receptor blockers and systemic corticosteroids for severely ill COVID-19 patients. The use of Baricitinib in combination with Remdesivir is also recommended for patients unable to receive steroids. Despite these medications, some patients may still worsen and progress to ARDS and require high flow oxygen or intubation. These patients typically have a more morbid clinical course.[5] Since the main pathogenic mechanism in COVID-19 pneumonia and ARDS is an uncontrolled inflammatory state, hemoperfusion is seen as a potential adjuvant treatment to mitigate excessive inflammation in patients with COVID-19.

Hemoperfusion (HP) was first introduced as a therapeutic procedure in the 1960s. Hemoperfusion, as a tool for blood cleansing, has many benefits over other non-selective forms of extracorporeal detoxification (e.g. plasmapheresis and plasma filtration) due to advances in discovering new adsorbents, as well as changes in the initially proposed adsorbents. Hemoperfusion was shown to be an effective way to remove cytokines and reduce the side effects of cytokine storm. Cytokine removal following extracorporeal therapies may prevent cytokine-induced organ damage, and patients who undergo these therapeutic approaches in the early phase of cytokine storm may have a better clinical outcome.6 In patients with sepsis and septic shock, HP has been shown to stabilize plasma cytokine levels.[7] In the setting of COVID, increased levels of cytokines have been linked to a poorer prognosis. Specifically, it was found that the virus induces macrophages to produce interleukin-6 (IL-6), to enhance neutrophil chemotaxis, as well as lymphocyte necrosis.[8] Other studies have also shown a link between severe COVID-19 infection and cytokine storm, which results in difficult clinical scenarios.[9,10] A trial that evaluated 97 patients with severe sepsis or septic shock and acute lung injury or ARDS showed that HP was able to remove IL-6 from the blood.[11] Overall, the theoretical foundation for the use of HP in severe and critical COVID-19 remains limited. A few case reports and case series by Shadvar et al. (2021), Hajian et al. (2021), and Rampino et al. (2021) showed that patients improved after hemoperfusion, while Vardanjani et al. (2021) found that early hemoperfusion abated the progression to critical state and prevented intubation.[12,13,14,15] A prospective single-arm trial done by Asgharpour et al. (2020), showed a significant improvement in capillary oxygen saturation before and after hemoperfusion from 89.6 + 3.94% to 92 + 3.38%.16 The efficacy of hemoperfusion in patients with COVID-19 has yet to be established with trials or large observational studies.[17] The FDA approval for hemoperfusion devices was based on "bench performance testing and reported clinical

experience".[18] More generally, hemoperfusion has been found to be ineffective in reducing mortality in patients with sepsis. An initial small trial suggested improved survival with hemoperfusion for septic shock, but subsequent larger randomized controlled trials suggested no significant mortality benefit.

This study aimed to compare and describe the clinical outcomes of severe and critical COVID-19 patients admitted in the Lung Center of the Philippines with and without hemoperfusion. Specifically, it aimed to determine the proportion, demographics and clinical factors of severe and critical COVID-19 patients with and without hemoperfusion.

METHODOLOGY

This study was a retrospective cohort, where hospital records of patients diagnosed with severe and critical COVID-19 with and without hemoperfusion were reviewed. Patients admitted in the Lung Center of the Philippines from August 1, 2020 to July 31, 2021 were included. Two groups of patients were identified: severe and critical COVID-19 patients without hemoperfusion (HP), and severe and critical COVID-19 patients with HP. The needed sample size was calculated using OpenEpi ver 3.0, with a confidence level of 95%. It was assumed that patients without hemoperfusion was significantly less in number than patients with hemoperfusion, thus the entire pool of patients without hemoperfusion was used as the population size for that group. Random sampling was done for patients with hemoperfusion using computerized random number generation by sequentially assigning a number to each patient, then generating a list of random numbers using the Randomness and Integrity Services website (random.org) based on the computed sample size.

Patients in both groups were sub-classified into severe COVID and critical COVID subgroups, depending on their corresponding disease severity. Patients excluded from the study were those with incomplete data, those transferred from other institutions, patients with end stage malignancy, GCS 8 and below, with advance directives of do not resuscitate, or do not intubate, post arrest, and expired within 48 hours from the time of admission. Chart review was done, and laboratory data as well as radiographic results were collected through the hospital's digital database. Results were encoded using Microsoft Excel, with the completeness of data, as well as error-checking, being reviewed during data entry. Statistical analysis was done using Chi-square and Kaplan Meier survival analysis, through SPSS version 22. The study was conducted in accordance with the Data Privacy Act of 2012, and the protocol was approved by the Lung Center of the Philippines Institutional Ethics Review Board (LCP-IERB).

RESULTS

Demographics

A total of 997 severe and critical COVID-19 patients were admitted during the prescribed timeframe. A total of 435 patients were included in the study, 155 of whom were severe and critical patients without hemoperfusion, and 280 were severe and critical patients with hemoperfusion (Figure 1).

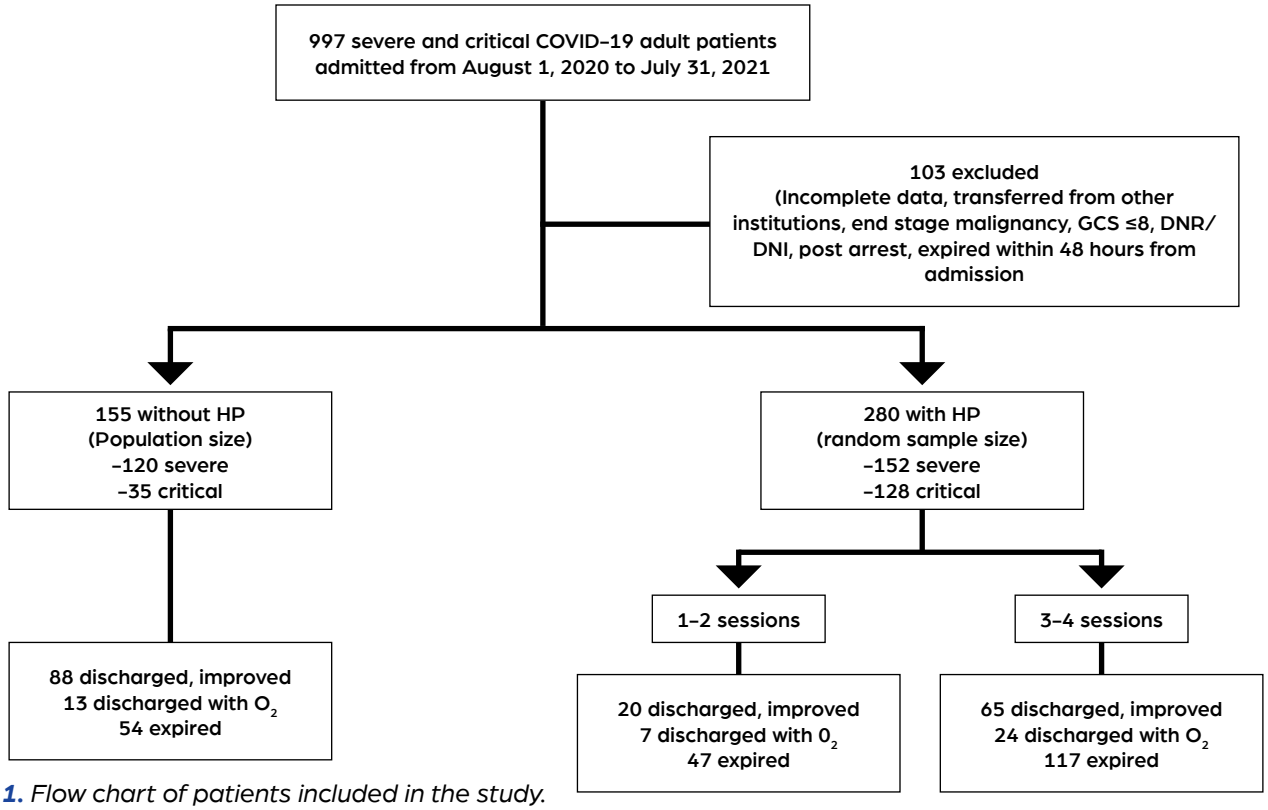


Figure 1. *Flow chart of patients included in the study.*

Notable was a male predominance in all groups. Most of the patients admitted were between 41–60, and 61–70 years old, although their distribution was not comparable between the groups (p-value <0.01). Majority of patients included had hypertension and diabetes mellitus. Most patients are non-smokers, followed by patients who quit smoking for more than 6 months (table 1). We found that patients included in the study had statistically comparable gender, comorbidities, history of smoking, and treatment received as part of the standard of care.

Table 1. *Demographic data and baseline laboratory parameters of patients*

	Without Hemoperfusion		With Hemoperfusion		p-value
	Severe N = 120	Critical N = 35	Severe N = 152	Critical N = 128	
Age					<0.01*
19–40	26 (21.7%)	2 (5.7%)	12 (7.9%)	5 (3.9%)	
41–60	31 (25.8%)	17 (48.6%)	57 (37.5%)	43 (33.6%)	
61–70	36 (30%)	8 (22.9%)	44 (28.9%)	37 (28.9%)	
71–80	16 (13.3%)	6 (17.1%)	32 (21.1%)	33 (25.8%)	
>80	11 (9.2%)	2 (5.7%)	7 (4.6%)	10 (7.8%)	
Sex					0.97
Male	71 (59.2%)	21 (60%)	92 (60.5%)	74 (57.8%)	
Female	49 (40.8%)	14 (40%)	60 (39.5%)	54 (42.2%)	
Co-Morbidities					0.72
Diabetes Mellitus	39 (32.5%)	17 (48.6%)	40 (26.3%)	37 (28.9%)	
Hypertension	56 (46.7%)	23 (65.7%)	90 (59.2%)	70 (54.7%)	
COPD	5 (4.2%)	1 (2.9%)	6 (3.9%)	4 (3.1%)	
Asthma	7 (5.8%)	1 (2.9%)	6 (3.9%)	10 (7.8%)	
Cardiac Disease	3 (2.5%)	2 (5.7%)	4 (2.6%)	9 (7.0%)	
Cancer	4 (3.3%)	1 (2.9%)	1 (0.7%)	2 (1.6%)	
PTB	7 (5.8%)	3 (8.6%)	9 (5.9%)	10 (7.8%)	
History of Smoking					0.78
Never Smoked	88 (73.3%)	23 (65.7%)	108 (71.1%)	96 (75%)	
Ex-smoker (quit >6mo)	18 (15%)	5 (14.3%)	26 (17.1%)	17 (13.3%)	
Smoker <10 pack years	12 (10%)	5 (14.3%)	11 (7.2%)	9 (7.0%)	
Smoker >10 pack years	2 (1.7%)	2 (5.7%)	7 (4.6%)	6 (4.7%)	
PF Ratio					<0.01*
>300	50 (41.7%)	3 (8.6%)	16 (10.5%)	4 (3.1%)	
>200 to 300	40 (33.3%)	6 (17.1%)	38 (25.0%)	14 (10.9%)	
>100 to 200	24 (20.0%)	11 (31.4%)	65 (42.8%)	62 (48.4%)	
<100	6 (5.0%)	15 (42.9%)	33 (21.7%)	48 (37.5%)	
Other interventions					0.74
Remdesivir	85 (70.8%)	14 (40.0%)	112 (76.2%)	190 (65.7%)	
Tocilizumab	14 (11.7%)	5 (14.3%)	23 (15.6%)	60 (20.8%)	
Dexamethasone	106 (88.3%)	28 (80.0%)	134 (91.2%)	266 (92.0%)	
Convalescent Plasma	7 (5.8%)	3 (8.6%)	10 (6.8%)	12 (4.1%)	
Proning	4 (3.3%)	7 (20.0%)	7 (4.8%)	57 (19.7%)	
Chest CT scan					<0.01*
Transient areas of GGOs	4 (3.3%)	0	3 (2.0%)	2 (1.6%)	
Unilateral/bilateral GGOs	69 (57.5%)	15 (42.9%)	68 (44.7%)	29 (22.7%)	
Bilateral segmental consolidation	47 (39.2%)	20 (57.1%)	81 (53.3%)	97 (75.8%)	
Chest X-ray					<0.01*
No infiltrates	12 (10.0%)	1 (2.9%)	11 (7.2%)	2 (1.6%)	
Unilateral/bilateral GGOs	88 (73.3%)	25 (71.4%)	105 (69.1%)	76 (59.4%)	
Bilateral segmental consolidation	20 (16.7%)	9 (25.7%)	36 (23.7%)	50 (39.1%)	

**GGOs – ground glass opacities*

Comparison of Clinical and Laboratory Data

Patients with critical COVID had worse baseline chest CT scan findings as well as lower PaO_2/FiO_2 ratio than patients with severe COVID, regardless of HP status. Under the group of patients without hemoperfusion, comparing the baseline inflammatory markers of severe patients to those of critical patients, we note a significantly higher LDH (p-value 0.02), ferritin (p-value <0.01), D-dimer (p- value <0.01), and IL-6 (p-value <0.01). A lower oxygen saturation (p-value 0.03) was also noted among critical patients without hemoperfusion compared to severe patients without hemoperfusion. As for patients with hemoperfusion, we also see higher baseline inflammatory markers, specifically LDH (p-value 0.01), Procalcitonin (p-value 0.01), and D-dimer (p-value =0.01) for critical patients when compared against severe patients. Oxygen saturation was comparable between severe and critical COVID (p-value 0.93) (table 2).

Table 2. *Comparison of baseline parameters between patients according to severity of COVID-19 infection*

	Without Hemoperfusion			With Hemoperfusion		
Inflammatory Markers	**Severe N = 120 mean (+SD)**	**Severe N = 35 mean (+SD)**	**p-value**	**Severe N = 152 mean (+SD)**	**Severe N = 128 mean (+SD)**	**p-value**
CRP (mg/L)	162.5 (75.43)	137.2 (74.68)	0.08	175.8 (75.27)	179.9 (74.70)	0.65
LDH (U/L)	435.1 (301.55)	575.5 (297.87)	0.02*	549.7 (296.30)	647.8 (297.36)	0.01*
Ferritin (ng/mL)	630.0 (598.71)	1169.6 (587.28)	<0.01*	1018.6 (645.65)	829.1 (588.85)	0.01*
Procalcitonin (ng/mL)	1.74 (27.62)	11.66 (27.13)	0.06	2.75 (26.97)	10.70 (27.13)	0.01*
D-Dimer (mg/L)	309.3 (817.15)	1122.1 (845.22)	<0.01*	473.5 (847.82)	530.6 (847.82)	0.57
IL-6 (pg/mL)	42.6 (77.28)	105.7 (78.54)	<0.01*	82.1 (77.28)	47.3 (79.21)	<0.01*
O2 saturation (%)	96.43 (5.06)	94.27 (5.05)	0.03*	95.13 (5.03)	95.18 (5.05)	0.93

Table 3 shows comparison of the baseline inflammatory markers among severe and critical COVID patients stratified according to HP status. There was noted significantly higher levels of LDH (p-value <0.01), ferritin (p – value<0.01), and IL-6 (p-value <0.01) in severe COVID patients with HP compared to patients without HP. Severe patients with HP also had significantly lower SpO2 (p-value 0.04) compared to severe patients without HP. Conversely, for critical COVID patients with hemoperfusion had significantly lower levels of ferritin (p-value <0.01), D-dimer (p-value <0.01), and IL-6 (p-value <0.01) compared to those without hemoperfusion. Oxygen saturation was comparable between the two subgroups (p-value 0.35).

Table 3. *Comparison of baseline parameters between COVID-19 patients with and without hemoperfusion*

	Severe COVID			Critical COVID		
Inflammatory Markers	**Severe N = 120 mean (±SD)**	**Severe N = 152 mean (±SD)**	**p-value**	**Severe N = 35 mean (±SD)**	**Severe N = 128 mean (±SD)**	**p-value**
CRP (mg/L)	162.5 (75.43)	175.8 (75.27)	0.15	137.2 (74.68)	179.9 (74.70)	<0.01*
LDH (U/L)	435.1 (301.55)	549.7 (296.30)	<0.01*	575.5 (297.87)	647.8 (297.36)	0.20
Ferritin (ng/mL)	630.0 (598.71)	1018.6 (645.65)	<0.01*	1169.6 (587.28)	829.1 (588.85)	<0.01
Procalcitonin (ng/mL)	1.74 (27.62)	2.75 (26.97)	0.76	11.66 (27.13)	10.70 (27.13)	0.85*
D-Dimer (mg/L)	309.3 (817.15)	473.5 (847.82)	0.11	1122.1 (845.22)	530.6 (847.82)	<0.01*
IL-6 (pg/mL)	42.6 (77.28)	82.1 (77.28)	<0.01*	105.7 (78.54)	47.3 (79.21)	<0.01*
O2 saturation (%)	96.43 (5.06)	95.13 (5.03)	0.04*	94.27 (5.05)	95.18 (5.05)	0.35

Table 4 compares the average values of inflammatory markers and oxygen saturation before and after HP, with patients grouped according to severity. We note significant decrease in CRP (p-value <0.01), LDH (p-value 0.02), ferritin (p-value <0.01), and D-dimer (p-value <0.01) among severe COVID patients post hemoperfusion however there was no significant difference in oxygen saturation (p-value 0.09). As for critical COVID patients, only CRP (p-value <0.01) decreased significantly post-hemoperfusion while oxygen saturation dropped significantly post-HP (p-value 0.01). Post-HP, there was also noted significant decrease in hemoglobin and hematocrit, as well as increase in white blood cell count (WBC) for both groups (p-values <0.01). We also see a significant improvement of chest x-ray findings among critical COVID patients (p<0.01).

Table 4. *Comparison of pre- and post-hemoperfusion laboratory results of severe and critical COVID-19 patients*

	Severe COVID (N = 152)			Critical COVID (N = 128)		
	Pre-HP mean (±SD)	Post-HP mean (±SD)	p-value	Pre-HP mean (±SD)	Post-HP mean (±SD)	p-value
Inflammatory Markers						
CRP (mg/L)	175.8 (75.27)	107.9 (84.37)	<0.01*	179.9 (74.70)	126.2 (84.74)	<0.01*
LDH (U/L)	549.7 (296.30)	463.5 (347.10)	0.02*	647.8 (297.36)	578.9 (348.30)	0.09
Ferritin (ng/mL)	1018.6 (645.65)	762.9 (314.48)	<0.01*	829.1 (588.85)	806.2 (306.77)	0.70
Procalcitonin (ng/mL)	2.75 (26.97)	3.05 (18.69)	0.91	10.70 (27.13)	10.69 (18.77)	0.99
D-Dimer (mg/L)	473.5 (847.82)	59.0 (412.34)	<0.01*	530.6 (847.82)	426.3 (416.83)	0.21
IL-6 (pg/mL)	82.1 (77.28)	552.9 (1002.45)	<0.01*	47.3 (79.21)	38.81 (1002.45)	0.92
CBC						
Hgb	134.89 (19.81)	123.13 (23.00)	<0.01*	133.54 (19.80)	117.43 (24.99)	<0.01*
Hct	39.60 (5.08)	36.82 (6.76)	<0.01*	39.58 (5.83)	35.40 (2.82)	<0.01*
WBC	9.99 (4.52)	16.22 (9.74)	<0.01*	13.62 (9.57)	19.90 (9.75)	<0.01*
Platelet	252.30 (111.63)	270 (125.46)	0.19	272.11 (112.69)	257.62 (125.70)	0.33
Chest X-ray findings						
No infiltrates	11	15	0.65	2	10	<0.01*
Unilateral/bilateral GGOs	105	105		76	90	
Bilateral segmental consolidation	36	32		50	28	
O2 saturation	95.13 (5.03)	96.23 (6.34)	0.09	95.18 (5.05)	93.36 (6.36)	0.01*

**GGOs – ground glass opacities*

Clinical Outcomes

Critical patients who did not receive HP had a significantly longer time from onset of symptoms until admission when compared to severe patients (p-value <0.01). Patients with hemoperfusion also stayed significantly longer in the hospital compared to those without hemoperfusion. In general, we noted higher mortalities among critical patients compared to severe and among patients with hemoperfusion when compared to those without hemoperfusion. The most common complication seen in all groups was nosocomial pneumonia (table 5).

Table 5. *Clinical outcomes of patients with and without hemoperfusion*

	Without HP			With HP		
	Severe N = 120	Severe N = 35	p-value	Severe N = 152	Severe N = 128	p-value
Day of illness on admission	8.42	10.40	<0.01*	6.97	7.20	0.55
Length of hospital stay (days)	9.5	5.4	<0.01*	17.61	13.81	<0.01*
Condition on discharge			<0.01*			
Improved	95 (79.2%)	6 (17.1%)		88 (57.9%)	28 (21.9%)	<0.01*
Expired	25 (20.8%)	29 (82.9%)		64 (42.1%)	100 (78.1%)	
Complications			0.85			0.07
Nosocomial pneumonia	12	5		55	54	
Pneumothorax	1	0		1	1	
Bleeding	2	1		9	15	
Arrhythmia	6	4		10	25	
Thrombocytopenia	0	0		26	18	

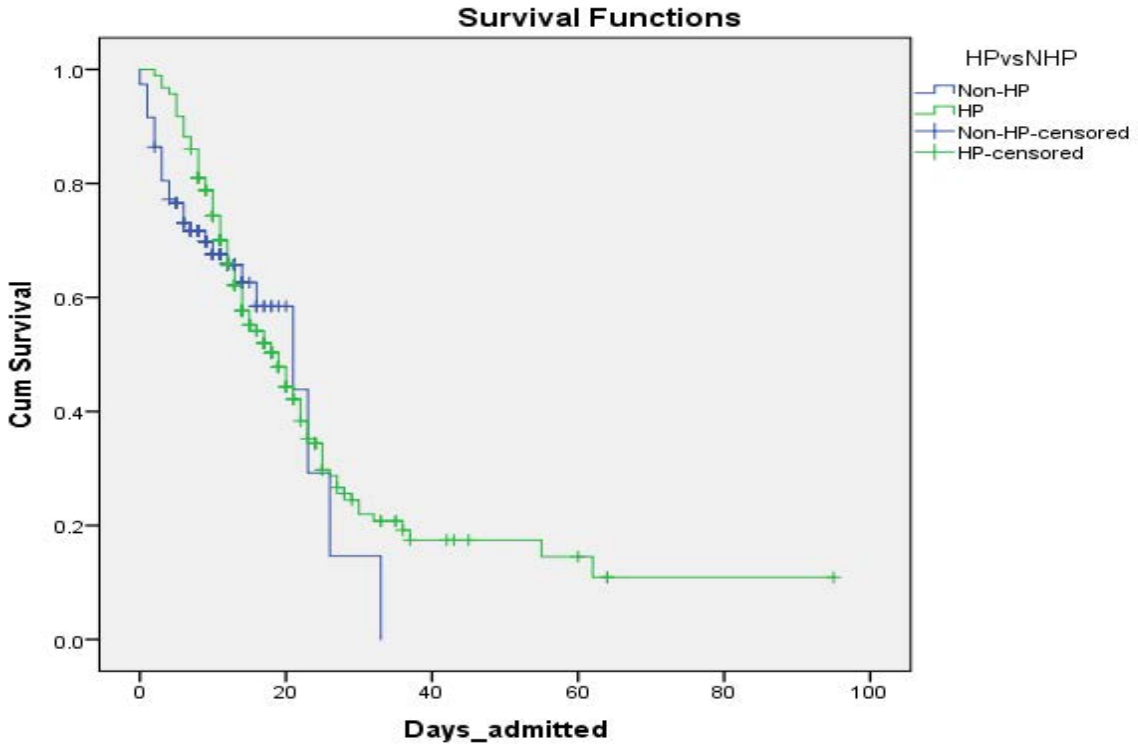
Comparing outcomes based on the number of hemoperfusion sessions, we still note higher mortalities in critical COVID patients in all subgroup who succumbed to the illness, especially among patients who only received 1–2 HP sessions (63.5%). Total length of hospitalization was also noted to be longer for patients with hemoperfusion (table 6).

Table 6. *Clinical outcomes of patients based on number of HP sessions*

	Without HP			1–2 HP sessions			3+ HP sessions		
Condition on discharge	**Severe** N=120	**Critical** N=35	**Total** N=155	**Severe** N=36	**Critical** N=38	**Total** N=74	**Severe** N=116	**Critical** N=90	**Total** N=206
Discharged, improved	84 (70.0%)	4 (11.4%)	88 (56.8%)	17 (47%)	3 (7.9%)	20 (27.0%)	48 (41.4%)	17 (18.9%)	65 (31.5%)
Discharged with oxygen	11 (9.2%)	2 (5.7%)	13 (8.4%)	6 (16.7%)	1 (2.6%)	7 (9.5%)	17 (14.7%)	7 (7.8%)	24 (11.7%)
Expired	25 (20.8%)	29 (82.9%)	54 (34.8%)	13 (36.1%)	34 (94.4%)	47 (63.5%)	51 (43.9%)	66 (73.3%)	117 (56.8%)
Length of hospital stay (days)	9.51	5.40	8.58	13.22	9.53	11.32	18.97	15.73	17.55
Days from onset of symptoms to admission	8.42	10.40	9.20	7.28	8.29	7.80	10.97	7.00	9.23

Survival Probability

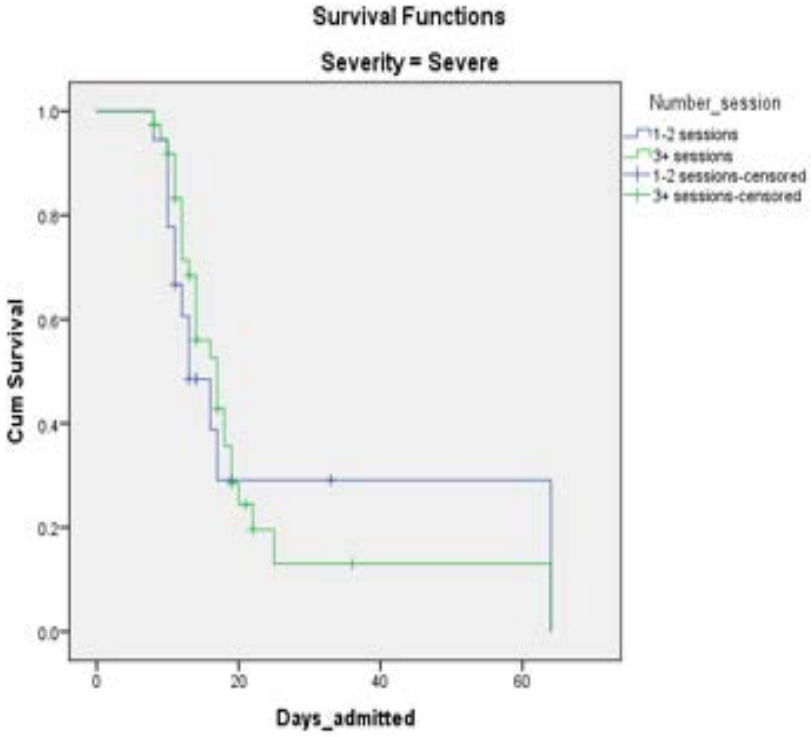
Plotting the survival of patients with and without HP using Kaplan Meir survival analysis shows that the cumulative survival is not statistically different (p–value 0.165), thus the survival among both groups is comparable. The estimated probability of surviving is 60% on 10th and 20thh day of admission among patients without hemoperfusion while the hemoperfusion group had 50% on 10th and 30% on 20th day (figure 2).

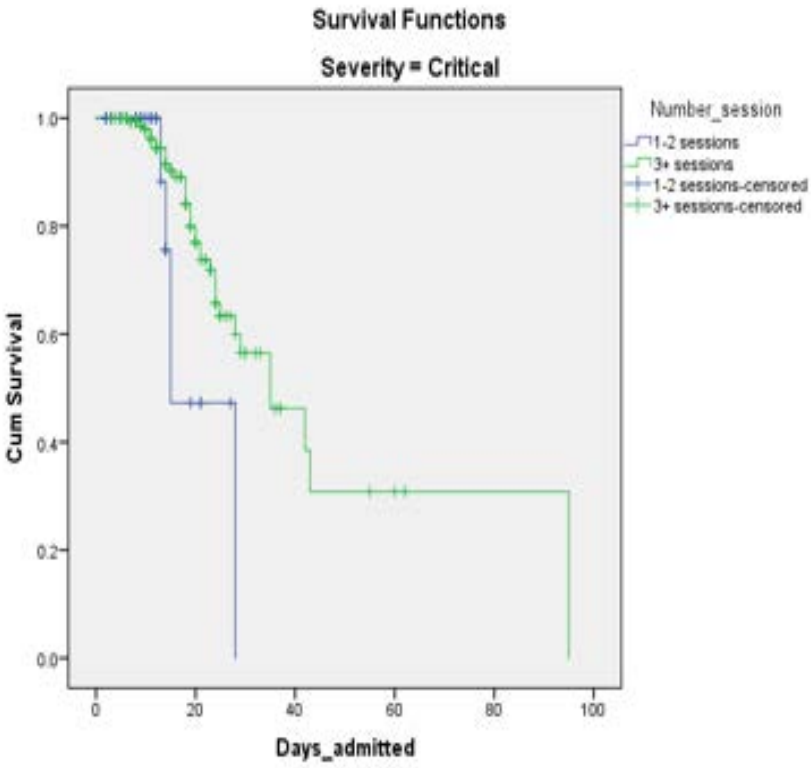


	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	1.926	1	0.165

Figure 2. *Survival of patients with and without hemoperfusion*

Grouping patients based on severity and number of HP sessions, we see no statistical difference (p-value 0.95) both for severe COVID patients and critical COVID patients. However, we can note that the cumulative survival among severe COVID patients with 3 or more sessions is lower than patients with 1–2 sessions, with 20% and 30% probability respectively by 20th day of admission (figure 3). On the other hand, critical COVID patients with 3 or more sessions had higher median survival probability than 1–2 sessions with 60% and 50% on the 20th day of admission.

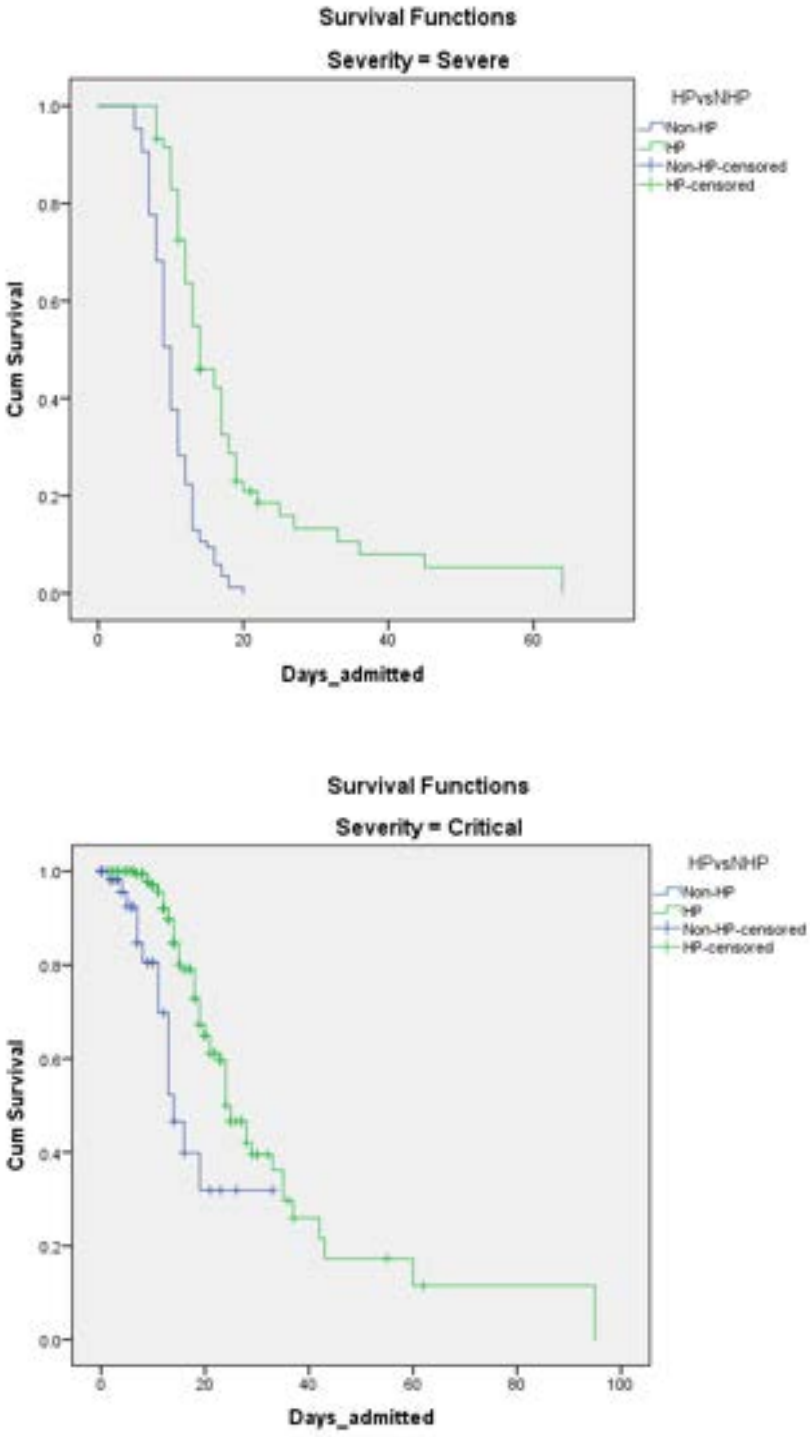




	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	2.781	1	.095

Figure 3. *Survival of patients based on severity and number of HP sessions*

Comparing patients with and without HP, we note that severe COVID patients had a higher survival probability for patients with HP compared to those without, with cumulative survival estimates of 45% and 30% on the 10th day of admission respectively, and cumulative survival of 20% and 0% respectively on the 20th day of admission. It is statistically significant (p-value <0.001) which means HP for severe COVID patients has an increased probability of survival across time compared to those without hemoperfusion. As for critical COVID patients, no survival benefit was noted (figure 4).



	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	157.703	2	.000

Figure 4. *Survival of patients with or without hemoperfusion stratified according to severity*

Table 7 shows total mortalities according to age groups. We see that the younger individuals had a higher likelihood of mortality (87%) among severe patients as compared to the older age groups, while the 40–59-year-old group had the highest mortality (25%) among critical patients.

Taable 7. *Mortalities stratified by age group*

Severity	Age	Total patients	Mortalities (% among group)
Severe	20–39 y/o	23	20 (87.0%)
	40–59 y/o	49	41 (83.7%)
	60–79 y/o	67	51 (76.1%)
	80+	5	3 (60.0%)
Critical	20–39 y/o	16	4 (25.0%)
	40–59 y/o	91	25 (27.5%)
	60–79 y/o	151	23 (15.2%)
	80+	30	3 (10.0%)

The vast majority of severe COVID patients who do not progress to intubation have high survival rates. This significantly decreases for patients if they are intubated (p-value <0.01 for those without HP, and p-value 0.02 for those with HP). However, when comparing the two groups, we note a significantly improved survival rate of 34.4% among patients with HP, compared to only 9.5% among those without HP (p-value 0.02) (table 8).

Taable 8. *Clinical outcomes of severe COVID-19 patients who progressed to intubation*

	Without HP			With HP			Survival of severe patients who progressed to critical
	Severe patients, never intubated N = 99	Severe patients, progressed to intubation N = 21	p-value	Severe patients, never intubated N = 56	Severe patients, progressed to intubation N = 56	p-value	p-value
Outcome			<0.01*			<0.01*	0.02*
Improved	93 (93.9%)	2 (9.5%)		55 (98.2%)	33 (34.4%)		
Expired	6 (6.1%)	19 (90.5%)		1 (1.8%)	63 (65.6%)		

DISCUSSION

The study found that majority of patients who were admitted for critical COVID-19 were elderly men with comorbidities such as hypertension and diabetes mellitus. It was noted that patients who were admitted and eventually received hemoperfusion had a shorter interval from their onset of symptoms until their day of admission. The timeline of illness upon admission as aforementioned are congruent with Wang et al. (2020), wherein risk factors of clinical progression of COVID-19 was linked to risk factors including male sex, older age, and presence of co-morbidities.[19] Likewise, shorter time of interval from symptom onset to admission could be explained by faster disease progression compared to those who did not receive hemoperfusion. Patients with hemoperfusion might have shown worse symptoms, hence sought consult and were admitted at an earlier time compared to patients without hemoperfusion. This was in line with a review done by Henderson (2020), wherein a shorter time from symptom onset to hospitalization was linked to disease severity and death, which may translate to faster onset and worse symptoms among severe and critical patients.[20] We can also note that cytokine storm might have been worse and earlier among critical patients, which led to organ damage and eventually death. The same observation was correlated by Kim et al (2021), where they found that higher cytokine levels translated to faster deterioration and higher mortality in severe and critical COVID patients was related to cytokine storm.[21]

We noted that critical patients had significantly higher inflammatory markers compared to severe patients, and patients without HP. According to a meta-analysis by Mehrdad and Hassan (2020), and a systematic review by Huang et al. (2020), there is a direct correlation between several biomarkers, including D-dimer and Procalcitonin,

and COVID-19 severity.[22,23] Baseline oxygen saturation for critical COVID-19 patients was also the lowest among the groups. Altogether, we can surmise that the critical COVID-19 patients included in the study were predisposed to have a worst prognosis upon admission and least survival probability compared to the other groups. Oxygen saturation upon admission has also been shown to be a good predictor of disease progression and severity, which was seen as significantly lower among critical patients in our study.24

Comparing the patient's pre- and post-HP lab results, we can note a significant decrease in inflammatory markers for the severe COVID group with hemoperfusion. This is in line with the study made by Rosalia et al (2021) wherein hemoperfusion was noted to show a decrease in inflammatory biomarkers.[25] As for critical COVID-19 patients, only CRP had decreased significantly post-hemoperfusion, but there was also a general trend of improvement for the rest of the inflammatory markers, although not statistically significant. We also noted a significant decrease in oxygen saturation for critical patients post-HP, which further solidifies our observation that these patients are already far along the course of disease, and that hemoperfusion does little to improve their condition. There was also a statistically significant increase in WBC across the group, although this could probably be attributed to the use of dexamethasone and possible bacterial co-infection such as nosocomial pneumonia, as many patients with hemoperfusion developed this complication.

We can note that a higher percentage of patients with hemoperfusion expired compared to those without HP, with a 2:1 proportion in population. One of the factors that might have affected a higher number of critical patients who underwent hemoperfusion was due to clinical judgement and experiences of the attending physician to prioritize these patients for hemoperfusion during time of surge, lack of cartridges and manpower. Hence, if patients are triaged to have moderate to severe illness and/or with lower oxygen support, they are least prioritized to receive Hemoperfusion. Looking at the Kaplan-Meier survival curve comparing patients with and without hemoperfusion, we can note that the expected survival for both groups were comparable which means that use of hemoperfusion does not change the likelihood of survival. It can be ascertained that although these patients gave them the chance to survive longer with the use of hemoperfusion, they were prone to acquire nosocomial infection due to longer hospital stay. Since critical patients seemed to have lower survival probability, critical patients were stratified by age groups and were analyzed. It was found that the age bracket of 80+ years-old had higher chances of survival compared to other age groups. This in contrast with a review done by Mueller et al. (2020) where older patients with COVID tended to have lower chances of survival due to aging innate immunity, and presence of comorbidities.[26] However, the result cannot be used to conclude that elderly patents have a higher chance of survival due to the small sample size of these patients included in the study. Rather, these findings can suggest that physicians should not limit the use of hemoperfusion for the elderly. It was also found that despite lower chances of survival among the 18-39 years old age group compared to elderlies, this age group had a higher stable cumulative survival rate over time and shorter hospital stay, probably due to less comorbidities. On the other hand, comparing patients the number of sessions, we can see that there is lower survival probability among critical patients with 1-2 HP sessions than those who had 3 or more sessions, but this was not found to have a statistical significance. Hence, the number of HP sessions does not seem to give patients a better chance of survival and additional sessions thereafter will be the physician's call to continue or not. This is congruent with the findings of Darazam et al. (2021), where patients with hemoperfusion had lower mortality rate and improved oxygen saturation, but the number of hemoperfusion sessions and type of cartridge used had no effect on clinical outcomes.[27] It was also cited in Mardani et al. (2020) that increased levels of inflammatory markers, specifically CRP, was associated with acute respiratory distress syndrome, hence apt timing of initiation of hemoperfusion during the early course of disease can decrease a patient's likelihood of mortality.[28]

It was also found that severe patients had significantly higher mortality if they were eventually intubated. However, patients who received hemoperfusion had a higher chance of extubating and survival than those who did not receive hemoperfusion. Thus, hemoperfusion is associated with better survival among severe patients who were intubated during admission. This is comparable with findings of Vardanjani (2021), where hemoperfusion improved survival among intubated patients.[15]

In summary, there was an association between the use of hemoperfusion and a reduction in inflammatory markers in both groups. Severe COVID patients tend to benefit more with the use of hemoperfusion, manifested by significant decrease of inflammatory markers, and higher survival probability than those without hemoperfusion (cumulative survival estimates of 45% vs 30% on the 10th hospital day, and 20% vs 0% on the 20th hospital day, respectively).

RECOMMENDATIONS

The subset of patients who were prioritized to have hemoperfusion in this local setting appear to have had a worse clinical picture in the first place, hence they had generally poorer prognosis and likely to die. The reason for the need to prioritize patients was the scarcity of hemoperfusion cartridges during times of surge, as well as the limited manpower. It is therefore recommended that future studies be done in institutions where hemoperfusion is not part of standard care, to have a true control population.

ACKNOWLEDGEMENT

The researchers acknowledge Louey Mari Ilustre, Maria Kathleen Villa, MD, and Jem Marie Barruga, MD, who worked as clinical research assistants. The researchers thank adviser Racquel Ibanez, MD, FPCP, FPCCP and the Medical Records Department of the Lung Center of the Philippines for their assistance during our chart review.

FUNDING

None.

CONFLICT OF INTEREST

None declared.

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APPENDIX

Data Collection Tool

Patient code: _____

1. Date admitted: _____
2. Date discharged: _____
3. Length of hospital stay (calendar days): _____
4. Date of onset of symptoms: _____
5. Day of illness on admission: _____
6. Day of illness on 1st Hemoperfusion: _____
7. Gender: ☐ 1. M ☐ 2. F
8. Age: _____
9. Smoking History: ☐ 1. Never smoked ☐ 2. Ex-smoker ☐ 3. Smoker (pack-years _____)
10. Co-morbid Conditions:
    - ☐ 1. Hypertension
    - ☐ 2. Type 2 Diabetes Mellitus
    - ☐ 3. Bronchial Asthma
    - ☐ 4. Chronic Obstructive Pulmonary Disease
    - ☐ 5. Hypertensive Cardiovascular Disease/Coronary Artery Disease
11. Date HP initiated: _____
12. Initial impression prior to HP: ☐ 1. ARDS ☐ 2. ARF
13. Number of sessions completed: _____
14. Clinical status:

	Baseline	After last HP
O2 support		
pO2		
SpO2		
PF ratio		
CBC: Hb/Hct		
WBC		
Nt/Lym		
Platelet		
Ferritin		
LDH		
CRP		
d Dimer		
Procalcitonin		
Chest X-ray		
Chest CT scan		

15. Complications during HP: ☐ Yes ☐ No
16. What complication/s:
    - ☐ 1. Bleeding
    - ☐ 2. Arrhythmia
    - ☐ 3. Thrombocytopenia
    - ☐ 4. Pneumothorax
    - ☐ 5. Others _____
17. Developed Nosocomial Pneumonia: ☐ Yes ☐ No
18. Other treatment given:
    - ☐ 1. Remdesivir
    - ☐ 2. Interferon B1a
    - ☐ 3. Tocilizumab
    - ☐ 4. Dexamethasone/Hydrocortisone
    - ☐ 5. Convalescent Plasma
19. Date intubated (if applicable): _____
20. Outcome:
    - ☐ 1. Discharged alive
    - ☐ 2. Mortality

    Cause of death:
    - ☐ 1. HAP/VAP
    - ☐ 2. Arrhythmia, ACS
    - ☐ 3. Others _____

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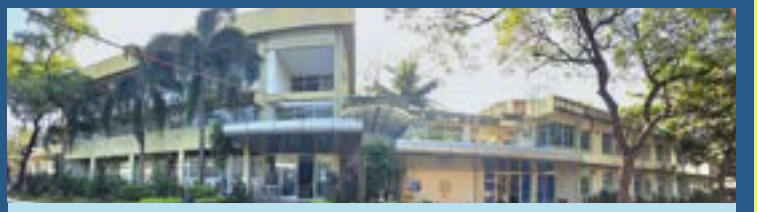

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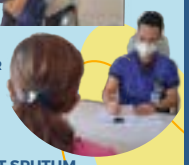

- PROVISION OF ANTI TB MEDICATIONS (DSTB/DRTB) FOR ADULT AND CHILDREN FOR FREE

- DIRECT SPUTUM SMEAR MICROSCOPY TEST FOR ENROLLED PATIENTS

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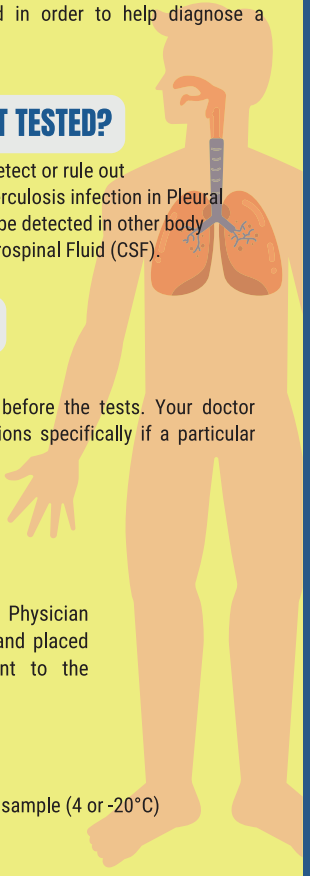
ADENOSINE DEAMINASE (ADA)

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

1 WHY GET TESTED?

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



2 WHEN TO GET TESTED?

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

3 SAMPLE COLLECTION

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

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

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Time of collection is indicated on the request form

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Cut off Time: 10:00AM
Releasing of result: Same day, 4:00PM

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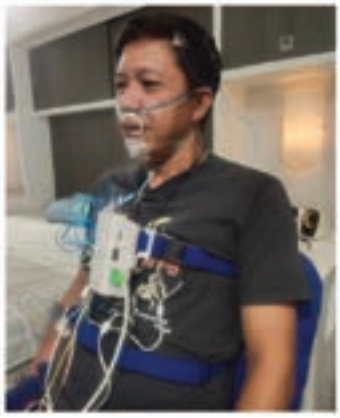

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  Libshitz HI, Mckenna RJ, Haynie TP, et al. Mediastinal evaluation in lung cancer. Radiology 1984; 151:295-99.

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

  Book

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

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

  Website

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

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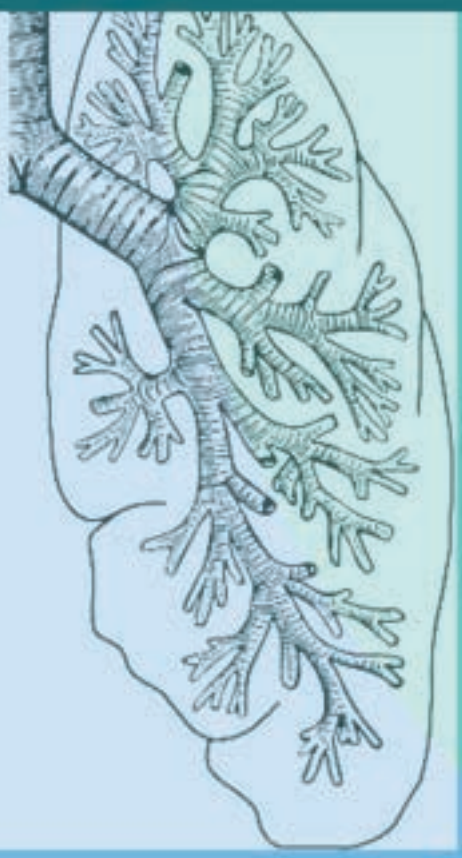

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