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

BOOK: Kelley MA, Fishman AP. Exercise Testing In Pulmonary Diseases. 2 edition. Fishman AP, (ed) McGraw Hill Book Co; 1989. pp 2525 253

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

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EDITORIAL

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

"Research in the Time of the COVID-19 Pandemic"

The COVID-19 pandemic has affected the lives of people globally in various ways. Patients were suffering and dying from the infection, government authorities were racing against time to contain the spread of the virus, and the general population was struggling with the health and economic consequences of the pandemic on their lives.

While healthcare workers were overwhelmed in the care of the rising numbers of COVID-19 patients and scientists racing against time to understand the new virus, looking for drug treatments and developing vaccines against the new virus, medical research has taken a new direction. To quote Heather Synder, PhD (an advocate of Alzheimer's research):

> *"The pandemic is having a significant impact on Alzheimer's research, and medical research in general.. As you can imagine, things are changing on a daily basis."*

Indeed things were changing on a daily basis in the early months of the pandemic and it has also impacted medical research. Due to the novelty of the COVID-19 and the urgency to know more of the disease to save lives, mitigate the spread of the virus and fight misinformation about the disease, medical researches were then prioritized on the new disease. Data from these researches have helped the medical community identify treatments and other management strategies for COVID-19. But due to this public health crisis, investigation of other disease types has slowed significantly. Eventually as time passed through the pandemic and better understanding of COVID-19 was achieved, research investigations of other diseases have once again been advancing.

After a hiatus in the publication of the Philippine Journal of Chest Diseases (PJCD) due to the pandemic, the PJCD returns with the first issue for 2022 with renewed vigor to publish the research outputs of our PCCP members (fellows-in-training and consultants).

EDITORIAL

Since the PCCP has accepted pulmonary researches from internal medicine residents-in-training in the PCCP Research Contests, we have included their submitted researches in our pool of manuscripts for potential PJCD publication. In addition to original researches, case reports and case series, we have included systemic reviews and meta-analyses. To ensure scientific quality of PJCD published articles, accepted articles for publication are peer-reviewed. The peer review process ensures that PJCD publications exemplify the best research practices in the field of pulmonary medicine.

In this January – June 2022 PJCD issue, we have four original researches tackling varied topics which include: use of tocilizumab in COVID-19 treatment, nutrition practices in the medical intensive care unit, knowledge and attitude of OSA among pulmonology training fellows, and COPD discharge bundle. Two systematic reviews assessed the use of lung ultrasound-guided protocol among critically ill patients and local pulmonary administration of tranexamic acid in the control of hemoptysis. Included in this issue is the recent April 2022 Interim Update of the guideline *"Recommendations for the resumption of urgent and elective lung-related procedures during the COVID-19 Pandemic"* by the PCCP Council on Diagnostics and Therapeutics. We look forward to publishing more updates of other PCCP Council guidelines or consensus statements in future PJCD publications. The PJCD Editorial Board is optimistic and looking forward to publishing more quality researches in the forthcoming PJCD issues.

Recommendation for the Resumption of Urgent and Elective Lung-related Procedures During the COVID-19 Pandemic: April 2022 Interim Update

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INTRODUCTION

Efforts to maintain COVID-19 led to the cessation of all aerosol-generating diagnostic and therapeutic pulmonary procedures. These procedures remained suspended over the last 12 months with the onset of multiple variants and the threat of recurrent surges[1].

With the current evidence of a declined community transmission as we enter Alert Level I, as well as with the improved and sustained vaccination status of the community, a return to pre-pandemic service levels is strongly encouraged to avoid delay in management of patients with respiratory diseases[1].

Let us now revisit the evidence and different safety precautions needed to resume these procedures.

LUNG FUNCTION TESTING

As with other areas of respiratory medicine, there is a paucity of published evidence relating specifically to the transmission of SARS-CoV-2 during lung function testing (LFT). The following are the recommended precautions to take into consideration when resuming lung function testing:[1-5]

1. Practice necessary infectious disease transmission precautions (i.e., airborne, droplet and contact transmission precautions) as advocated by CDC :[1]
    a. Ensure that the ***patient*** does not have any influenza-like illness (ILI) symptoms within the last 10 days, and has a negative COVID-19 RT-PCR swab within 48-72 hours prior to the procedure. It is advisable to deploy a completed patient questionnaire online within 72 hours before patient appointment, and reconfirm patient triage on the day of procedure.

**Patients with chronic symptoms (e.g., post-COVID 19 syndrome) may be re-evaluated by the physician, accordingly.*

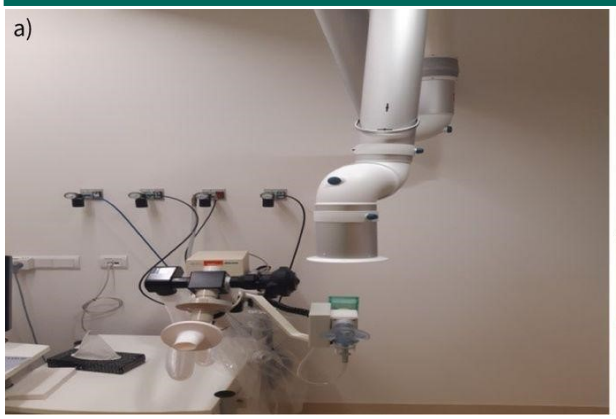

Figure 1. Installation of filters for the unit

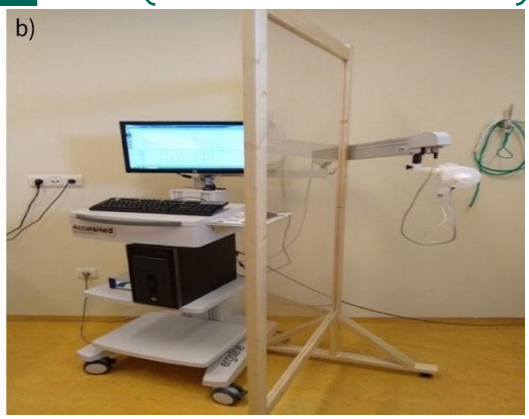

Figure 2. Provision of protective barrier between operator and patient

b. Ensure that the ***healthcare worker*** does not have any ILI symptoms.
c. The healthcare worker must wear a properly fitted N95 mask and high-level PPE at all times since LFTs require physical distancing of <1m most of the time.
d. Ensure that the waiting room and testing area is well-ventilated with the recommended air exchange per hour (at least 6, but 12-15 is best for particle removal). The room must have a (1) high-efficiency particulate absorbing (HEPA) filter or portable HEPA air purifier, (2) plexiglass barrier/shield, and (3) equipment covers if physical distancing will be compromised. Room temperature and humidity must be controlled.
e. Ask the patient to put back their face mask as soon as they remove themselves from the mouthpiece.
f. Room cleaning must always be undertaken in between procedures. Allow a 23-35-minute time interval in between procedures to remove 99-99.9% of airborne contaminants.
g. Equipment cleaning must likewise be done in between procedures, according to manufacturer's instructions.
h. Ensure that proper hand hygiene and cough etiquette is enforced.

2. Prioritize groups of patients for whom diagnostic spirometry will potentially impact their treatment pathway or determine their onward care (1,2):
   a. Category 1: Urgent/essential – required for the initiation of lifesaving interventions
      i. *Pre-operative risk stratification for urgent surgery (thoraco-abdominal surgery) or treatment (transplant, pre-chemotherapy, pre-radiation therapy)*
   b. Category 2: Non-urgent but with potential to be life-limiting
      i. Monitoring patients at risk for drug-related pulmonary toxicity
      ii. Monitoring lung transplant patients
      iii. Monitoring Post-COVID-19 rehabilitation
   c. Category 3: Routine testing (delaying testing will not result in acute harm to the patient)
      i. *Accurate diagnosis of asthma or COPD IF peak-flow monitoring cannot be done or is unavailable*

**Spirometry to confirm diagnosis is valuable but not an immediate priority*

3. Consensus for Specific Tests
   a. Spirometry
      i. Spirometry tests must be carried out using high-efficiency inline filter. The risk is only reduced while the patient remains breathing on the mouthpiece.
      ii. End all spirometry maneuvers with 2-3 tidal breaths before instructing the patient to remove themselves from the mouthpiece.
      iii. The patient must be advised to replace or put back their face mask without delay between trials.

b. Drug delivery as part of bronchodilator response testing
   i. *Use of valve chambers/spacers with a pressurized metered dose inhaler (pMDI) is preferable to nebulizers for bronchodilator administration as part of reversibility testing during high prevalence.*
   ii. *Careful and rigorous decontamination of all re-used equipment is advised.*
c. Lung volumes/body plethysmography/diffusing capacity/transfer factor
   i. *Use a high-efficiency inline filter when performing any lung volume testing.*
   ii. *End all vital capacity maneuvers with 2-3 tidal breaths before removing the mouthpiece.*
d. Exhaled nitric oxide tests
   i. *Use an inline filter when performing the test.*
e. Capnography
   i. *Appropriate in-circuit filter must be used.*
f. Respiratory muscle pressure/sniff test
   i. *A flanged mouthpiece with inline bacterial/viral filter must be used to prevent cross-contamination.*
   ii. *Use disposable nasal olive and tubing.*
g. 6-minute walk test
   i. *The corridor must be low traffic and have natural ventilation.*
   ii. *The patient must wear at least a surgical mask during the entire test.*
   iii. *For patients who cannot tolerate a surgical mask due to severe lung disease, an alternative option is a plastic face visor.*
h. Cardiopulmonary exercise test
   i. *Single-use masks, sensors, turbines and gas lines should be used to prevent transmission from repeated use.*
i. Bronchial challenge tests
   i. *Use breath-actuated nebulizer with single-use filters on the expiratory port of the nebulizer.*

4. Testing outside the hospital (spirometry in the community and primary care)
   a. Recommend "in-car" spirometry, similar to "in-car" COVID-19 RT PCR testing if the site will not be safe to conduct the procedure. Make a demonstration video focused on the maneuvers for correctly performing spirometry and give a copy of the video to the patient beforehand or project it in the waiting area. This will enable patients to be prepared for the visit. Alternatively, provide educational posters if instructional videos are not feasible.
   b. If "in-car" spirometry will not be feasible, refer the patient to nearest testing facility. for safety purposes.

NEBULIZED MEDICATIONS

There remains to be asymptomatic infected patients who can shed the virus and transmit the virus to other patients and healthcare workers even though community transmission is decreased. Use of nebulized medications should still be avoided if possible. The use of pMDI with spacer/mouthpiece or tightly fitting facemask is recommended if bronchodilators are warranted. The following are the recommended precautions and/or recommendations to take into consideration when administering nebulized medications:[6-8]

- Should the patient be proven to be NEGATIVE for COVID-19, nebulization can be used, provided that minimum institutional health standards are observed by the healthcare provider administering the treatment and decontamination of the apparatus after every use should be done.

- The use of a negative-pressure room or tent is recommended if nebulized medication is warranted and unavoidable in the hospital with unknown COVID-19 status. If this is not available, a single room with the door closed must be used.
- Previous recommendations from the 2021 guide is still applicable:
    1. Do not use a jet nebulizer or pMDI for aerosol delivery to ventilator-dependent COVID-19 suspects or confirmed cases due to the breakage of the circuits for the placement of the device before aerosol therapy.
    2. Use mesh nebulizers in critically ill COVID-19 suspects or confirmed cases receiving ventilator support as they can stay in-line for up to 28 days. The reservoir design allows adding medication without requiring the ventilator circuit to be broken for aerosol drug delivery. Unlike jet nebulizer, the medication reservoir of mesh nebulizers is isolated from the breathing circuit that eliminates the nebulization of contaminated fluids.
    3. Placing the mesh nebulizer prior to the humidifier can improve the efficiency of the treatment and further reduce retrograde contamination from the patient.
    4. Attach a HEPA filter to the expiratory limb of the ventilator to reduce secondhand aerosol exposure and prevent the transmission of infectious droplet nuclei through the ventilators.
    5. Do not combine aerosol therapy with pulmonary clearance techniques such as chest physical therapy and suctioning.
    6. Wear personal protective equipment, including an N95 respirator, goggles/face shield, double gloves, gown or apron if the gown is not fluid resistant.

BRONCHOSCOPY

Non-infectious indications for bronchoscopy may now be resumed, provided that these patients do not have acute ILI symptoms within the last 10 days and has a negative COVID-19 RT-PCR result 48-72 hours prior to the intended procedure. Triaging/scheduling of patient should be guided by time-sensitivity of disease condition, and these includes:[9-10]

1. Emergent
    a. Acute foreign body aspiration
    b. Severe and symptomatic central airway obstruction
    c. Massive hemoptysis WITHOUT obvious source for embolization
2. Acute
    a. Lung nodule or mass (for biopsy, for diagnosis, staging or re-biopsy for suspected disease progression)
    b. Lobar atelectasis
3. Subacute
    a. Airway inspection for minor hemoptysis
    b. Chronic atelectasis
    c. Airway stent surveillance
4. Elective
    a. Bronchial thermoplasty
    b. Bronchoalveolar lavage (BAL)
    c. Surveillance transplant bronchoscopy

For infectious indications, bronchoscopy is discouraged and should not be a first-line

testing modality, unless there is an URGENT need for diagnosis – and provided that the underlying infection is not COVID-19 (patient is COVID-19 negative). These set of patients would include:

1. Patients with neutropenic fever with infiltrates and no clinical diagnosis or improvement;
2. Transplant patients with clinical decline despite administration of empiric antimicrobials; and,
3. BAL for suspected Mycobacterium avium complex or other atypical chronic infection with minimal symptoms.

For COVID-19 positive patients, bronchoscopy is still discouraged. It is advised to delay bronchoscopy until the patient is rendered non-infectious by the attending physician. Potential diagnostic indications to be evaluated by the bronchoscopist would include:

1. Additional testing in patients with suspected COVID-19 infection and negative nasal swabs;
2. Evaluation of alternative infection or co-infection;
3. Bronchial toilette;
4. Massive hemoptysis (as complication of anticoagulation); and,
5. Acute lobar atelectasis.

****After weighing the risk vs benefit ratio, should patients with COVID-19 need to undergo bronchoscopy, use of single-use (disposable) flexible bronchoscopes is advocated.*
****Bronchoscopy should be performed in a negative-pressure ventilation room with a minimum of 12 air exchanges per hour.*

In resuming bronchoscopy, it is still advocated that (1) healthcare workers practice hand hygiene, (2) wear high-level PPE with proper donning and doffing, and (3) wear a properly fitted N95 mask or powered air purifying respirators. Equipment disinfection must be followed based on the manufacturer's recommendation. Proper specimen handling must also be observed by allied healthcare professionals. Environmental check to see adequate ventilation, placement of HEPA filter, adequate temperature and humidity control, should also be taken into consideration by the bronchoscopist.

CONCLUSION

Pulmonary Function Testing and bronchoscopy can now be resumed for COVID-19 negative patients, provided that proper screening and adherence to international as well as institutional health protocols are observed.

The role of bronchoscopy among COVID-19 positive patients are limited and is still discouraged.

Nebulization is still discouraged, as there are still asymptomatic COVID-19 positive patients who continue to shed the virus.

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Tocilizumab Treatment in Severe to Critical COVID-19 Patients in a Tertiary Hospital in Cebu City

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PAPER PRESENTED IN THE FOLLOWING CONFERENCES: American Thoracic Society International Conference (May 2021); 25th BAGA Postgraduate Course—1st Place (August 2021)

ABSTRACT

BACKGROUND: Tocilizumab is used in severe to critical patients with SARS-CoV-2 to attenuate the cytokine storm phase of COVID-19. We hypothesized that the timing of administration of tocilizumab may be pertinent in its utility in this disease.

OBJECTIVE: To determine the survival outcome of early administration of tocilizumab among severe to critical COVID 19 confirmed patients.

METHODS: We conducted a retrospective observational analytical study of all COVID-19 confirmed patients admitted in the intensive care unit (ICU) from March 1 to August 30, 2020 wherein the effect of administration timing relative to intubation between two treatment groups: "early" (pre-intubation) versus "late" (during or after intubation) administration of tocilizumab was analyzed. The primary outcome was death or intubation at 28 days of admission. The secondary outcome was 28-day survival post intubation, with death or discharge as censoring variable. Kaplan-Meier survival curves were used to describe outcome between two treatment groups. Covariates that were analyzed included age, gender, concomitant use of steroids, and Acute Physiology and Chronic Health Evaluation II (APACHE II) scores. Univariate and multivariate analysis of each covariate on the time to death were explored using Cox proportional hazards models.

RESULTS: A total of 90 severe to critically ill patients were admitted at the ICU from the period of March to August 2020. There were 84 intubated patients and 65 of them received tocilizumab. Of these 65 intubated patients, 26 (40%) received the drug "early" (pre-intubation) while 39 (60%) received it "late" (during or after intubation). The 28-day mortality in the "early" group was 30.77% (8/26), which was significantly lower than the 56.41%, (22/39) in the "late" group (p=0.042). "Early" treatment demonstrated a protective effect with a hazards ratio of 0.4350 (95% CI = 0.1982, 0.9548, p=0.038) with a significantly higher mean day survival of 61.25 days while the "late" treatment group only had 38.25 days, p = 0.026. The use of dexamethasone also led to better survival with a hazards ratio of 0.76 (CI 0.496, 1.14, p=0.189) (Figure 5a). Survival curves of both tocilizumab plus dexamethasone among the ICU patients in this study had superior protective effect compared to either of the drug given alone or none at all.

CONCLUSION: Tocilizumab has potential survival benefit in COVID patients with severe to critical disease when given early before respiratory failure. Combination of dexamethasone and tocilizumab improves outcome.

KEYWORDS: *tocilizumab, SARS-COV 2, intensive care unit, mortality, respiratory failure, COVID-19, cytokine storm*

INTRODUCTION

The cases of COVID-19 continue to increase with over 4 million new cases reported globally as of early January, 2021. According to the World Health Organization's weekly epidemiological update released last January 5, 2021, the cumulative number of reported cases globally has reached 83 million and there have been 1.8 million deaths since the start of the pandemic.[1] While majority of people with COVID-19 only have mild flu-like symptoms, approximately 10% to 15% have moderate or severe disease requiring hospitalization and oxygen supplementation, and up to 5% progress into critical pneumonia that requires mechanical ventilation and admission to an intensive care unit (ICU).[2]

The infection causes acute respiratory distress syndrome (ARDS) and multiorgan failure through an overwhelming release of pro-inflammatory cytokines and chemokines known as cytokine storm. High serum levels of pro-inflammatory cytokines such as IFN-γ, IL-1, IL-6, IL-12, and TGFβ and chemokines specifically CCL2, CXCL10, CXCL9, and IL-8 were noted among cases of severe disease compared to individuals with mild infection.[3] Tocilizumab is a humanized monoclonal antibody against the IL-6 receptor. It effectively inhibits the IL-6 signal transduction pathway and thus is hypothesized to successfully control an impending cytokine storm in severe COVID-19 patients.[4]

In patients with confirmed COVID-19 pneumonia and hyperinflammatory states, several observational retrospective studies have shown that tocilizumab may improve outcomes.[5-7] However, several randomized controlled trials failed to meet its primary endpoint of improved clinical status or death.[8-10] The effect of tocilizumab on mitigating the consequences of cytokine storm in COVID-19 infection has been widely studied worldwide. In the Philippines, tocilizumab is an investigational drug available for compassionate use with patient consent. Initially, our guidelines had allowed its use in severe to critical patients with COVID-19.[11]

Tocilizumab was often given during or after intubation when the cytokine surge has already occurred. We hypothesized that the timing of administration of tocilizumab determines its effectiveness as a treatment. This study aimed to determine whether the early administration of tocilizumab among severe to critical COVID-19 patients improves survival as compared to the late administration of the drug.

OBJECTIVES

To determine the survival outcome of early administration of tocilizumab among severe to critical COVID 19 confirmed patients. More specifically to determine the baseline characteristics of critical COVID-19 patients admitted in the intensive care unit in terms of age, sex, APACHE II Scores, RALE Score, dexamethasone use, PaO2/FiO2 ratio, C-reactive protein, D-dimer, ferritin, and, lactate dehydrogenase.

METHODS

This was a single-center, retrospective, analytical study conducted from March 2020 to August 2020 at Chong Hua Hospital, Cebu City - a 660-bed capacity private tertiary hospital. All COVID-19 ICU admissions from the period of March to August 2020 were included. The study was approved by the Institutional Review Board. The study included patients that are at least 18 years old of any gender, who were confirmed to have COVID-19 infection through a positive RT-PCR for SARSCOv-2, admitted in the ICU, with an oxygen saturation in ambient air of less than 94% requiring oxygen supplementation or mechanical (invasive/non-invasive) ventilation, and a PaO2/FiO2 ratio of less than 300 mmHg. Patients that were excluded were those with known hypersensitivity to tocilizumab, with pre-existing conditions that required tocilizumab as treatment, with conditions wherein tocilizumab is contraindicated, chronic glucocorticoid use, absolute

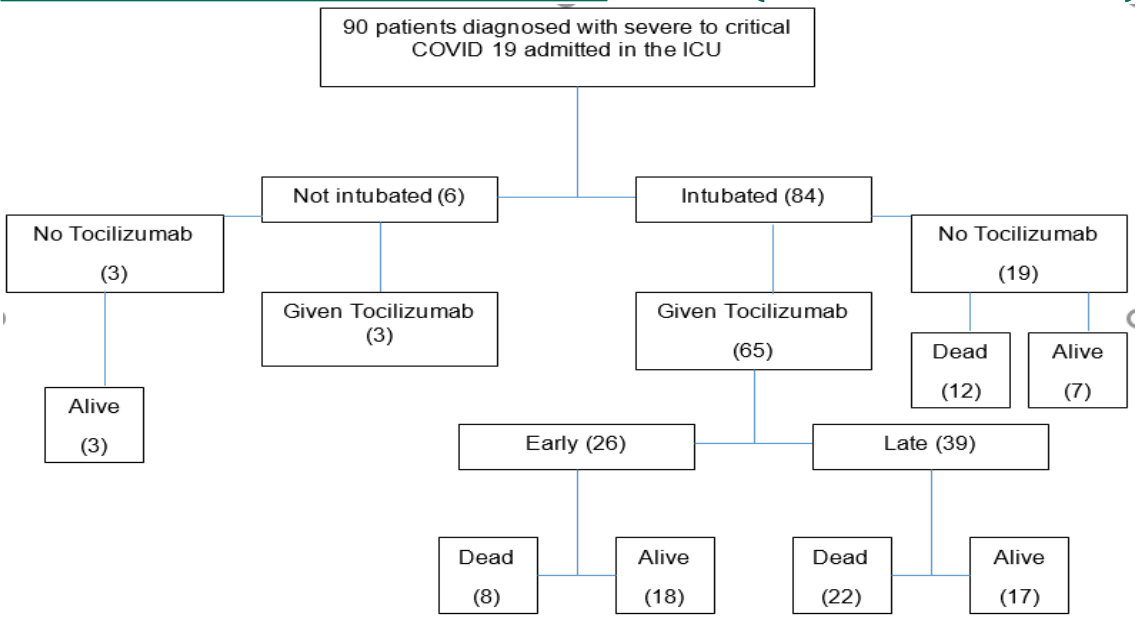

Figure 1. Schematic illustration of the study. A total of 90 patients were included in the statistical analysis after applying the exclusion criteria

neutrophil count of less than 500 per uL or platelet count less than $50x10^9$, and those who were intubated for conditions unrelated to COVID-19. Tocilizumab preceded the widespread use of dexamethasone, which became the standard of care after the RECOVERY outcome trial was released. Likewise, the subgroup of patients that received tocilizumab who were not given dexamethasone were still included in the study. Shown in Figure 1 is the schematic illustration of the study, with a total of 90 patients included.

RESULTS

A total of 90 severe to critically ill patients were admitted at the ICU from the period of March to August 2020, and 52 patients died with an overall mortality rate of 46.7%. Tocilizumab was given to 75.6% (n=68) with a 44.12% (30/68) mortality rate whereas among those not given the drug, the mortality rate was 54.55% (12/22).

In this population, 84 patients were intubated, while 6 of them were not. Among the intubated subgroup, 65 patients or 77.39% received tocilizumab, and among the non-intubated, half received tocilizumab. Of the 65 intubated patients who received tocilizumab, 26 (40%) received the drug early with a mean (±SD) 3.96 ±3.46 days prior to intubation or non-invasive ventilation while 39 (60%) received it late with a mean (±SD) of 0.762 ± 3.18 days. Among intubated patients, the 28-day mortality in the early group was 30.77% (8/26) which was significantly lower than the 56.41%, (22/39) in the late group (p=0.042).

Dexamethasone was added to standard of care upon the release of the RECOVERY trial results. Nearly two thirds of patients who received tocilizumab also received dexamethasone as shown in Table 1. Other baseline characteristics were presented in the table as well. A significant difference was noted on the APACHE II scores of baseline PaO2/Fio2 ratio, baseline D-dimer and post-tocilizumab D-dimer. Table 1 points out that patients who were given tocilizumab late sought hospital care when they were already at the peak of the cytokine storm, hence the worse baseline laboratory values. The CRP levels post-tocilizumab administration was also significantly better (137.89 ± 58.7 vs 223.28 ± 142.97, p =0.03).

Table 1. Baseline Clinical and Laboratory Variables of ICU Patients on Admission

Characteristics	Tocilizumab Group (n=65)		
	Early (n=26)	Late (n=39)	P value
Age	63.38 (13.47)	63.10 (12.14)	0.930
Sex			
Male	17 (65.38%)	23 (58.97%)	0.236
Female	9 (34.62%)	17 (41.03%)	
Mortality	8 (30.77%)	22 (56%)	0.042
APACHE* II	11.23 (4.20)	16.025 (7.72)	0.005
RALE** score baseline	14.71 (12.47)	17.64 (9.29)	0.302
RALE** score post-tocilizumab #1	22.69 (9.28)	18.15 (8.98)	0.061
Dexamethasone			
Yes	20 (76.92%)	23 (58.97%)	0.134
No	6 (23.08%)	16 (41.03%)	
PFR baseline	206.87 (118.93)	148.76 (89.56)	0.032
PFR post-tocilizumab #1	124.02 (53.65)	124.01 (68.05)	0.999
CRP baseline	150.62 (116.37)	196.80 (141.81)	0.239
CRP post-tocilizumab #1	137.89 (58.75)	223.28 (142.97)	0.031
D-dimer baseline	1.60 (1.94)	6.34 (8.55)	0.017
D-dimer post-tocilizumab #1	1.40 (1.22)	7.07 (6.25)	0.036
Ferritin baseline	2693.63 (2103.28)	2072.48 (2397.61)	0.318
Ferritin post-tocilizumab #1	4251.28 (4284.95)	5101.11 (7616.70)	0.667
LDH baseline	530. 65 (290.96)	567.50 (275.03)	0.613
LDH post-tocilizumab #1	686.88 (143.27)	767.38 (419.68)	0.601

Data is presented as n (%) or mean (SD)
APACHE: Acute Physiology and Chronic Health Evaluation; RALE: Radiographic Assessment of Lung Edema; PFR: PaO2/FiO2 Ratio; CRP: C-reactive protein; LDH: Lactate dehydrogenase

The 28-day survival analysis of the two treatment groups (early vs late) computed from the day of admission is shown in Figure 2. The hazard ratios for early treatment with tocilizumab alone, without adjusting for covariates, is 0.40 (95% CI, 0.1821,0.8771, p=0.022). Hazard ratios (HR: 0.37; 95% CI 0.1667,0.8115, p=0.013) remained significant after adjusting for both age and sex.

During the 28-day observation period post-intubation, the timing of giving tocilizumab did not show any significant effect on the patients' survival after intubation as presented in Figure 3. The mean days' survival of the early tocilizumab group was 17.42 days (SD 12.238, 95% CI 12.48, 22.37) whereas that of the late tocilizumab group was 18.62 (SD 9.95, 95% CI 15.39, 21.84), with a p-value of 0.6676.

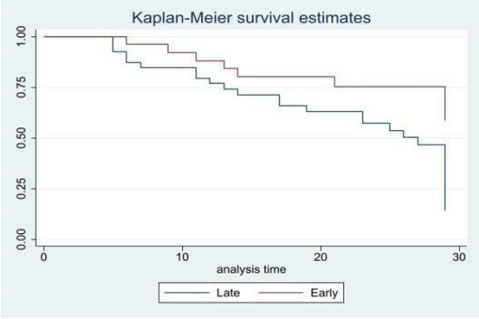

Figure 2. Comparison between early treatment versus late treatment with tocilizumab on the survival of ICU patients within 28 days from day of admission

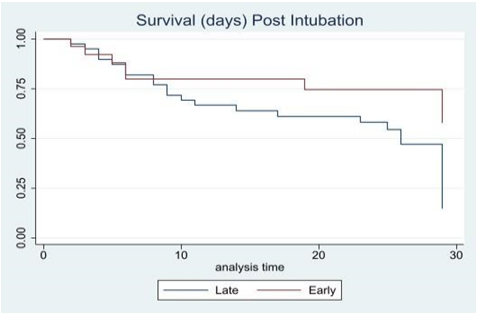

Figure 3. Survival post intubation in 28 days from day of intubation in early versus late treatment with tocilizumab

Figure 4 however shows that early treatment with tocilizumab demonstrated a protective effect with a hazards ratio of 0.4350 (95% CI 0.1982, 0.9548, p = 0.038) using survival post-intubation as a time variable. In-hospital mortality of the patients in the study also showed that early treatment with tocilizumab demonstrated a significantly higher mean day survival of 61.25 days while that of the late treatment group only had 38.25 days, p = 0.026.

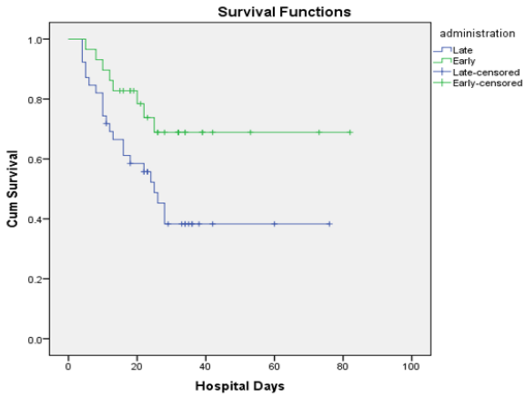

Figure 4. In-hospital survival from day of admission in early versus late treatment with tocilizumab

The use of dexamethasone also led to better survival with a hazards ratio of 0.76 (CI 0.496, 1.14, p=0.189) (Figure 5a). Survival curves of both tocilizumab plus dexamethasone among the ICU patients in this study had superior protective effect compared to either of the drug given alone or none at all (Figure 5b)

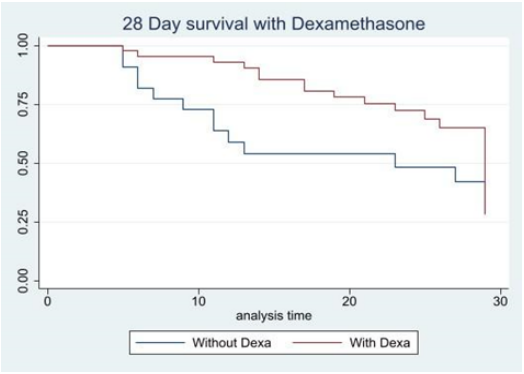

Figure 5a. Comparison between dexamethasone treated and non-treated groups

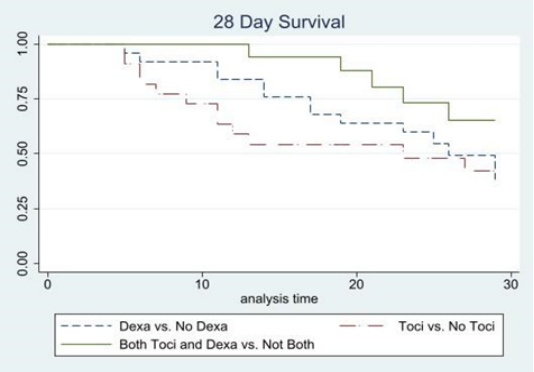

Figure 5b. Comparison between dexamethasone treated and non-treated groups in relation to the administration of tocilizumab

DISCUSSION

COVID-19 infection commonly presents with respiratory symptoms, with pneumonia as a well-recognized severe complication.[12] Respiratory failure caused by SARS-CoV2 infection has been attributed to the cytokine release syndrome, which is an overwhelming inflammatory response characterized by the increase in pro-inflammatory cytokines such as IL-6 and IL-1, as well as inflammatory markers like ferritin, C-reactive protein (CRP), D-dimer and lactate dehydrogenase (LDH) in response to the ongoing infection.[15]

Tocilizumab is a recombinant humanized IL-6 receptor monoclonal antibody that has been employed to potentially mitigate of the effects of the cytokine storm caused by COVID-19. Our observational study showed that early administration of tocilizumab to patients with COVID-19 pneumonia before respiratory failure seemed to offer a protective effect with improvement of survival. Although our baseline characteristics showed a worse presentation for the late treatment group, univariate and multivariate analysis adjusting for age, sex, concomitant use of steroids and APACHE II scores using the Cox proportional hazards model consistently showed that early treatment has better survival than late treatment. This finding concurs with the findings of one of the earliest published studies on

the use of tocilizumab in COVID-19 in China, wherein 21 patients with severe or critical COVID-19 pneumonia were treated with tocilizumab and showed a reduction of oxygen requirement, resolution of CT lesions, normalization of lymphocyte count, reduction of CRP levels, hospital discharge with an average hospitalization duration of 13.5 days 18.

The RECOVERY trial has shown that the use of dexamethasone resulted in lower 28-day mortality among those who were receiving either invasive mechanical ventilation or oxygen alone at randomization but not among those receiving no respiratory support in hospitalized COVID-19 patients. Furthermore, this trial has shown that tocilizumab improved survival among COVID-19 patients with hypoxia and systemic inflammation 21. In our study, the addition of dexamethasone indeed showed a better survival outcome. Both drugs may exhibit a synergistic effect on immunomodulation, particularly when given prior to the hyperinflammatory phase thereby blunting the effects of the cytokine storm, thus improving survival.

Literature had suggested that treatment with tocilizumab in patients with COVID-19 resulted in a reduction in oxygen requirement, improvement in inflammatory markers and shortened hospital stay 6. Our study however showed that oxygenation did not improve immediately and the only inflammatory marker that significantly improved twelve hours after the administration of tocilizumab was CRP levels.

Oxygenation may not have improved immediately because the patients in the study were severely ill at baseline, with chest X-ray findings showing high RALE score signifying severe ARDS. Radiologic lag in pneumonia may explain what seemed to be a worsening chest X-ray result after treatment. Furthermore, included patients generally had worse PF ratios to begin with, suggesting that the cytokine storm have ensued already. Perhaps a clearer distinction of the benefits of early treatment will be better appreciated when COVID-19 patients with less severity of illness were employed.

The inflammatory markers for both early and late tocilizumab groups were also significantly high for both groups, albeit, worse in the latter. This may reflect severe disease at baseline and although the CRP value decreased, it remained elevated even after giving tocilizumab, which portended a poorer prognosis, particularly for the late group. Of note, CRP was the only marker that significantly improved probably because of its direct correlation with IL-6, which tocilizumab directly inhibits. IL-6 suppression decreases CRP synthesis, hence early treatment of tocilizumab may be beneficial due to early inhibition of the hyperinflammatory response in a cytokine storm.

Our study also showed that our patients generally had prolonged hospital stay, despite being given tocilizumab. There was a longer hospital stay of the early tocilizumab group. During the duration of the 28-day observation period from admission, patients were still intubated on the 28th day, which probably explained the insignificant post-intubation mean day survival for both groups. The early group though had a longer in-hospital mean day survival. This shows that while both groups of patients may generally have prolonged in-hospital stay with a mean survival time of 49.15 days, survival was higher in the early treatment group.

The overall mortality for our intubated patients was 46%. The study population were generally older, with an average age of 63 years for both groups. The TOCIVID-19 prospective trial conveyed that old age is a poor prognostic factor in COVID-19, coupled with lower PaO2/FiO2 ratio 20. The age could have played a role in the course of the admission. Furthermore, multiple comorbid illnesses associated with aging may also have contributed to the long hospital

course. The PF ratio for both groups were also very low at first hospital contact, although, the late group had worse baseline PFR, thus predicting a worse outcome.

COVID-19 infection presents with a high expression of IL-6, which is the key pathophysiological basis for the severe inflammatory response that occurs in COVID infection 4. An elevated IL-6 level which characterizes the cytokine storm, is correlated with respiratory failure, need for mechanical ventilation and ultimately, mortality 16. Theoretically, the surge of these inflammatory markers can be halted by IL-6 inhibitors such as tocilizumab, potentially preventing disease progression, and consequently, better outcomes. Pre-emptive intervention through administration of tocilizumab earlier in the course of the disease before an overdrive of cytokine release occurs may be the rationale for the better outcomes seen in the early tocilizumab group as opposed to the late group. The onset of ARDS in COVID-19 could mean that we have missed the window for immunomodulator treatment.

Previous literature in other syndromes similar to COVID-19 such as SARS and MERS-COV also explored the beneficial effect of glucocorticoids 24, however, randomized controlled trials on its use during these pandemics were scarce. There was also an observed heterogeneity in glucocorticoid doses used in the treatment, comorbidities among subjects, and disease severity in the studies conducted. Perhaps, the benefit of glucocorticoids in severe viral respiratory infections is dependent on choosing the right patient, the right dose and right timing for administration. During the early phase of the COVID-19 infection occurring on the first week of the disease, viral replication is more prominent than inflammation, while in the second week of illness, inflammatory processes are heightened 21. This may explain why dexamethasone was more beneficial among oxygen-requiring patients compared to those who do not need oxygen support. Tocilizumab may exhibit a synergistic effect when given with dexamethasone since it serves as an immunomodulator during the onset of the inflammatory phase, however, caution must be exhibited in its use. As with any other treatment, risks and benefits must be weighed through identifying the right patient to be given the drug, the right dose and the right timing.

LIMITATIONS

To the investigators' knowledge, this is the first local study in the Philippines to determine the effect of the timing of administration of tocilizumab among COVID-19 patients admitted in the ICU. Admittedly, the present study has some limitations. First, the study is retrospective. This is significant as a more in-depth course of the illness during history taking may have been omitted prior to the admission.

A prospective study may be more advantageous as a stricter acquisition form of pertinent data can be devised prior to data collection with decrease in recall and observation bias. A longer survival outcome measure point, such as 60-day mortality is also suggested since secondary infections were not measured and these may result to increased mortality beyond the 28-day period.

Moreover, the population is heterogenous and several data were missing due to the heterogeneity of the management and in-hospital monitoring particularly in terms of laboratory exams taken during the hospitalization. The management of COVID-19 has been noted to be evolving during the time period that this study has been conducted thus, the effect of other adjuvant therapies employed in the management of these patients were not accounted for.

The sample size may be underpowered to detect the effect of tocilizumab alone (without dexamethasone) and a larger population may demonstrate individual outcome measures with less confounding.

Patients in this population also exhibit ARDS requiring mechanical ventilation and complications of prolonged ICU stay such as ventilator-associated pneumonia, catheter-related infections and complications like acute kidney injury requiring hemodialysis may also contribute to mortality. All these may make detecting the survival advantage difficult for immunosuppressives like tocilizumab.

CONCLUSION

The severe hyperinflammatory state in COVID-19 pneumonia in some patients has led to respiratory failure and increased mortality. Early administration of tocilizumab may ameliorate this hyperinflammatory response but late administration, such as after mechanical ventilation, may have no benefit. Randomized clinical trials are needed to define not only the effectiveness of tocilizumab but also the timing of administration.

RECOMMENDATION

We recommend future investigation with a larger, randomized, multi-center study as the results of using larger population can be more reflective of the association of the timing of administration of tocilizumab to survival of critically ill COVID-19 patients. A prospective approach may also diminish recall bias by the patients, and a more structured interview can be devised and utilized among patients with confirmed COVID-19. A prospective study can also allow symptomatologic evaluation of patients which is difficult in retrospective studies. Tocilizumab's benefits may also be seen in moderate cases since ARDS and subsequent mechanical ventilation adds to mortality regardless of etiology.

DISCLOSURE

No funding from any company or organization was given for this research.

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Philippine Journal of Chest Diseases

Original Research

Nutrition Practices in the Medical Intensive Care Unit in a Tertiary Hospital

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ABSTRACT

BACKGROUND: The optimal amount of energy and caloric requirement is important in reducing morbidity, mortality and improving outcomes among patients in the intensive care unit (ICU). Internationally published studies aimed to determine application of these recommendations shows a large gap between recommendations and actual practices. In the Philippines, there is no published study available to determine nutrition practices in the ICU.

OBJECTIVE: To describe the current nutrition practices among physicians in the medical ICU.

METHODS: A descriptive prospective cohort study evaluating nutrition practices among physicians in the medical ICU for three months to examine adequacy of nutritional intake, choice of route of feeding and associations between these practices and outcomes of ICU patients.

RESULTS: A total of 54 patients were enrolled in three months with majority having cardiac etiology. There is no significant difference between average prescribed target caloric requirement at 27 kcal/kg versus actual caloric intake at 26 kcal/kg (p=0.188), with 92.5% of physicians initiating either enteral feeding within 48 hours of ICU admission. Analysis shows significant correlation between timing of feeding and meeting caloric requirement in the duration of ICU stay.

CONCLUSION: Physicians in the medical ICU meet their target ICU caloric requirement for the patients with an isocaloric diet during the first 48 hours of ICU admission using either enteral or oral route of feeding.

KEYWORDS: *nutrition, critically ill, intensive care*

INTRODUCTION

Critically ill patients are generally at risk for malnutrition as they are mostly unable to provide sufficient nutrition for themselves. Further, their altered metabolism – marked by increased catabolism, anabolic resistance and lack of signals to set anabolism – worsens the nutritional status and leads to muscle wasting and worse clinical outcomes.[1] A study done in 2014 reported an overall prevalence rate of 54.5% of malnutrition in the ICU. The study also shows an increase in the prevalence of malnutrition with an increased hospital ICU admission.[2]

Various studies on optimal nutrition among critically ill patients demonstrates a significant decrease in the odds of post-discharge hospital mortality[3] and 30-day hospital readmission[4]. Adequate nutritional support leads to reduction of catabolism, attenuation of muscle wasting, and maintenance of nutritional status. This is supported by studies which shows that failure to meet nutritional targets, especially during the first week of ICU admission, negatively influences skeletal mass and physical or functional ability during and post-ICU discharge.[5-7]

Studies in critically ill adults are in agreement that malnutrition is associated with poor clinical outcomes in both short-term (i. e., mortality, length of hospital stay, nosocomial infections)[8-11] and long-term (i.e., survival and functional capacity) basis.[10] However, despite the awareness of the importance of nutrition for recovery in critical illness, there remains a large gap between recommendations and application. Reports published in the US showed that achieving optimal nutrition is widely varied (30% to 85%) and reflects a discordance between nutrition knowledge and applications among health care providers.[12]

A study to assess the nutritional practices in the ICU was conducted by Vallejo et. al. in 2017. The study shows that 70% of the patients had moderate to severe malnutrition using the SGA questionnaire (compared to the 13% set by European Society for Clinical Nutrition and Metabolism (ESPEN) using ESPEN score), 24% of the patients had no energy requirement set by clinicians, and around 40% of the patients in the ICU did not meet the caloric requirement set on admission with either enteral or parenteral nutrition.[13] A more recent study by Zaki et. al. in 2018 shows that malnutrition was highly prevalent among patients admitted in the medical ICU with a mortality rate of 55.9% versus the well-nourished group.[16] Another study by Osooli et. al. in 2019 showed that more than 80% of surgical and medical ICU patients failed to receive at least 80% of protein and energy target with malnutrition developing in 84% of the study population.[17]

No similar study has been conducted yet in the Philippines. As such, data on the actual prevalence of malnutrition in the ICU as well as nutritional practices and compliance to the recommended guidelines are lacking. Recent evidence-based guidelines set by ESPEN have emphasized the need to (1) identify ICU patients at risk, (2) provide extensive clinical assessment on the nutritional status of such patients, (3) define nutritional goals in terms of energy, protein, carbohydrate, lipid and micronutrients, and, (4) set the appropriate route and diet-progression steps.[7] ESPEN, being the most recent and most comprehensive of the available guidelines for the critically ill, aims to lessen the length of hospitalization, length on mechanical ventilation, and improve short-term and long term survival of these patients. There is a foreseen benefit in the implementation of this recommendations given the current available evidence on the optimization of nutritional status among critically ill patients in improving outcomes. Despite the benefit of these evidences, there remains a gap between theory and practice with the absence of published local data on the current practices of medical professionals, particularly among physicians in the ICU who are taking care of these critically-ill patients.

Without local data, policies cannot be crafted to optimize nutrition and subsequently improve the outcomes among patients admitted in the ICU.

OBJECTIVES

We aim to describe the current nutrition practices among physicians in the medical ICU. More specifically, to (1) describe the timing of initiation and preferred route of feeding among critically ill patients; (2) compare actual versus prescribed caloric intake; (3) identify interventions initiated by attending physicians to meet and monitor prescribed caloric intake; and (4) determine clinical outcomes of patients admitted until demise or discharge from the ICU. With these data, potential associations between nutrition practices and outcomes among critically ill patients can be determined and areas where recommendations can be provided to improve outcomes of patients admitted at the medical ICU can then be identified.

METHODS

A descriptive prospective cohort pilot study was done to determine the current nutrition practices among physicians in the medical ICU. These practices include timing of initiation of feeding, route of feeding (i.e., oral, enteral, parenteral, nil per orem (NPO)), changes made during the course of ICU admission, amount of calories provided, escalation/de-escalation of caloric intake, breakdown of nutrient requirements, monitoring of prescribed caloric intake versus actual calories consumed, and outcomes of patients admitted at the ICU for three months. These were compared to the currently available recommendations for critically ill patients. Chart review was done for all admitted patients in the medical ICU during the determined period. Only adult patients admitted at the medical ICU were included in this study. Adult critically ill patients admitted at the ICU who died less than 24 hours after being admitted, adult critically ill patients discharged from the ICU less than 24 hours after being admitted, and those who did not consent were not included in the study. All admissions in the medical ICU from November 1, 2019 to January 31, 2020 were eligible for inclusion in the study. The primary investigator coordinated with the medical ICU senior residents to ask for new admissions on a daily basis. Consent for inclusion in the study was secured from the patient or the next of kin of the critically ill patient in situations wherein the patient was deemed unfit to give consent. Patients and/or relatives who did not consent were excluded. Chart review of the admissions were done by a resident co-author with the project assistant. There was no direct patient or clinician interaction during the data collection process.

Chart review looked at the prescribed diet as written in the chart together with the computed prescribed caloric intake, route, timing of administration of feeding, and interruptions (if present). This was compared to the actual caloric requirement taken by the patient by computing the food intake of patients feeding per orem, counting the amount of osterized feeding or milk feeding tolerated by patients on enteral route, evaluating the duration and frequency of total parenteral nutrition (TPN) and time on NPO among patients prescribed on TPN and NPO, respectively. The time to admission at the medical ICU to the start of feeding was monitored and interventions documented on the chart to meet and monitor prescribed caloric were documented. The patients were followed up until discharge from the ICU or until demise.

A data extraction form was used during the chart review which included the baseline characteristics of the patients, Acute Physiological Assessment and Chronic Health Evaluation (APACHE) score, indication for ICU admission, length of ICU stays, and a baseline nutritional risk assessment tool using the Nutritional Risk Screening (NRS) 2002. Total caloric prescription, timing of

initiation of feeding, escalation/de-escalation of feeding, initial and subsequent route of feeding, nutritional status monitoring, outcomes of patients, and actual caloric intake were tabulated twenty-four (24) hours into admission until the patient was discharged from the ICU or until demise. Data were encoded in Microsoft Word for documentation and summarized descriptively using number and percentage for categorical variables in Microsoft Excel. A linear regression model was used to determine the association between baseline characteristics and caloric balances.

RESULTS

A total of 54 patients with a mean age of 54 years old were included in the three-month recruitment period. The summary of the baseline characteristics of all the patients included in the study during the data collection period is shown in Table 1. Most of the patients admitted were male with BMI in the 23 – 24.9 category. Majority of the patients were started on either oral or parenteral nutrition and stayed in the ICU for 3 days or less. Most of the patients admitted had primarily cardiac indications for admission and had an APACHE score of less than 15.

Table 2 shows that out of the 54 patients admitted in the ICU, 35% had a score of zero with normal nutrition status, 9.0% had an NRS score of 1, 22% with an NRS score of 2 and 34% with scores of 3 and higher. These results indicate a high risk for malnutrition.

Table 1. Table of Baseline Characteristics

Characteristic	Total (n = 54)
Age, years	
Mean (SD)	54
Median (range)	55
Sex	
Male	39
Female	15
BMI	
<18.5	3
18.5 - 22.9	18
23 – 24.9	22
25 – 29.9	8
>30	3
Type of Nutrition	
Oral	26
Enteral only	27
Parenteral only	2
Both enteral and parenteral nutrition	1
Nil per orem	0
Primary Reason for ICU admission	
Cardiac	31
Respiratory	16
Sepsis	19
Neurologic	2
Trauma	0
Abdominal	1
Others	2
APACHE Score on admission	
<15	27
15 to 19	16
20 – 27	9
≥ 28	2
Duration of ICU Stay	
0-3 days	24
3-6 days	13
7-10 days	4
10-14 days	3
> 14 days	10

Table 2. Risk for Malnutrition

NRS 2002 Score	Mean
Score 0	19
Score 1	5
Score 2	12
Score 3	10
Score > 3	8

Table 3 shows the caloric balance of patients admitted in the medical ICU. The average kcal requirement prescribed in the ICU is 1566 kcal/day or 27 kcal/kg with an average caloric intake of 1547 kcal/kg or 26 kcal/kg. Paired test of the actual versus the prescribed caloric intake shows no statistical difference between prescribed and actual diet (p-value=0.188).

Table 3. Caloric Balance (Entire ICU Stay)

Characteristic	Mean (SD)	p-value	Median
Caloric Target Kcal Kcal/kg	 1566 kcal/day (313 kcal) 27 kcal/kg (5 kcal)		 1712 kcal 30 kcal/kg
Caloric Intake Kcal Kcal/kg	 1547 kcal/day (342 kcal) 26 kcal/kg (5 kcal)		 1587 kcal 29 kcal/kg
Caloric Balance Kcal Kcal/kg	 19 kcal/day 1 kcal/kg	0.188	

Table 4 shows that there is a strong positive correlation between the type of nutrition and NRS score with meeting the prescribed caloric requirement. The rest of the baseline characteristics have no direct relationship with caloric requirement.

Table 5 shows that almost 93% of patients admitted in the medical ICU were started with either oral or enteral feeding within 48 hours from ICU admission with only 4 patients initiated 48 hours after. Reasons for delay in the initiation of feeding include uncontrolled shock, severe dyspnea, and pathology requiring NPO.

Table 4. Association Between Caloric Target and Baseline Characteristic

	Caloric Requirement	
Variable	Correlation coefficient	p value
Age	0.214	0.119
Sex	0. 097	0.486
BMI	0. 099	0.475
Type of Nutrition	-0.668	0. 001
Indication of ICU admission	0. 062	0.656
APACHE Score on admission	-0. 008	0.955
Duration of ICU Stay	0.190	0.169
NRS Score	0.554	0. 001

Table 5. Timing of Feeding Initiation (within 48 hours versus beyond 48 hours)

	Within 48 hours (n = 50)		Beyond 48 hours (n = 4)	
Initiation of feeding	Frequency	Percentage	Frequency	Percentage
Oral	25	50.00%	1	25.00%
Enteral	25	50.00%	1	25.00%
Parenteral	0	0.00%	1	25.00%
Both	0	0.00%	1	25.00%
NPO	0	0.00%	0	0.00%

Table 6. Monitoring Strategies for ICU Patients (Intervention and Monitoring)

Intervention	Frequency	Percentage	Monitoring	Frequency	Percentage
Interview/Monitor subjective feeling of wellness of patients	21	44.68%	Every day	0	0.00%
Estimate muscle mass	1	2.13%	Every 3 days	18	85.71%
Estimate serum albumin	2	4.26%	Every 7 days	3	14.29%
Monitor body weight	2	4.26%	Never	0	0.00%
Check on residuals	21	44.68%			

Monitoring strategies for ICU patients listed in Table 6 includes patient interview to assess subjective feeling of wellness (44.68%), estimation of muscle mass (2.13%) and serum albumin (4.26%), monitoring of body weight (4.26%) and checking of residuals (44.68%). Majority of the ICU physicians monitors the nutrition of their patients every 3 days.

DISCUSSION

The optimal amount of energy and caloric requirement is important in reducing morbidity and mortality among ICU patients.[14] Current studies and recommendations have caused a paradigm shift in viewing nutrition among critically ill patients from an adjunct to that of definitive therapy in improving outcomes.[15] This study aimed to describe the nutrition practices among physicians in the medical ICU of the University of the Philippines-Philippine General Hospital. This study examined the adequacy of nutrition intake, choice of route of feeding, and monitoring strategies for ICU patients.

The study enrolled a total of 54 patients during the three-month data collection period. Assessment of the baseline characteristics show that admitted patients have generally good APACHE scores, with adequate BMI and are low risk for malnutrition. In addition, majority of these patients are cardiac patients with a short duration of ICU stay. As such, the baseline characteristics of population being represented in this study has better clinical outcomes being identified as "low-risk" ICU patients. Majority of the patients admitted were also able to meet the ESPEN recommendation of oral and enteral therefore feeding leading to better outcomes.

Compared with a similar published study in 2017[13] wherein 40% of the patients in the ICU did not meet the caloric requirement set on admission, this 2020 study was able to show that (1) ICU physicians are more liberal in their caloric targets with an average target of 27 kcal/kg and (2) these targets are actually met and given to the patients. In addition, there was prompt initiation of feeding 50 patients within 48 hours of admission. Factors which could have contributed to meeting the prescribed caloric requirement are the less critically ill state of the patient along with an option for a more efficient route of feeding. As such, there had been less limitations and difficulties in ensuring adequate nutritional support.

The study reported a total of seven mortalities during the three-month period. Only two out of the seven deaths had feeding initiation after 48 hours with one started between the 48^{th} – 72^{nd} hour and the other started beyond 72 hours of ICU admission. The two mortalities with delay in initiation of feeding both had normal BMI (18.5 – 22.9 range) and were initially fed in the enteral route, with one patient eventually shifted to parenteral route. Notable are the high NRS scores (≥3) and APACHE scores (20-27) resulting to an increased baseline risk of malnutrition and mortality.

Table 4 shows the association between the baseline characteristics of the patients included in the study with meeting the caloric requirement. Only two factors are seen with correlation with caloric requirement – the type of nutrition and the NRS. For nutrition, this implies that as we shift from oral and enteral to parenteral and/or both, there is increased risk of being unable to meet the target caloric requirement. This also applies for NRS score with increased risk of failing to meet prescribed caloric requirement with increasing risk of malnutrition.

The study also included monitoring strategies employed by the ICU physicians to check the adequacy of nutrition. Majority used either the subjective well-being of patients for patients on oral feeding and residual per nasogastric tube for patients on enteral feeding with these measures done every 3 days. However, it was observed in the study that physicians do not employ these monitoring strategies on all ICU patients and arbitrarily monitor patients who they perceive as "more critically ill" and have a baseline high risk for malnutrition.

LIMITATIONS

Factors that could have affected the result of the study includes the skewed population with more patients having a lower baseline risk for malnutrition and mortality. These patients were able to tolerate oral or enteral feeding resulting to a more efficient delivery of nutrition to the already baseline low risk patients. As such, the authors recommend that a follow-up study be conducted in the ICU enrolling patients with higher APACHE and NRS scores. In addition, a longer observation period to include nutrition status post-ICU discharge would give a more holistic approach in potentially creating protocols for nutrition in the ICU. Since this study is a pilot study, the sample size was smaller and limited to the medical ICU which could also have affected the results and conclusion of the study. Therefore, a bigger sample size including patients with higher baseline risk for malnutrition and mortality, a longer follow up period, and including other ICUs (surgical, neurological) would provide a more representative data of the nutrition practice in the ICU of a tertiary hospital which will be crucial in creating policies to improve and optimize our standard of care for critically ill patients.

CONCLUSION AND RECOMMENDATION

Physicians in the medical ICU are able to meet their target ICU caloric requirement with an isocaloric diet during the first 48 hours of ICU admission using either enteral or oral route of feeding. Oral or enteral route of feeding within the first 48 hours of ICU admission was associated with better outcomes versus patients who were fed after 48 hours. A lower baseline risk of malnutrition with a less critically ill state provide less difficulties in ensuring adequate nutritional support resulting in a decrease risk for malnutrition and mortality during ICU stay.

Although ICU physicians employ ways to assess adequacy of nutrition, their methods are arbitrary and lack standardization. A "protocolized" approach in monitoring adequacy of nutrition including using more objective monitoring parameters such as muscle mass determination and pre- and post-ICU activities of daily living might be necessary to better quantify and qualify correlation between nutritional support with skeletal mass, physical and functional ability which are important end points for patients admitted in the ICU.

Ensuring adequate nutritional intake is important in improving outcomes in the medical ICU. For patients who are low risk for malnutrition and mortality, meeting the prescribed caloric requirement though oral or enteral feeding is highly encouraged and is associated with improved outcomes and ICU discharges.

DISCLOSURE

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Original Research

Effect of a Chronic Obstructive Pulmonary Disease Discharge Bundle on Re-admission Outcomes

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ABSTRACT

BACKGROUND: Chronic obstructive pulmonary disease (COPD) is one of the leading causes of morbidity and mortality worldwide. A history of hospital admission for a COPD attack increases the risk of subsequent hospitalizations. Interventions should be employed after the first admission to decrease the risk of subsequent hospitalization.

OBJECTIVE: To fill the gap between medical information and effective patient communication through implementation of discharge care bundle for COPD patients and validate its utility by measuring compliance to interventions, readmission rates and patient outcomes before and after utilization of COPD discharge bundle.

METHODS: This study investigated the readmission rates and outcomes at 30, 60 and 90 days' post discharge, before and after the implementation of a COPD discharge bundle. Retrospective chart review was done for 30 patients in the non-bundle group to examine their discharge instructions. Conversely, 32 patients enrolled in the bundle group were visited by a nurse educator and were instructed on the components of the bundle prior to discharge, and were followed-up through phone calls on the 30th, 60th and 90th day post discharge to check for readmission rates and outcomes, as well as compliance with the bundle.

RESULTS: The use of the COPD discharge bundle ensured that all patients in the bundle group were instructed on the following: (1) list of medications, (2) follow-up schedule, (3) inhaler technique, (4) smoking cessation, and (5) pulmonary rehabilitation. On the other hand, patients in the non-bundle group only received instructions on medications and follow-up schedule, and received a varying number of instructions on the other interventions for COPD. Upon analysis, there was a statistically significant difference in the rate of readmission on the 30th day follow-up. Those who received the COPD discharge bundle had a higher chance of not being readmitted within 30 days with a relative risk (RR) 1.17 (p=0.042).

CONCLUSION: COPD discharge bundle is a useful tool to ensure continuity of care as COPD patients transition from in-patient to out-patient care setting. Structured discharge instruction with emphasis on interventions such as smoking cessation, inhaler technique, pulmonary rehabilitation and list of medications significantly decreased 30-day readmission rate in the bundle group as illustrated in this study.

KEYWORDS: *chronic obstructive pulmonary disease (COPD), COPD discharge bundle, readmission*

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a disease characterized by persistent and progressive airflow limitation. It is one of the top causes of morbidity and mortality worldwide. According to the World Health Organization (WHO), COPD ranks fifth in leading causes of death in 2002, and is projected to rank fourth in the leading causes of death among middle and low-income countries by year 2030. Likewise, it is expected to be the 7th leading cause of disability adjusted life years (DALYs).[1]

An international study which included the Philippines as one of its sample sites showed that Manila was one of the top three cities with a high burden of COPD, having more samples with COPD Global Initiative for Chronic Obstructive Lung Disease (GOLD) class II.[2] A prevalence study done on the burden of COPD in a rural setting in the Philippines showed similar results. The most common risk factor in developing COPD especially in high income countries is current smoking and total smoking load measured in pack years. Increasing age and the male gender are also seen as factors for more severe COPD GOLD classification. The inability to perform activities of daily living is also identified as an independent risk factor of early and late mortality aside from these risk factors. Moreover, the severity of functional impairment increases rate of re-admission.[2] Co-morbidities such as heart failure, diabetes, liver and renal failure also increase in-hospital and post-discharge mortality.[3]

Some interventions including smoking cessation, inhaler technique, pulmonary rehabilitation, education on medication and follow-up have been studied to have an impact in the management of COPD patients. As such, previous studies have observed that these interventions collectively improved COPD outcomes if incorporated in a discharge bundle.[4]

OBJECTIVE

To fill the gap between medical information and effective patient communication by implementing a discharge care bundle for patients admitted for COPD and measuring readmission rates and outcomes after its introduction. This study considered the demographics, patient characteristics of admitted COPD patients, their readmission rates before and after the utilization of a COPD discharge bundle, and their compliance rates on the interventions given.

METHODS

Population and Sample

COPD patients aged 40 and above who were admitted for exacerbations at The Medical City, Philippines, a private tertiary hospital, between January 2016 to February 2019 were included in this study. Those with severe sepsis, acute decompensated heart failure, myocardial infarction, chronic kidney disease on hemodialysis and those on tracheostomy, chronic ventilator support and/or with advanced directives/ do not intubate patients, as well as patients with decreased sensorium and who cannot follow commands were not included in the population.

For the non-bundle group, patients admitted between January 2016 to December 2017 with the discharge diagnosis of COPD exacerbation, and who fit the inclusion and exclusion criteria were identified in the hospital database by random sampling. A final number of 30 patients for the non-bundle group were eligible to be included in the study, and chart review was done on these subjects. For the bundle group, patients admitted between January 2018 to February 2019 who were qualified to join the study were recruited. A total of 32 patients were included in the bundle group.

An informed consent form was explained by the investigator and was signed by all participants. The outcome measures investigated were readmission rates, readmission

and compliance to the bundle group.

Non-bundle Group

A retrospective chart review was done on patients who did not receive the bundle. Demographics were obtained. Discharge instructions were reviewed and checked if the patients received instructions on inhaler technique, home medications, smoking cessation, follow-up and pulmonary rehabilitation. Emergency room visits and readmission outcomes (rate of readmission and invasive or non-invasive mechanical ventilation) in the same institution 30, 60 and 90 days after initial discharge were obtained.

Bundle Group

For the bundle group, a COPD discharge bundle was introduced prior to discharge. The bundle used in this paper is adapted from the study of Hopkinson, et. al.5 Two nurse educators were oriented and trained on the components of the COPD discharge bundle:

1. Advise on smoking cessation- a brief overview on the adverse effects of smoking and the benefits of quitting smoking;
2. Correct inhaler technique – instruction on how to correctly use the prescribed inhaler based on the instruction leaflet of each medication, then a return demonstration;
3. Introduction to pulmonary rehabilitation- introduction on the benefits of pulmonary rehabilitation on COPD patients;
4. Written home medications- a list of home medications given to the patient upon discharge; and
5. Written follow-up- a list of the date and doctor's clinic number for the next outpatient follow-up.

The items that were performed were documented in a form by the nurse educator. Written home medications and follow-up schedule were also given prior to discharge. A third-party contact center hired by The Medical City Continuity of Care Center followed-up the subjects through a telephone call 30, 60 and 90 days after discharge to inquire about ER visits, readmissions (in the same or other institutions), compliance with inhaler regimen, smoking cessation and pulmonary rehabilitation. Patient demographics, rate of readmission and rate of mechanical ventilation were also determined.

Analysis

The following attributes were included in the statistical analysis: (1) patient demographics (i.e., age, sex); (2) clinical characteristics (i.e., smoking history, concomitant respiratory infection, inhaler use, and co-morbidities); (3) discharge instructions (i.e., advise on smoking cessation, correct inhaler technique, introduction to pulmonary rehabilitation and written home medications, and follow-up instructions); (4) compliance rates; and, (5) readmission outcomes (i.e., rate of readmission, rate of invasive or non-invasive mechanical ventilation). Data analysis was performed using SPSS. Quantitative variables were summarized as mean and standard deviation, while qualitative variables were tabulated as frequency and percentage. Comparison of baseline characteristics between COPD discharge bundle and non-bundle group were analyzed using independent t-test for quantitative variables, and Fisher's exact test for qualitative variables. Association between outcomes and use of the COPD Discharge bundle were analyzed using logistic regression. The level of significance was set at 5%.

RESULTS

Description of Samples

A total of 63 subjects were originally recruited for the study with one patient drop out. The final analysis was carried out with 30 patients in the non-bundle group and 32 in the bundle group.

The baseline characteristics were similar between those who received the COPD bundle and those who did not. The mean age was 68 years old from the control group (41 years old to 87 years old), while the mean age from the COPD bundle group was 69 years old (48 years old to 91 years old). The non-bundle group had 6 females and 24 males; 27 of the subjects had pulmonary infection and were using inhalers. Four of those in the non-bundle group had bronchiectasis, and 5 had pulmonary tuberculosis. The bundle group had 8 females and 24 males; 28 of them had infection, 4 had bronchiectasis, 2 had pulmonary tuberculosis, and 1 had obstructive sleep apnea. 31 were using inhalers (Table 1).

The subjects in the non-bundle group had a mean of 32 (SD 24.44) smoking pack years, while those in the bundle group had approximately 34 (SD 20.63) smoking pack years. The average number of years - stopped smoking in the control group was more than 17 years (SD 11.17), and more than 14 (14.97) years for the COPD bundle group (Table 1).

Table 1. Characteristics of the Sample

	(-) COPD Bundle Mean (SD) / %	(+) COPD Bundle Mean (SD) / %	p-value
Age	68.47 (11.313)	69.88 (10.90)	0.312
Pack Years	32.88 (24.44)	34.45 (20.63)	0.002
Years stopped	17.68 (11.17)	14.65 (14.97)	0.008
Gender			< 0.000
Male	80 %	75 %	
Female	20 %	25 %	
Infection	90 %	87.5 %	< 0.000
Co-Morbidity			< 0.000
Bronchiectasis	13.3 %	12.5 %	
PTB	16.7 %	6.3 %	
OSA	0	3.1 %	
None/Others	70 %	78.1 %	
Inhaler Use	90 %	96.9 %	< 0.000

According to the chart review, all of those under the non-bundle group received instructions about their list of medications and their follow-up as part of hospital protocol. There was no record on being instructed on inhaler technique, while only 2 out of the 30 or 6.7% were introduced to pulmonary rehabilitation. In contrast, those who received the COPD bundle were all instructed on inhaler technique, list of medications, follow up, smoking cessation (for those who are still smoking) and pulmonary rehabilitation (Table 2).

Table 2 showed that the Chi Square test showed that the two comparison groups were significantly different in proportion of patients who received specific instructions of inhaler techniques, smoking cessation, and pulmonary rehabilitation ($p < 0.000$). The control group had a significant proportion of those who did not receive the instruction compared to the bundle group.

Table 2. Comparison between the two groups receiving discharge instructions

	(-) COPD Bundle %	(+) COPD Bundle %	p-value
Inhaler Technique	0 %	100 %	< 0.000
List of Medication	100 %	100 %	-
Follow Up	100 %	100 %	-
Smoking Cessation			< 0.000
Yes	0 %	25 %	
No	20 %	0 %	
No Data/Not applicable	80%	75 %	
Pulmonary Rehab	6.7 %	100 %	< 0.000

There was a statistically significant difference in the rate of admission for the COPD bundle group on the 30th day follow-up. There were no readmissions after 30 days for those subjects who received the COPD discharge bundle, whereas 13.3% of those who did not receive the bundle were readmitted within 30 days of discharge. The relative risk of not being admitted within 30 days is 1.17 times higher among those who

received the COPD bundle as compared to those who did not (p = 0.042). There were no subjects who were invasively or non-invasively ventilated within 30 days following discharge in the bundle group. Furthermore, all subjects in the bundle group had regular inhaler use and went for follow-up after 30 days. Among the 21.9% who were still smoking at the time of the study, 12.5% stopped smoking after the intervention, and 3.1% enrolled in pulmonary rehabilitation (Table 3a).

Table 3a. Comparison of Outcomes after 30 days

	(-) COPD Bundle %	(+) COPD Bundle %	p-value
Admission			0.042
Yes	13.3 %	0 %	
No	80 %	100 % (RR =1.17, CI=1.003 – 1.36)	
Inhaler Use	-	100 %	-
Follow Up	-	100 %	-
Smoking Cessation			-
Yes	-	12.5 %	
No	-	9.4 %	
Not Applicable	100 %	78.1 %	
Pulmonary Rehab	-	3.1 %	-
MV	-	-	-
NIV	-	-	-

While not statistically significant, the trend of admissions and mechanical ventilation within 60 and 90 days is higher for those who did not receive the bundle. The RR for being admitted within 60 days is 2.4 (CI 0.825,6.978, p = 0.091) for the no bundle group. The RR for not being admitted within 90 days is 2.4 (CI 0.825,6.978, p = 1.000) for those under the bundle group (Table 3b and 3c). On the 60th day of follow-up, there were no mechanically ventilated subjects under the bundle group, while 3.3% were mechanically ventilated in the non-bundle group. Ten percent of those admitted in the non-bundle group was hooked to non-invasive ventilation, as compared to 3.1% in the bundle group.

Those who received the COPD bundle were followed-up to trace their admissions and their compliance with the interventions. There was a decrease in inhaler use from 100% after the 30th day to 84.4% and 68.8% after 60 and 90 days, respectively. There was a significantly decreasing trend of patients who go on follow-up after 30 days compared to 60 (p = 0.041) days, and 30 days compared to 90 days (p = 0.000). Despite all these, there was no significant association between inhaler use and readmissions, and between number of follow-up and readmissions on any of the follow-up time points. There was a significant association between pulmonary rehabilitation and readmissions (RR: 14.49; CI 3.807,55.225, p= 0.013) (Table 4).

Table 3b. Comparison of Outcomes after 60 days

	(-) COPD Bundle %	(+) COPD Bundle %	p-value
Admission			0.091
Yes	30 % (RR =2.4, CI=0.825 – 6.978)	12.5 %	
No	70 %	87.5 %	
Inhaler Use			-
Yes	6.7 %	84.4 %	
No	-	9.4 %	
No Data	93.3 %	6.3 %	
Follow Up			-
Yes	-	62.5	
No	3.3 %	37.5	
No Data	96.7 %	-	
Smoking Cessation			-
Yes	-	12.5	
No	-	9.4	
No Data	100 %	78.1	
Pulmonary Rehab			-
Yes	3.3 %	6.3	
No	-	90.6	
No Data	96.7 %	3.1	
MV			-
Yes	3.3 %	-	
No	23.3 %	12.5 %	
No Data	73.3 %	87.5 %	
NIV			1.000
Yes	10 %	3.1 %	
No	20 %	9.4 %	
No Data	70 %	87.5	

Table 3c. Comparison of Outcomes after 90 days

	(-) COPD Bundle %	(+) COPD Bundle %	p-value
Admission			1.000
Yes	10 %	6.3 %	
No	90 %	81.3 % (RR =1.4, CI=0.252 – 7.767)	
No Data	0%	12.5 %	
Inhaler Use			-
Yes	-	68.8 %	
No	-	9.4 %	
No Data	100 %	21.9 %	
Follow Up			-
Yes	-	40.6 %	
No	-	46.9 %	
No Data	100 %	12.5 %	
Smoking Cessation			-
Yes	-	6.3 %	
No	-	6.3 %	
No Data	100 %	87.5 %	
Pulmonary Rehab			-
Yes	-	15.6 %	
No	-	71.9 %	
No Data	100%	12.5 %	
MV			-
Yes	-	-	
No	3.3 %	6.3 %	
No Data	96.7 %	93.8 %	
NIV			-
Yes	-	-	
No	3.3	6.3	
No Data	96.7	93.8	

Table 4. Association of Predictor Variables and Admission of patients with (+) COPD Bundle

	30 Days	60 Days	90 Days
Admission	0 %	12.5 %	6.3 %
	p-value/Cramer's V (Risk Ratios, Confidence Interval)		
Inhaler Use	-	1.000 / 0.131 (*RR=1.17, CI=1.003-1.37)	1.000 / 0.109 (*RR=1.100, CI=0.96-1.25
Follow Up	-	1.000 / 0.098 (OR=1.94, CI=0.178-21.119 RR=1.8, CI=0.210-15.407)	1.000 / 0.020 (OR=1.17, CI=0.66-20.72, RR=1.15, CI=0.080-16.67
Smoking Cessation	-	-	-
Pulmonary Rehab	-	0.013 / 0.682 (RR=14.5, CI=3.81-55.23)	0.026 / 0.595 (*RR=1.67, CI=0.81-3.41)
MV	-	-	-
NIV	-	-	-

DISCUSSION

In this study, all the subjects under the bundle group were given instructions on all applicable interventions by trained nurse educators. The members of the non-bundle group were noted to receive instructions on home medication and follow-up instructions as per hospital protocol, but had been given variable instructions by their attending physicians on other aspects covered by the components of the COPD discharge bundle; these variable instructions were not properly documented in the discharge form. This study also illustrates that there is a significant decrease in the rate of readmissions following 30 days of discharge when the COPD discharge bundle was implemented. This outcome can have an enormous impact on COPD patients since mortality among these patients can be as high as 12.6% after the first hospitalization, and exacerbations usually re-occur within eight weeks with re-hospitalization rates of 25%-55%.[6] Different studies show that there is a high rate of re-admissions for COPD patients. Readmission after 30 days' post index admission for COPD

patients is as high as 67.9%. The risk of further readmissions per year increases after at least one readmission for COPD.[6] Furthermore, lack of proper education and coordination with the patient regarding his or her medication and follow-up are other factors that increase readmissions.[7] This type of discharge instructions is also adopted in other institutions in other countries, and observed similar results. In the United States, one report showed that providing a bundle of medical intervention, which includes: a) imparting patient education on the disease and prognosis, b) providing a checklist of evidenced based management, and c) continuing close follow- up via phone calls and outpatient visits, decreased 30-day readmission rate of patients with chronic diseases such as COPD in different institutions. Additionally, the said study recommended that a COPD bundle be included in patient-centered hospital readmissions reduction programs.[8] In another paper, two European countries which employed usual care—like the instructions given to the control group in this paper, as opposed to discharge bundle, were observed. The usual care consisted discharge from the attending physician with home medications and regular outpatient follow-up. This was compared vis-a-vis an integrated care group which included an orientation on self-management of the disease, non-pharmacologic technique, and assessment of patient's inhaler technique as well as regular follow-up via phone call to reinforce the intervention. When compared with usual care, integrated care that is started prior to discharge of patients admitted for COPD exacerbation resulted in lower rate of readmission.[9]

While there was a significant decrease in the rate of readmissions after 30 days, there was no noted significant decrease in the rate of readmissions between the control and bundle groups after 60 and 90 days. This may be due to the time frame and number of subjects recruited in this study. A trial that tracked COPD patients who were given intensive discharge instructions versus those who were not given similar instructions showed that there was a decrease in hospitalizations among the intervention group after a one year follow up.[8] A longer follow-up thus may reveal more significant results.

Therefore, based on the statistics gathered in this paper and supported by the studies, the beneficial outcomes of having a COPD discharge bundle with the previously-discussed components are apparent. Hence, it is recommended that discharge instructions to COPD patients through a bundle be institutionalized and standardized.

Compliance with inhaler use and follow-ups decreased over time was seen in the results. This may be the result of patients feeling better after the first 30 days after discharge and first follow-up. While there was no noted significant association between inhaler use and admission rate in this study, Dudvarsi reported that patients who underwent a seven-step discharge instruction during three visits had markedly improved inhaler technique, decreased respiratory symptoms and night time symptoms, and had better control of their disease.[10] In the same way, while there was no note of significant association between follow-up and admission rate in this study, another paper showed that outpatient follow-up within 30 days after discharge decreases the rate of readmission.[6] The finding of no association in inhaler use, follow-up and readmission may be due to the specific study design, wherein the two (2) groups were not simultaneously followed-up and the control group had no compliance study.

There was low compliance with pulmonary rehabilitation in this study. Reasons of patients vary from not being advised by their physicians, inconvenience and doing alternative self-exercises. The same statistics was also observed by Morso et. al. where there was low referral to pulmonary rehabilitation by attending physicians, and patients

had reservations regarding the pulmonary rehabilitation program because of their perception that they will not be able to tolerate the physical rigors required by the said program. The authors also noted that pulmonary rehabilitation was tolerable among patients with severe COPD and among those who were discharged within two weeks after being admitted due to an exacerbation.[11]

Relating these findings to our present study, the significant association between pulmonary rehabilitation and readmission may likely be explained by disease severity. The more severe the disease, the higher the rate of readmission, and the increased need for pulmonary rehabilitation to improve physical conditioning.

It is important to note that the number of subjects may have affected the outcome of the study. It is recommended that a bigger sample size and a longer follow-up time are more ideal in investigating COPD readmission rate and compliance rate. Examining both the control and bundle group simultaneously with follow-up on compliance on the COPD discharge bundle will aid in identifying which variables in the bundle affect readmission rates and outcomes.

Using the COPD discharge bundle in our local setting can help improve patient outcomes through decrease in hospital readmission. With proper discharge instructions, patients can maximize the use of their medications and understand the importance of non-medical interventions in helping them have a more stable course. These can greatly decrease patients' expenses as well as improve QOL. To our knowledge, this is the first time a COPD discharge bundle was applied in a study here in the Philippines.

RECOMMENDATION

We recommend the use of a COPD discharge bundle in a hospital setting to ensure that all patients will have uniform instructions on interventions that can decrease the number of readmissions especially after 30 days.

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Original Research

Knowledge and Attitude on Obstructive Sleep Apnea Using the OSAKA Questionnaire Among Pulmonology Training Fellows in the Philippines

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ABSTRACT

BACKGROUND: Assessing the competence of Filipino doctors in dealing with obstructive sleep apnea (OSA) has yet to be documented. This study was done to assess the competence of pulmonary fellows undergoing training since sleep-related breathing disorders (SBD) have been incorporated in the pulmonology fellowship training programs in the country to address the needs of a good and healthy sleep. The authors chose pulmonary training fellows as subjects because they had sleep medicine content incorporated into their curriculum. It is very important to check if the knowledge and skills of the subjects are at par with the objectives of the curriculum implemented by the Philippine College of Chest Physicians (PCCP) and may serve as a backbone on how future sleep training curriculum could be implemented among future Filipino doctors.

OBJECTIVE: To evaluate the knowledge and attitude of the pulmonology fellows-in-training of PCCP- accredited training institutions in years 2019-2020 about OSA.

METHODS: Ninety-five fellows from the PCCP-accredited training institutions who were undergoing training during the year 2019-2020 completed the English OSA Knowledge and Attitudes (OSAKA) questionnaire.

RESULTS: The PCCP fellows-in-training's knowledge had a mean score of 14.10 ±1.66 out of 17 items. There was significant knowledge difference (p = 0.03) by year level of fellow with the senior having higher scores. With regard to attitude, the fellows showed a mean score of 3.89 ± 0.54 out of 5 items. Though a high proportion gave importance to OSA as a clinical disorder (90%), they seemed to have a lower confidence level in managing OSA as a disorder (53.68%) and the use of CPAP therapy (49.47%). There was significant attitude score difference (p=0.02) by year level of fellow and by number of years since medical board examination (p=0.003) with the more senior and experienced fellows having higher scores. These findings showed that the knowledge and attitude of the fellows on OSA is at par with the expected training core curriculum since the training has incorporated the sleep medicine rotation under the second-year rotation curriculum hence the seniors scored higher in knowledge and attitude than their junior counterparts.

CONCLUSION: While the overall knowledge and attitude scores of the fellows on OSA seem satisfactory and at par with the objectives of PCCP training core curriculum, there is a lower confidence level in managing OSA as a disorder and the use of CPAP therapy. Hence, there appears a need to improve the fellows' knowledge and confidence regarding OSA diagnosis, physical findings and management.

KEYWORDS: *knowledge and attitude study, sleep apnea, awareness, pulmonology fellow*

INTRODUCTION

Sleep disordered breathing (SBD) is a general term used to describe a breathing disorder that occurs primarily during the sleep period. SDB has been increasingly recognized as a major contributor of various deleterious health outcomes.[1]

According to the American Association of Sleep Medicine (AASM), about 2-4% of the adult population are affected by OSA. The presence of OSA among individuals carries the risk of important deadly health outcomes. It can also impair mood, cognition, and memory.[2]

The clinical features and consequences of OSA are due to derangements that occur due to repetitive collapse of the upper airway bringing about in sleep fragmentation, hypoxemia, hypercapnia, marked swings in intrathoracic pressure, and increased sympathetic activity. Clinically, OSA can result in occurrence of daytime sleepiness, loud snoring, witnessed breathing interruptions, or awakenings due to gasping or choking in the presence of specified numbers of apneas, hypopneas or respiratory effort related arousals per hour of sleep. The greater the number of events, the greater is the risk of important health consequences.[2]

The gold standard for the diagnosis of OSA is an attended, in-laboratory polysomnogram. The presence of OSA must be confirmed and its severity determined before initiating treatment in order to identify those patients at risk of developing the complications of sleep apnea, to guide selection of appropriate treatment and to provide a baseline to establish the effectiveness of subsequent treatment.[3] Management using a multidisciplinary approach should commence once the diagnosis and severity classification of OSA has been established.

Continuous Positive Airway Pressure (CPAP) at a fixed pressure is the standard initial treatment of choice for OSA in adults. It is strongly recommended for moderate to severe OSA and recommended only for mild OSA. The rationale for using PAP in OSA is that it provides pneumatic splinting of the upper airway and is effective in reducing Apnea Hypopnea Index (AHI). For mild OSA, the following are the alternatives to CPAP: conservative or medical therapy, dental appliance or surgery.[3]

Despite OSA being a common disorder, assessment of the competence of doctors in dealing with it in the local setting have yet to be documented. The reasons for such are probably that sleep medicine is not extensively taught as a topic in medical school.

Recent studies in China and Saudi Arabia have assessed medical students' knowledge about sleep disorders, but neither study specifically measured knowledge about OSA and its treatment.[4,5] A recent study of Latin American general practitioners found no significant association between knowledge of OSA and number of years in practice suggesting an overall lack of sleep medicine content in the medical school curriculum in Latin American countries over time.[6]

In Ecuador, universities have a 40 hours of Respiratory Medicine curriculum and only 10% are dedicated to teach sleep apnea. The level of medical students' knowledge of OSA at the time of graduation, therefore, can provide insight into their future medical practice in diagnosing OSA and prepare them to be alert when a patient presents with possible sleep apnea.[7]

The deficiency of sleep medicine knowledge in medical school curriculum can lead to under recognition of sleep disorders such as OSA among physicians; thereby, failure to promote public awareness of the disease. In the Philippines, there are no studies yet noted which assessed medical students'

nor physicians' knowledge of OSA and its treatment. The lack of such research prompted us to conduct this study.

In order to expand the awareness and to develop educational strategies for physicians with regard to SBD in promoting public awareness of the disease, it is important and useful to first establish a pulmonologists' baseline familiarity with SDB and OSA. Once this has been accomplished, educational programs about SDB could be developed to address any areas of weakness in the physicians' knowledge base.

As SBD have been incorporated in the pulmonology fellowship training programs in the country to address the needs of a good and healthy sleep, our study was done to assess the competency of pulmonary fellows undergoing the training.

In our study, we will evaluate the knowledge and attitude of pulmonology fellows-in-training about OSA. This study will establish the baseline familiarity on OSA among the pulmonology fellows-in-training of PCCP-accredited training institutions. Our study is very important to check if their knowledge and skills of the respondents are at par with the objectives of the curriculum implemented by the Philippine College of Chest Physicians (PCCP), and may serve as a backbone on how future sleep curriculum could be implemented or enhanced.

The PCCP-accredited pulmonary fellowship training is for most a two-year program. The competency-based core curriculum in Philippine Adult Pulmonary Medicine Fellowship Training incorporated the sleep medicine rotation under the second-year rotation curriculum to allow an individual trainee to obtain wider exposure to different particular areas of interest or in areas that can be pursued in further subspecialty training. The choice of specialty rotations is on an elective basis since the basic skills and competencies are already expected to be achieved in the general rotation. The objectives of sleep medicine rotation included the following: (1) to learn basic concepts of sleep physiology and pathophysiology of sleep and sleep disorders; (2) to perform and interpret the diagnostic tests used to evaluate patients with SBDs; and (4) to recognize, diagnose and treat SBD (8). Our study will also establish the current picture of OSA knowledge among training fellows in pulmonary medicine in all institutions which will assist in formulating programs to help educate doctors in the future.

To date, only four measuring tools have been developed and validated to measure physicians' knowledge on sleep disorders. The ASKME Survey that was published last 2001 by Zozula et al. is a well-validated tool that assesses knowledge of medical students, students in clinical psychology, nursing and other health-related professions (i.e., school nurses, practicing physicians and accredited sleep specialists) about sleep but does not focus exclusively on symptoms, risk factor identification, suspicion of the disease, initial diagnosis and treatment options, and that the questions were too general, involving both adults and children.[9]

The OSAKA (obstructive sleep apnea knowledge and attitudes) study questionnaire by Schotlanda, et. al. that was published last 2003 is also a well-validated tool that focuses specifically on OSA knowledge and attitude rather than other forms of SBD.[10] OSAKA-KIDS which was published last 2005 by Uong, et. al. focuses exclusively on OSA among children.[11]

The study by Southwell et. al. that was published last 2008 is a modified version of the OSAKA questionnaire that focuses mainly at how frequently cardiologists are screening for OSA.[12] A low physicians' knowledge and clinical suspicion about OSA leads to serious under diagnosis. Few studies have examined whether length of physicians' practice experience is associated with

knowledge and attitudes about OSA, and its treatment.

Our study utilized the OSAKA questionnaire which is a validated English-language questionnaire that was developed to assess physicians' knowledge and attitudes regarding the identification and management of patients with OSA.[13] The English version of the questionnaire was used because English is an official language of the Philippines and physicians' responses would not be affected by a language barrier. The cohorts of patients utilized by the questionnaires were physicians associated with the Washington University Physicians Network (WUPN). It was initially piloted by one group consisting of internal medicine hospitalists at Barnes-Jewish Hospital and the other of physicians attending a WUPN sponsored lecture on OSA (the questionnaire was administered to this group of physicians prior to the OSA lecture). The type of validity measure for reliability analysis to assess internal consistency of factor items used was Cronbach alpha.[13]

OBJECTIVE

To evaluate the knowledge and attitude of the pulmonology fellows-in-training of PCCP- accredited training institutions in years 2019-2020 about OSA. More specifically, (1) to describe the demographic profiles of the study population (pulmonology fellows-in-training of PCCP-accredited training institutions) about OSA, (2) to conduct a knowledge and attitude survey on pulmonology fellows-in-training of PCCP-accredited training institutions about OSA, and (3) to determine if the knowledge of pulmonology fellows-in-training of PCCP-accredited training institutions is at par with the objectives of PCCP training core curriculum for training institutions.

METHODS

We used the pre-tested and validated English OSAKA questionnaire to assess the knowledge and attitude of the pulmonology fellows-in-training of PCCP-accredited training institutions in years 2019-2020 towards OSA awareness. The OSAKA questionnaire includes 18 knowledge items and five questions related to attitudes about OSA (Supplementary Table 1). The knowledge items covered different OSA domains about epidemiology, pathophysiology, symptoms, diagnosis, and treatment. Options for answers to knowledge questions were "true," "false," and "do not know." A "do not know" answer is scored as an incorrect response. Total knowledge scores were computed as the percentage of correct answers to the 18 knowledge questions and ranged from zero to 100%. Upon our discretion, one question was disregarded due to the question being outdated. This question was about epidemiologic information on OSA. Two attitude questions asked about importance of OSA and responses were scored on a 5-point Likert scale, ranging from not important [1] to extremely important [5]. The other three attitude questions dealt with one's confidence in diagnosing and treating patients with OSA, and responses were scored from strongly disagree [1] to strongly agree [5] (6). Using modified Bloom's cut-off points, we categorized patient's overall knowledge as good if the score was between 80-100% (13.6-17 points), moderate if the score was between 50-79% (8.5-13.43 points), and poor if the score was less than 50% (8.33 points). Using Bloom's cut-off points, we also categorized the overall level of attitude, as positive if the score was 80-100% (4-5 points), neutral if the score was 60-79% (3-3.95 points) and negative if the score was less than 60% (3 points).[14]

After obtaining written informed consent from the respondents, we distributed the questionnaires in printed form to the respondents via a face-to-face meeting format and they were accomplished by the respondents under our supervision. We did it to enhance the response rate and to maintain honesty on the part of the respondents.

We treated all data with privacy and confidentiality. The joining in the study of the participants did not affect his/her status and evaluation as a fellow or trainee. Sleep fellows-in-training were excluded from the study since they were considered experts on the subject matter. We included all fully completed questionnaires in the analysis. We performed data analysis using Stata SE Version 13. We summarized quantitative variables as mean and standard deviation, while qualitative variables were tabulated as frequency and percent.

To help us target areas for sleep education, we compared and analyzed between -fellow characteristics and knowledge and/or attitude scores using independent t-test for normal distribution of quantitative variables and Fischer exact test for the qualitative variables. We used analyses of variance (ANOVAs) to examine differences in the mean scores for knowledge and attitudes (importance of OSA and confidence) by 3 or more variables such as the number of years since medical board examination. We calculated the correlation between knowledge score and attitude score using the Spearman correlation coefficient. We also compared and correlated fellows who had low knowledge and attitude scores to their characteristics using chi square test for 2 ordinal variables and logistic regression analysis for 3 or more ordinal variables. All p values were two-tailed, and p values below 0.05 were considered statistically significant.

The Manila Doctors Hospital Investigational Review Board approved the protocol for our study. It did not involve any new studies of human or animal subjects performed by any of the authors. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 and 2008.

RESULTS

Of 97 pulmonology fellows, 95 out of 97 completed and returned the questionnaires, and formed our study sample. One fellow was excluded from the study due to being the author of the paper. Another fellow was also excluded upon our discretion due to him/her giving incomplete answers to the questionnaires. Our subjects' demographic data, year level, number of years since medical board examination, presence of sleep laboratory and fellowship were shown in Table 1. We detailed the characteristics of the 95 pulmonary fellows in training using Table 1. The mean age was 33.23 +/- 3.17 years old. There was a total of 53 (55.79%) first year fellows in comparison to 42 second year fellows (44.21%). Majority of the fellows took their medical board examination 6-10 years ago (52.63%). Seventy (73.68%) fellows had sleep laboratory in their training institution, however, only 42 (44.21%) fellows had sleep fellowship in their institution.

Table 1. Main characteristics of the PCCP fellows-in-training who completed the OSAKA questionnaire

Variable (n = 95)	Mean +/- SD or n (%)
Age, years	33.23 +/- 3.17
Gender	
Male	44 (46.32)
Female	51 (53.68)
Year Level	
First Year	53 (55.79)
Second Year	42 (44.21)
Years Since Medical Board Examination	
</= 5 years	37 (38.95)
6-10 years	50 (52.63)
>10 years	8 (8.42)
Presence of Sleep Laboratory	70 (73.68)
Presence of Sleep Fellowship	42 (44.21)

Note: Values are displayed as mean +/- standard deviation and mean +/- percentage of the mean
N, number of respondents; SD, Standard deviation; n (%), Percentage of the mean

Out of the 17 knowledge questions, the number of correct answers ranged from 8 (1.05%) to a perfect score of 17 (7.37%). The mean score was 14.10 ±1.66 for all participants corresponding to 82.97 ± 9.80 % mean corrected response rate. Overall, the median (interquartile range [IQR]) knowledge score was 13 (8-17). Only 2 fellows scored lower than 60% for the knowledge items as shown in Table 2.

Table 2. Distribution of knowledge scores among PCCP fellows

Number of Fellows	Total Knowledge Score	% Knowledge Score
1	8	47.06
1	10	58.82
3	11	64.71
12	12	70.59
10	13	76.47
29	14	82.35
22	15	88.24
0	16	94.12
7	17	100

Note: Values are presented as percentage of total knowledge score out of total 17 question items

As shown in Table 3, only one question was answered correctly by all respondents. The item answered correctly by all respondents was, "Cardiac arrhythmias may be associated with untreated obstructive sleep apnea." (Item 18- Complications). The three items that were answered incorrectly by most respondents were, "Laser-assisted uvuloplasty is an appropriate treatment for severe OSA," (54.74%) (Item 8 – Treatment), "Women with obstructive sleep apnea may present with fatigue alone" (35.79%) (Item 1 - Symptom), and "Uvulopalatopharyngoplasty is curative for the majority of patients with obstructive sleep apnea" (35.79%) (Item 2 – Treatment). The proportions of fellows answering each item correctly varied widely. The internal consistency of the 17 knowledge questions yielded a Cronbach's alpha of 0.52, which indicates a lower internal consistency, meaning there is poor interrelatedness between tests questions. It may also mean that there aren't enough questions on the test and adding relevant items might help[20]. This is consistent with the OSAKA questionnaires asking different aspects of knowledge on OSA.

Table 3. Percentage of correct answers among PCCP fellows-in-training based on the following knowledge items: epidemiology, pathophysiology, symptoms, physical findings, diagnosis, complications, risk factors, and treatment

Item (n = 17)	n (%)
1 (Symptoms)	61 (64.21)
2 (Treatment)	61 (64.21)
4 (Symptoms)	78 (82.11)
5 (Complications)	93 (97.89)
6 (Diagnosis)	86 (90.53)
7 (Treatment)	65 (68.42)
8 (Treatment)	43 (45.26)
9 (Pathophysiology)	92 (96.84)
10 (Risk Factors)	91 (95.79)
11 (Physical Findings)	90 (94.74)
12 (Risk Factors)	89 (93.68)
13 (Complications)	91 (95.79)
14 (Physical Examination)	67 (70.53)
15 (Epidemiology)	84 (88.42)
16 (Treatment)	76 (80.00)
17 (Diagnosis)	78 (82.11)
18 (Complications)	95 (100)

Note: Values are presented as the number of subjects and the percentage of correct answers by the subjects
N, number of items; n (%), number of subjects who scored correctly (percentage of correct answers) Please note that item 3 has been excluded from the study.

With regard to attitude items, the median (IQR) total score was 3.94 (1-5). The mean ± SD scores on the attitude segment of the OSAKA questionnaire was 3.89 ± 0.54 (Table 4).

Table 4. Responses of the PCCP fellows-in-training on the attitude segment of the OSAKA questionnaire

Item (n = 5)	Mean +/- SD
1 (OSA as a clinical disorder)	4.32 +/-0.64
2 (Identifying patients with possible OSA)	4.34 +/- 0.66
3 (Identifying patients at risk for OSA)	3.94 +/- 0.76
4 (Managing OSA)	3.45 +/- 0.80
5 (Managing OSA using CPAP therapy)	3.4 +/- 0.79

Note: Values are displayed as mean +/- standard deviation;
N, number of respondents; SD, Standard deviation

Out of the 95 fellows, 90.53% of the participants felt that OSA was a very important or extremely important clinical disorder. Likewise, 89.47% felt identifying patients at risk for OSA was very important or extremely important. When asked about patients at risk for OSA, 78.95% of the fellows felt confident identifying those patients, but only 53.68% felt confident in managing patients with OSA, and only 49.47% felt confident in managing patients with Continuous Positive Airway Pressure (CPAP) therapy (Figure 1). The internal consistency of the five attitude questions yielded a Cronbach's alpha of 0.78. This is indicative of an acceptable internal consistency[20], neither meaning the questions are highly nor poorly interrelated.

Table 5 shows the factors associated with higher knowledge and attitude regarding OSA among the fellows in training. No difference was found on total knowledge score by gender (p = 0.96), number of years since medical board examination (p = 0.37), presence of sleep laboratory (p = 0.45) and sleep fellowship (p = 0.22). However, there was note of significant difference in knowledge score by year level, with second years scoring higher scores than their first-year counterparts (p <0.03). With regard to attitude, there were no differences in attitude scores when analyzed by gender (p = 0.73), presence of sleep laboratory (p = 0.66) and presence of sleep fellowship (p = 0.10).

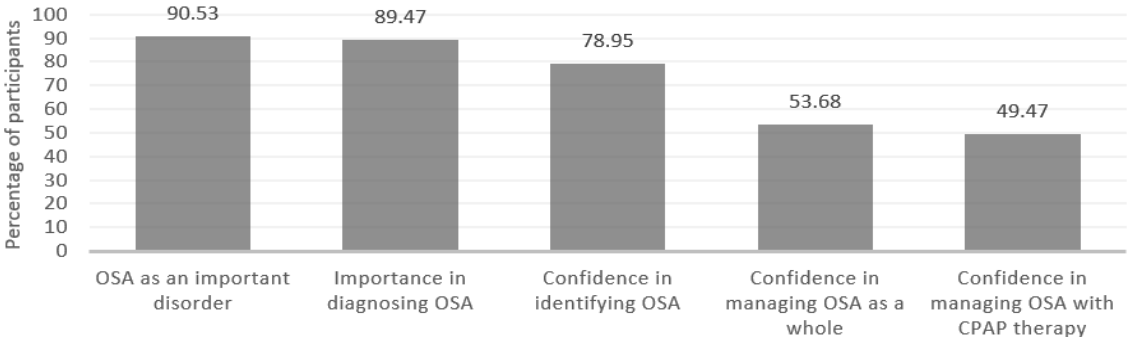


Figure 1.Percentage (%) of the 95 PCCP fellows-in-training who answered regarding attitude on OSA as an important disorder, importance in diagnosing it from not important [1] to extremely important [5], OSA as an importa nt disorder, importance in diagnosing it, confidence in identifying it and confidence in managing it as a whole and with CPAP therapy from strongly disagree [1] to strongly agree on

Table 5.Knowledge and attitude scores of PCCP fellows-in-training, by subject characteristics

Variable (n = 95)	Knowledge Mean +/- SD	P-Value	Attitude Mean +/- SD	P-Value
Gender		0.96†		0.73†
Male	14.11 +/- 1.50		3.87 +/- 0.57	
Female	14.10 +/- 1.81		3.91 +/- 0.51	
Year Level		0.03*†		0.02*†
First Year	13.77 +/- 1.84		3.77 +/- 0.52	
Second Year	14.52 +/- 1.33		4.03 +/- 0.52	
Years Since Medical Board Examination		0.37 §		0.003* §
</= 5 years	13.81 +/-1.68		3.66 +/- 0.48	
6-10 years	14.26 +/- 1.64		4.04 +/- 0.55	
>10 years	14.5 +/- 1.77		4 +/- 0.34	
Sleep Laboratory		0.45†		0.66†
With Sleep Laboratory	14.0.3 +/- 1.71		3.90 +/- 0.49	
Without Sleep Laboratory	14.32 +/- 1.55		3.85 +/- 0.65	
Sleep Fellowship		0.22†		0.10†
With Sleep Fellowship	14.28 +/- 1.66		3.99 +/- 0.40	
Without Sleep Fellowship	13.88 +/- 1.67		3.81 +/- 0.61	

Note: Values are displa yed as mean ± standard deviation; † Independent T-test; § ANOVA.
N, number of respondents; SD, Standard deviation; p values were computed using the independent T-test and ANOVA; all p-values with * are statistically significant

When attitudes toward OSA were analyzed by knowledge scores, we found a very weak correlation and the values were statistically insignificant (rs= 0.16, p= 0.12) (Figure 2).

We performed a subgroup analysis for subjects who had knowledge scores <88.24% (see Table 2) and attitude and correlation was done among them. Low knowledge score is defined as score less than 50%, but since only 1 respondents scored less than that, and only 3 respondents scored less than 70%, we decided to take the lower range of mean percentage score where majority of the participants' score were situated, which is less than 88.24%. With regard to level of attitude, low score is defined as having a neutral and negative level of the attitude (<4 points).

We presented summarized graphical figures (Figures 3, 4, and 5) on a subgroup analysis of the factors associated with lower knowledge and attitude regarding obstructive sleep apnea among the fellows-in-training who scored low. The following results were noted: Being a first-year fellow has a two-fold probability of having a low attitude score on managing OSA as a whole and managing OSA using CPAP therapy compared to second-years (Figure 3). Fellows-in-training having a sleep laboratory and sleep fellowship in their training institution are 2-4 times more likely to score low on knowledge and attitude (Figures 4 and 5). All values were statistically insignificant.

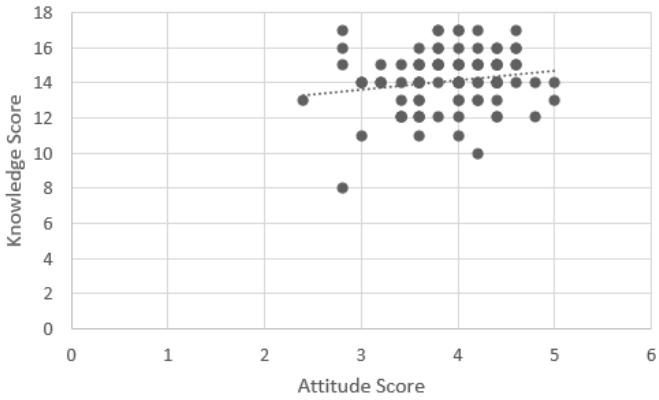


Figure 2.Correlation between knowledge and attitude scores of PCCP fellows-in-training. Scatter plot presented using Spearman Correlation Coefficient

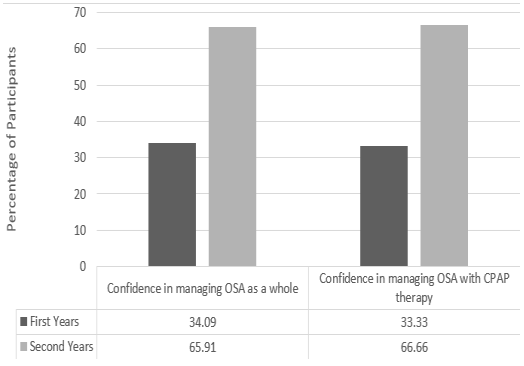


Figure 3.PCCP Fellows-in-training who scored low in attitude on managing OSA based on year level. All values were statistically insignificant.

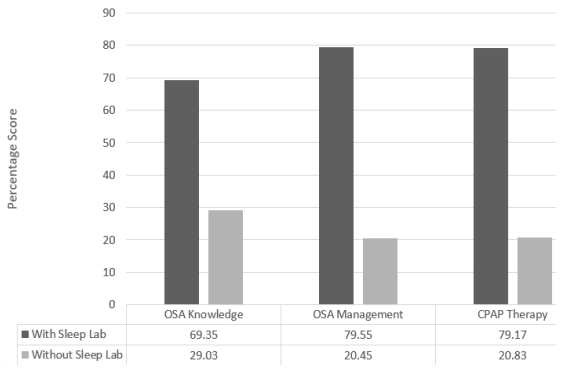


Figure 4.Percentage (%) score of the PCCP pulmonology fellows-in-training who scored low in knowledge and attitude on OSA management based on the presence of sleep laboratory in their institution. All values were statistically insignificant.

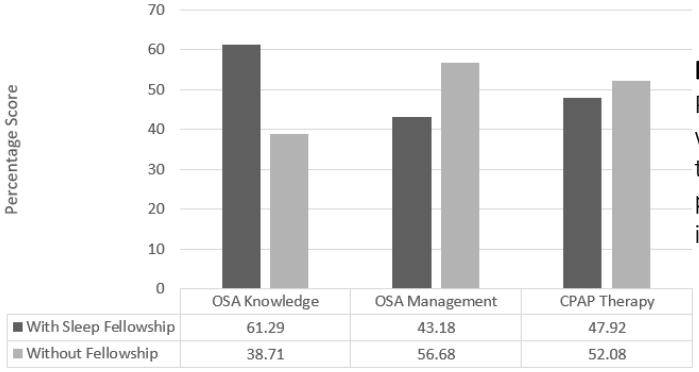


Figure 5.Percentage (%) score of the PCCP pulmonology fellows-in-training who scored low in knowledge and attitude on OSA management based on the presence of sleep fellowship in their institution.

The full numerical data presentation of this analysis including the p- value and prevalence ratio (PR) are presented in Supplementary Data Tables 2-5. It can be accessed through this link: https://bit.ly/OSAKASuppTables

Another stratification analysis was done based on percentage of pulmonology fellows answering each knowledge item incorrectly and it was compared with the respondent's characteristics in order to determine how each question has been difficult for the subjects. We disregarded Item 18 from the analysis since all subjects answered it correctly. The item was, "Cardiac arrhythmias may be associated with untreated obstructive sleep apnea. We again presented a summarized graphical figure on that analysis (Figures 6, 7, 8, 9, and 10). Our analysis revealed the following as shown in supplementary tables 3, 4 and 5. Being a first-year fellow has up to six- fold (PR = 1.13: CI 0.43,7.54, PR = 1.38: CI 0.61,3.14, PR = 2.97, CI 0.90,9.77, PR 5.94: CI 1.27,27.73) chance of answering incorrectly questions about OSA diagnosis and treatment and it was statistically significant (p = 0.0002, p = 0.02, p = 0.02, p = 0.003). Also, being a first-year fellow has an infinite risk of answering incorrectly question about OSA physical findings which was significant (p = 0.04); however, they have a 33% lower probability (PR = 0.33: CI 11,3.73) of scoring incorrectly about OSA symptoms which is also significant (p = 0.02) (Refer to Supplementary Table 3.)

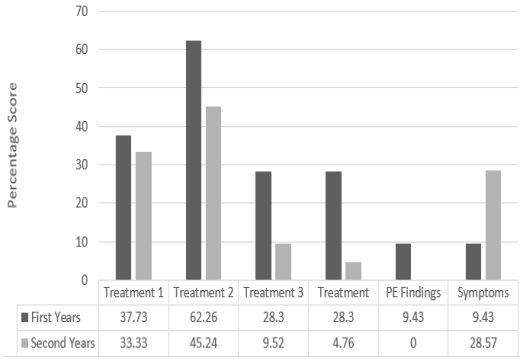


Figure 6. Correlation between different percentage (%) knowledge score <88.24% and attitude score <4 among the PCCP fellows-in-training. Scatter plot presented using Spearman Correlation Coefficient. Correlation between the percentage (%) knowledge scores <88.24% and attitude score <4 among the 95 PCCP fellows in training. There was a weak correlation found and it was statistically insignificant (rs = 0.0410, p = 0.7437).

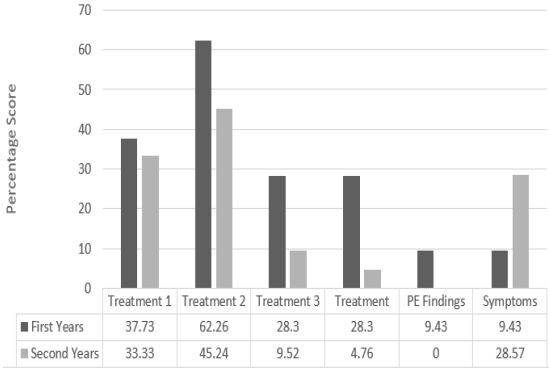
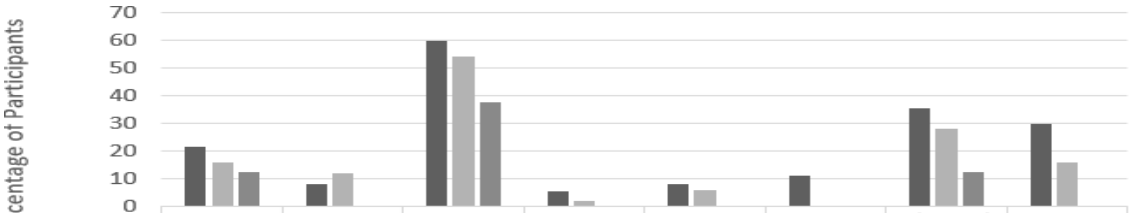


Figure 7. Percentage (%) score of the 95 years 2019-2020 PCCP pulmonology fellows in training who answered incorrectly each item based on year level. All were statistically significant.

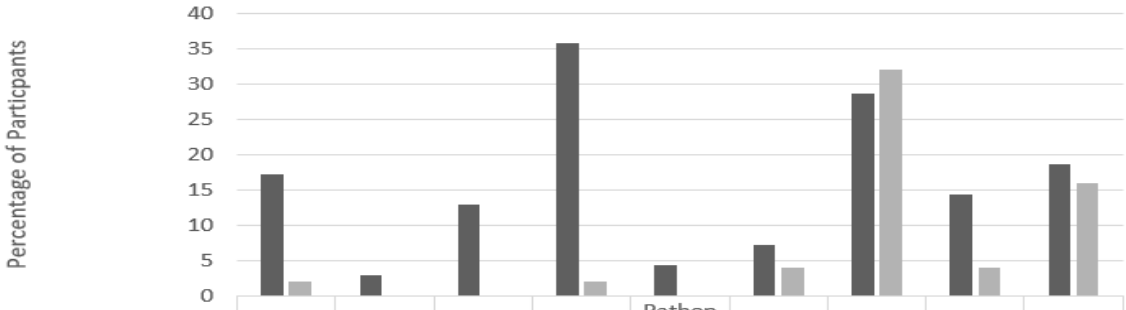
We conducted the association between the number of years since medical board examination and the percentage of each item answered incorrectly. It showed that majority of those fellows who took their board examination within 10 years has a 2-14-fold chance of answering incorrectly on different knowledge aspects of OSA than those who took it more than 10 years ago. Yet, only the question about OSA physical examination was statistically significant (PR=3.79: CI 0.42,34.27: p=0.04) (Refer to Figure 8).

Being a fellow in an institution with sleep laboratory has the highest risk of answering incorrectly majority (64.7%) of the questions up to 17-fold times to an infinite in the knowledge aspect, but results were insignificant (Refer to Figure 9). Being a fellow in an institution with sleep fellowship also has a 3-fold (PR=2.52: CI 1.00630) probability of answering incorrectly questions about treatment and result was significant (p = 0.003). Other knowledge questions affected by the presence of sleep fellowship included OSA diagnosis, pathophysiology and epidemiology but the results were insignificant (Refer to Figure 10). The full numerical data presentation of this analysis including the p- value and prevalence ratio (PR) are presented in Supplementary Data Tables 3-5.



	Symptom	Diagnosis	Treatment	Pathophysiology	Risk Factors	Complications	Physical Examination (Significant)	Treatment
</=5 years	21.62	8.11	59.45	5.41	8.11	10.81	35.14	29.73
6-10 years	16	12	54	2	6	0	28	16
>10 years	12.5	0	37.5	0	0	0	12.5	0

Figure 8.Percentage (%) of PCCP pulmonology fellows in training who answered incorrectly each item based on the number of years since medical board. Only the question about OSA physical examination was statistically significant (PR=3.79: CI 0.42,34.27: p=0.04).



	Symptom	Complications	Diagnosis	Treatment	Pathophysiology	Risk Factors	PE	Epidemiology	Diagnosis
With Sleep Lab	17.14	2.86	12.86	35.71	4.29	7.14	28.57	14.28	18.57
Without Sleep Lab	2	0	0	2	0	4	32	4	16

Figure 9.Percentage (%) of PCCP pulmonology fellows in training who answered incorrectly each item based on the presence of sleep laboratory. The results were insignificant.

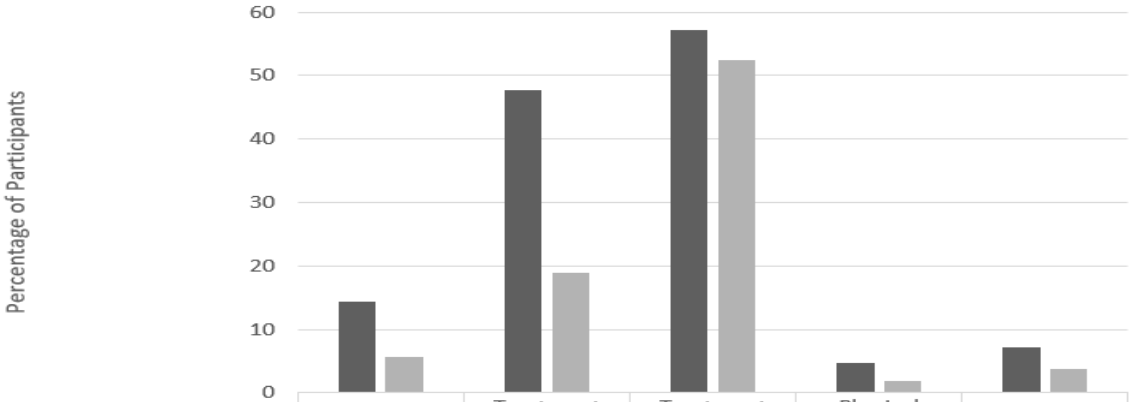


Figure 10.Percentage (%) of PCCP pulmonology fellows in training who answered incorrectly each item based on the presence of sleep fellowship. The result on OSA treatment was significant (p=0.003) .

DISCUSSION

Although SBD has been increasingly recognized as a major contributor of various deleterious health outcomes, the lack of knowledge among physicians on OSA contributes to its under diagnosis and treatment. In our study, we tested the knowledge and attitude of pulmonology fellows-in-training regarding OSA. To our knowledge, this is the first survey to explore the knowledge and attitudes regarding OSA among pulmonology fellows in the Philippines.

Our study found that the majority of participants possess good knowledge about obstructive sleep apnea, based on the modified Bloom's cut-off points with a mean score 14.10 ±1.66 for all participants corresponding to 82.97 ± 9.80 % mean corrected response rate. The reason for such is that our participants are pulmonology fellows-in-training and that sleep medicine content has been incorporated into their curriculum during their training.

Majority of the items answered incorrectly by the subjects were about treatments (45.26% and 64.21%) and atypical symptoms (64.21%) of OSA (Table 3).This suggests that the training committee should have the fellows focus more on such knowledge aspects.

A higher knowledge score was found to be associated with the level of training, with the second years scoring higher than the first years (14.52 +/- 1.33 vs 13.77 +/- 1.84 p = 0.03) while it was not associated with sex, presence of sleep laboratory and sleep fellowship in their institution.

The result of our study indicated that the training institutions are achieving the objectives of the training program curriculum discussed and enumerated in the introduction of the study, wherein the sleep medicine rotations were incorporated in the second-year curriculum are achieving the objectives of the training program curriculum.

There was also no significant difference in total OSA knowledge by their number of years since medical board examination.

Regarding attitudes towards obstructive sleep apnea, majority of the participants (>60%) were able to feel the importance of OSA as a disease, and were able to confidently identify patients with OSA; however, only less than two-thirds of the respondents

can confidently manage these patients. The overall level of attitude was neutral with a mean score of 3.89 ± 0.54.

A higher attitude score was found to be associated with the level of training, with the second years scoring higher than the first years (4.03 +/- 0.52 vs 3.77 +/- 0.52 p= 0.02) while it was not associated with sex, presence of sleep laboratory and sleep fellowship in their institution. However, there was a significant correlation between attitude and the number of years since medical board examination (4 +/- 0.34 vs 4.04 +/- 0.55, 3.66 +/- 0.48 p= 0.03). We hypothesized that such occurrences might be due to longer practicing physicians having higher confidence level. Other postulated reason is that there are many confounding factors than can affect the study such as background knowledge from medical school among the respondents, number of cases seen in the institution, actual training curriculum employed per institution, and the presence of mentors who specialized in Sleep Medicine.

Further sub analysis of our study found that though insignificant, a first-year fellow has a two-fold probability of having a low attitude score on OSA management and CPAP therapy compared to his/her seniors. Having a sleep laboratory and sleep fellowship in one's training institution is 2-4 times more likely to score low on knowledge and attitude. This proved that being trained in an institution with the presence of sleep laboratory and sleep fellowship does not necessarily make a fellow more superior in knowledge and attitude about OSA than the others. In fact, the fellowship training committee has ensured that all fellows regardless of their institution receive adequate knowledge about OSA. Those fellows whose institutions did not provide any sleep laboratory nor sleep fellowship are required to rotate in another institution with such criteria.

To determine how the questions have been difficult for the subjects, another stratification analysis was done. It showed that being a first-year fellow has up to six-fold chance of answering incorrectly questions about OSA diagnosis and treatment and it was statistically significant (p = 0.0002, p = 0.02, p = 0.02, p = 0.003). Being a first-year fellow also has an infinite risk of answering incorrectly question about OSA physical findings which was significant (p = 0.04). This means that the chance of a first year in answering questions regarding OSA physical findings is 100% likely to be incorrect. The first-years also have a 33% lower probability (PR = 0.33 CI 0.11,3.73) of scoring incorrectly about OSA symptoms which is also significant (p = 0.02). This could reflect the chances that majority of the information given about OSA prior to pulmonary sleep fellowship contains mostly about symptoms rather than other aspects like physical findings, diagnosis or treatment.

Majority of those fellows who took their board examination within 10 years have a two-14-fold chance of answering incorrectly on different knowledge aspects of OSA than those who took it more than 10 years ago. The question about OSA physical examination being only statistically significant (PR = 3.79 CI 0.42, 34.27: p=0.04). This would mirror an explanation that older fellows have a higher knowledge than younger ones from clinical experiences; though a pre-baseline assessment examination on OSA is warranted to prove this possible explanation again.

Being a fellow in an institution with sleep laboratory has the highest risk of answering incorrectly majority (64.7%) of the questions up to 17-fold times to an infinite in the knowledge aspect, but results were insignificant. Being a fellow in an institution with sleep fellowship also has a three-fold (PR = 2.52 CI 1.00,6.30) probability of answering incorrectly questions about treatment and result was significant (p = 0.003). Other knowledge questions affected by the presence of sleep fellowship included OSA diagnosis, pathophysiology and epidemiology but

the results were insignificant. Our statement proves that all fellows regardless of their training institution have received the same amount of knowledge on OSA based on the OSAKA questionnaires. Fellows training in institution with sleep fellowship scoring low on the management aspect are hypothesized to have some overreliance of the fellows-in-training on their senior "sleep fellow" in managing their OSA patients.

Our study demonstrated a higher level of knowledge and attitude scores among pulmonology fellows in training as evidenced using the Bloom's cut-off points. A number of different studies were conducted to test the knowledge and attitudes of physicians on OSA using the OSAKA questionnaires.[15-22] At present, there is no study yet conducted on pulmonology fellows outside the Philippines.

Comparing our study to that of a previously published study from Nigeria in 2015 that also used the OSAKA questionnaire, it showed a staggering difference in mean knowledge score among the subjects in comparison to our study participants. The mean knowledge score among the Nigerian physicians was 10.7 ± 2.6 (out of a maximum possible of 18) corresponding to 59 ± 14.4 % knowledge. This is in contrast to our subjects who scored a higher mean knowledge of 14.10 ±1.66 corresponding to 82.97 ± 9.80 % mean corrected response rate. The mean score on the attitude segment of the Nigerian physician was 3.4 ± 0.6 (maximum possible score of 5) for all participant in comparison to our fellows who had a higher mean attitude score of 3.89 ± 0.54.[15]

Another study done among Italian anesthesiologist showed that their knowledge items achieved only a mean corrected response rate of 66% ± 0.14% in comparison to our 82.97 ± 9.80 % mean corrected response rate.[16]

Another recent study published last June 2020 done among primary care physicians in Middle East and North African region showed only a mean total score of 12.6 (2.5) with internal medicine specialists showing the highest mean knowledge score of 14.1[2,3] similar to our subjects. Another finding in this study highlighted an important result in terms of physicians' attitudes similar to our study wherein majority (78%) of the physicians felt confident in identifying patients with OSA, but only few (26%) felt confident managing them with continuous positive airway pressure, with weak correlation between knowledge and attitude score. This study indicates a gap in knowledge that is subsequently translated upon practice, like lack of training in managing OSA using CPAP as well as application of skills and hands-on training on CPAP pressure calibration, mask fitting and troubleshooting.[17]

Two recent study by Navin Kumar Devarak and Al Saleem et. al. that was published last February 2020 and May 2020 conducting the OSAKA questionnaires showed similar findings among primary care physicians in Malaysia and Saudi Arabia. The mean total knowledge score was 11.6 (+/- 2.8) on the study by Devarak and only a median knowledge score of 10 on the study by Al Saleem et. al. with majority of respondents having positive attitude towards the importance of OSA but lacking confidence in managing it.[18,19]

Another study in Egypt using specialist physicians in critical care units noted a mean score of only 10.05 +/- 2.3 with a 33.3 % adequate response, while the mean score for attitude assessment was 3.75 +/- 1.22 with 59.3% adequate response. The mean knowledge and attitude score was highest among chest physicians (12.5 +/- 2.42; 5 +/- 0.78) but was still lower than our study group, and also those physicians who are affiliated in tertiary hospitals where sleep studies may be available.[20]

A significantly low score of only 9.85 +/- 3.9 on the OSAKA questionnaire was noted in this most recent study published last January 2021 conducted in Iran where volunteer participants are from the Iranian Residency Entrance Examination conducted last March 8, 2018, which warrants a comprehensive training courses in sleep medicine during residency.[21]

A different finding was found in cross-sectional studies conducted in Africa. This study showed that the median OSAKA knowledge scores was 83.3% (IQR 77.8-88.9) among South African physicians.[22] This is slightly higher than our fellows' score of 82.97 ± 9.80 % mean corrected response rate. However, this study could have some bias since the participants were contacted to receive online/paper-based OSAKA questionnaire at their free time with their prior access to the questionnaires. This is in contrast to our study and the above other studies wherein the questionnaires were given without prior knowledge of the participants; therefore, they have no prior information that a survey on OSA will be conducted hence avoiding possibility of participants to study before the actual conduct of the survey.

There was no correlation between knowledge and attitude scores ($r_s = 0.16$, $p = 0.12$). Our study suggests that despite understanding OSA-related problems, fellows are not confident in selecting the best method for its management.

Interestingly, our study again is in contrast to another study on Italian anesthesiologist wherein their correlation study confirmed that gender and professional title were statistically associated with the attitude score ($F = 14.6$, $p = 0.0002$ for gender; $F = 4.72$, $p = 0.0099$ for professional title). This might reflect some self-protection or social desirability bias among Italian anesthesiologist[13], which means that a person of a higher professional status may try to mask his low knowledge by improving his attitude scores.

Even if our fellows scored high in knowledge on OSA, a lower confidence in managing patients with them can be barriers to quality care for OSA patients and can be possibly attributed to a lack of exposure to sleep medicine in undergraduate and post-graduate medical education curricula here in the Philippines.

Our study had some limitations. It was a cross-sectional survey, and we cannot infer causation from any of the associations we observed. Several confounders that might likely affect the result needs to be gathered and analyzed. A pre-fellowship baseline examination is also warranted for future studies to justify basic knowledge of the trainees prior to fellowship. The strengths of our study include the use of a validated questionnaire.

We have determined that the knowledge of pulmonology fellows-in-training of PCCP Accredited Training Institution is at par with the objectives of PCCP training core curriculum for training institutions; however, supervision and strengthening the fellows' knowledge and confidence regarding OSA diagnosis, physical findings and particularly management is still warranted.

CONCLUSION

As previously reported in many different studies, it is noteworthy that our study showed that knowledge level towards obstructive sleep apnea among pulmonology fellows of PCCP accredited training institutions is good when compared with medical students or physicians in different fields based on different studies.[12-19] This is due to the fact that pulmonology fellowship has sleep medicine content incorporated into their curriculum. Additionally, it was noted in our study that being a senior pulmonology fellow is associated with higher knowledge and attitude scores than their junior

counterparts who also had a high chance of answering the questions incorrectly, highlighting that the trainings of different institutions are at par with the program curriculum. Duration of practice as a Filipino physician does not affect the overall knowledge score on OSA but rather affects their attitude score, implying some form of confidence among Filipino physicians. However, in the context of the difficulty of each question showed that fellows who took their board examination within 10 years has a higher chance of answering incorrectly on different knowledge aspects of OSA than those who took it more than 10 years ago.

The presence of sleep laboratory and sleep fellowship did not affect the overall knowledge and attitude of the pulmonology fellows with regard to OSA. Likewise, its presence does not necessarily make a fellow more superior in knowledge and attitude about OSA. The information given to the fellows about OSA prior to their pulmonary sleep fellowship probably contains mostly about symptoms rather than other aspects of the disease. But this cannot be fully justified unless exploration and analysis of confounding factors are done that might affect the result of the study.

Our study also showed that while the overall knowledge and attitude scores of the fellows on OSA seem satisfactory, there appears a need to improve their knowledge and confidence regarding OSA diagnosis, physical findings and management.

We recommend the following future studies be done among the training fellows: (1) to conduct a pre-fellowship baseline examination on OSA among the new fellows; (2) to explore and analyze other confounding factors as previously enumerated which might affect the result of this study; and, (3) to conduct an obstructive sleep apnea knowledge and attitude among other specialties and to further enhance the supervision of the pulmonology fellowship training focusing more on physical findings, treatment and management of obstructive sleep apnea.

DISCLOSURE

This study was self-funded by the authors and did not receive any grant from any institution or pharmaceutical company.

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Systematic Review & Meta-analysis

The Utility of Lung Ultrasound-Guided Protocol in Decreasing Intensive Care Unit Mortality Among the Critically Ill Patients

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ABSTRACT

BACKGROUND: Point-of-care ultrasound has been used with greater acceptance in the intensive care unit (ICU). Currently, various ICU protocols use bedside ultrasound in the care of a critically ill patients. However, literature presents conflicting evidence regarding its utility in improving survival among critically ill patients.

OBJECTIVE: To determine ICU mortality rate of lung ultrasound guided protocol versus standard of treatment.

METHODS: A systematic review and meta-analysis of all randomized and non-randomized trials determining ICU mortality between standard of care and the addition of a lung ultrasound-guided protocol was performed. The following data were extracted: (1) ICU mortality, (2) length of stay in the ICU, (3) duration of mechanical ventilation, (4) fluid infusion volume/fluid balance, and (5) number of additional radiographs used.

RESULTS: Five studies were included in the study. All included studies involved ICU patients with lung ultrasonography as a supplementary diagnostic tool and ICU mortality as a reported outcome. The addition of lung ultrasonography was associated with a decreased length of stay in the ICU (RR -0.88; 95% CI -1.55, -0.21; I^2 26%), number of chest radiographs (RR -1.95; 95% CI -3.00, -0.91; I^2 40%) and chest CT scans (RR -0.23; 95% CI -0.35, -0.12; I^2 36%). However, its use was not associated with improved ICU mortality (RR 1.06; 95% CI 0.83, 1.36; I^2 0%) and duration of mechanical ventilation.

CONCLUSION: Lung ultrasound is accessible, readily available at bedside, efficient and safe procedure which can potentially augment current standard of care through real-time assessment of management, outcomes, and complications.

KEYWORDS: *lung ultrasonography, critical illness, intensive care unit*

INTRODUCTION

Lung ultrasound is a non-invasive imaging modality that allows for quick visualization and assessment of structures within the thorax. It works by acoustic impedance wherein reflected waves travelling at different speeds processed by the transducer as different types of tissue. It can be performed easily without the ionizing radiation provided by the chest radiograph and lung computed tomography (CT) scan, hence, it has been used in the rapid assessment of the thorax to diagnose pathology and to implement and monitor treatment.[1,2]

Critically ill patients present dynamically and may need frequent imaging monitoring. Evaluation of the lungs may use other imaging modalities such as chest radiography and CT scan. Chest radiography has been the oldest and most common imaging modality used to evaluate the lungs due to its availability and cost effectivity. However, its utility in the dynamic patient in the ICU has been limited because of problems with exposure and adequate inspiration, radiologic lag and ionizing radiation.[3,7] Lung CT scan has also limited utility among critically ill patients because of the lack of portability, increased exposure to radiation, high cost, and unnecessary delays in facilitating and obtaining results. As such, lung ultrasound has gained utility in the diagnosis, management and monitoring of the critically ill patients.[1,3,4,7]

Currently, lung ultrasound has been used to assess lung aeration (i.e., absence of pleural effusion and consolidation) and deep intrathoracic structures. It is also used as a guide in shock assessment and fluid responsiveness.[5] It can also provide an assessment of the cardiac chamber functions and as such, help in the assessment of the etiology of shock in an undifferentiated patient which can be lifesaving.[7] While its acceptability in providing dynamic imaging has improved care in the critically ill, literature has conflicting evidence regarding its role in decreasing ICU mortality.[6-10] Without local data, policies cannot be crafted to optimize nutrition and subsequently improve the outcomes among patients admitted in the ICU.

METHODS

Search Strategy and Study Selection

The systematic review and meta-analysis was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Two independent authors did a systematic search of PubMed, Google Scholar, and the Cochrane Central Register of Controlled Trials (CENTRAL). The search terms used were the following: "lung ultrasound," "lung ultrasonography," "critical illness [Mesh]," "intensive care unit [Mesh]," "mortality," and "fluid management." Unpublished trials were identified using the clinicaltrials.gov database. All items found on the search strategy from year 2010 up to present were screened for eligibility. Pertinent articles identified through cross-referencing were also screened. Full-text articles of relevant studies were retrieved and reviewed by two independent authors. Any disagreement for final inclusion in the meta-analysis was resolved by a third reviewer.

Eligibility Criteria

The following inclusion criteria were used: (1) studies that used lung ultrasonography as an ancillary diagnostic tool for adult patients, (2) studies conducted on ICU patients, and (3) ICU mortality as a reported outcome. Only full-text English articles that included outcomes on ICU length of stay, mechanical ventilation duration, and number of additional radiologic imaging were included.

Study Quality Assessment

Quality assessment of all included studies was conducted by two independent reviewers. Risk of bias for randomized studies was assessed using the Cochrane Collaboration's tool. This includes an assessment for selection, performance, detection, attrition, reporting, and other possible sources of bias.

Non-randomized studies were assessed using the Newcastle-Ottawa Scale which evaluates studies using three domains: (1) selection, (2) comparability, and (3) outcomes. A good quality study should have a score of at least 1 on each domain and a total score of at least 6.

RESULTS

Study Selection

A total of 427 publications were identified in the electronic search (Figure 1). After removing duplicates, abstracts of 421 studies were screened. Twelve full-text articles were reviewed, seven of which were eventually excluded. Five studies were included in the final meta-analysis. All of the included studies involved ICU patients with lung ultrasonography as a supplementary diagnostic tool and ICU mortality as a reported outcome. ICU length of stay was reported in all the studies and mechanical ventilation duration in 3 studies. Two studies reported the effect of lung ultrasound on the number of additional radiographic imaging (chest x-rays and CT scans) needed.

Study Characteristics

The five included studies and their characteristics are shown in Table 1. Three studies were quasi-experimental observational studies using a before-and-after design. Two studies were randomized controlled trials (RCT) [9,11]. Three studies [9, 11,12] used ultrasound to evaluate pulmonary and extra-pulmonary structures. Two studies [8,10] only used lung ultrasound. Training procedures for certifying the physician ultrasonographers were detailed in three studies.[8,10, 11]

Table 1. List of Included Studies

Study (Publication year)	Design	Size	Setting (Country)	Exposure	Outcomes
Pontet et. al. (2019)	RCT	80	Medical & surgical ICU, step-down unit (Uruguay)	Point-of-care ultrasound-driven protocol	• ICU mortality rate, length of stay in ICU. duration of mechanical ventilation, number of radiologic, ultrasound, and CT studies, change in initial diagnosis, new unsuspected finding, association with subsequent pharmacologic, medical, procedural or surgical measures
Wang et. al. (2018)	Observational/ Quasi-experimental, before and after study	85	Surgical ICU (China)	Lung ultrasound and IVC ultrasound-guided protocol for fluid removal	• ICU mortality rate, length of stay in ICU, hospital expenses, time to start of fluid removal, time to end of fluid removal
Zieleskiewicz et. al. (2015)	Observational/ Quasi-experimental, before and after study	498	Medical & surgical ICU (France)	Daily lung ultrasound	• ICU mortality rate, length of stay in ICU, duration of mechanical ventilation, number of chest radiographs and CT scans per ICU stay
Wang et. al. (2014)	RCT	128	ICU (China)	Integrated cardiopulmonary sonography	• ICU mortality rate, length of stay in ICU, cumulative infusion volume, time to diagnosis of pulmonary edema etiology
Peris et. al. (2010)	Observational/ Quasi-experimental, before and after study	376	Medical & surgical ICU (Italy)	Daily lung ultrasound	• ICU mortality rate, length of stay in ICU, duration of mechanical ventilation, number of chest radiographs and CT scans

Risk of Bias Assessment

Risks of bias for the randomized controlled studies are summarized in Table 2. Allocation concealment and blinding of participants were not stated on both studies. Sonographic examination was done by an independent intensivist in one study.[11] No detail was given on who performed the ultrasound on the other study.[9] Although blinding of participants and outcome assessors was not done, the authors deemed that the outcomes (i.e., ICU mortality, ICU LOS, duration of MV) are unlikely to be influenced.

The quality assessment of non-randomized studies is shown in Table 3. Only one study (10) had good quality. The other two studies had poor quality due to failure in the comparability domain. Baseline characteristics of the study groups were not comparable, and no statistical adjustment was done to control for possible confounders.

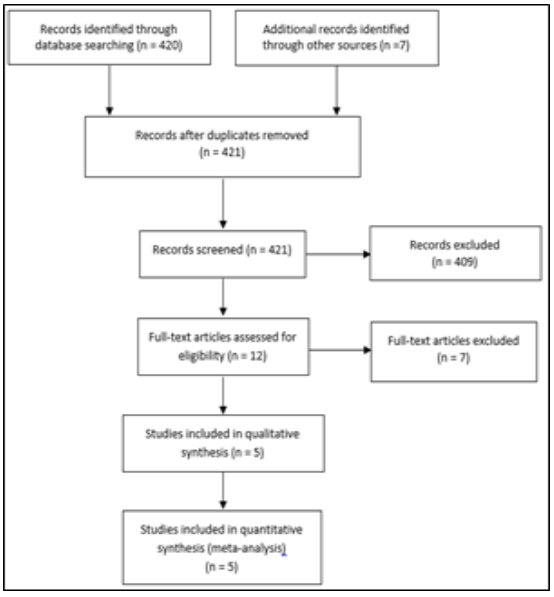

Figure 1. Flow Diagram of Study Selection

Table 2. Risk of Bias for Randomized Studies

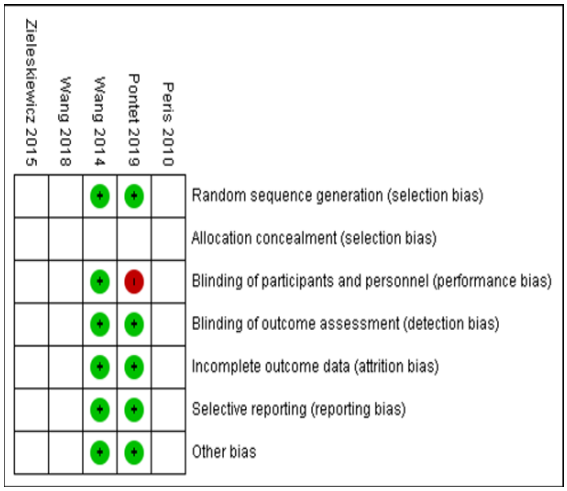

Table 3. Newcastle-Ottawa Scale for Non-Randomized Studies

	Peris 2010	Zieleskiewicz 2015	Wang 2018
Selection			
Representativeness of exposed cohort	1	1	1
Selection of non-exposed cohort	1	1	1
Ascertainment of exposure	1	1	1
Demonstration that outcome of interest was not present at start of study	1	1	1
Comparability			
Comparability of cohorts on the basis of the design or analysis controlled for confounders	1	0	0
Outcome			
Assessment of outcome	1	1	1
Was follow-up long enough for outcomes to occur	1	1	0
Adequacy of follow-up of cohorts	1	1	1
Total	8	7	6
Quality	Good	Poor	Poor

Lung ultrasonography and ICU mortality

The use of lung ultrasonography was not associated with improved ICU mortality (RR 1.06; 95% CI 0.83, 1.36; I^2 0%) in a fixed-effects meta-analysis (Figure 2). No association was still found even after exclusion of the studies that was deemed to have poor quality (RR 1.08; 95% CI 0.74, 1.59; I^2 0%).

Lung ultrasonography and ICU length of stay

All five studies reported ICU length of stay as an outcome. However, two studies (8,10) reported medians and quartile ranges instead of means and standard deviations. The addition of lung ultrasonography was associated with decreased length of stay in the ICU (RR -0.88; 95% CI -1.55, -0.21; I^2 26%) when these two studies were excluded due to the possibility of non-normal distribution (Figure 3). The studies excluded in this analysis separately showed no significant difference in ICU length of stay (p = 0.131 for Peris 2010, p = 0.5 for Zieleskiewicz 2015).

Lung ultrasonography and number of additional radiologic imaging

The use of additional radiologic imaging was reported by two studies (Figure 4, 5). Lung ultrasonography was associated with reduction in the number of chest radiographs (RR -1.95; 95% CI -3.00, -0.91; I^2 40%) and number of chest CT scans (RR -0.23; 95% CI -0.35, -0.12; I^2 36%).

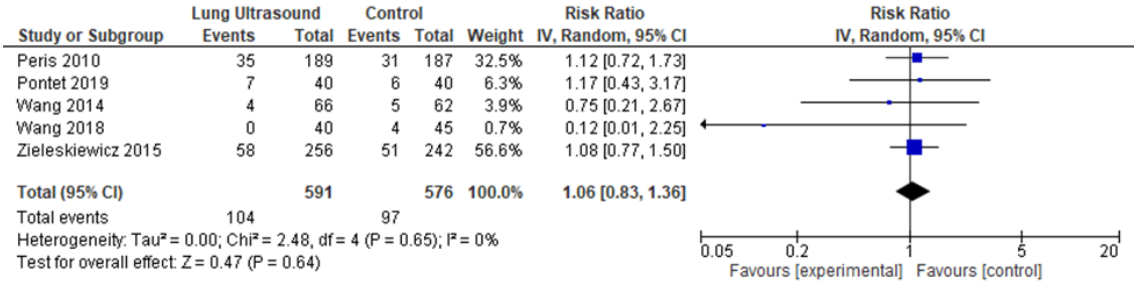

Figure 2. Fixed-effects meta-analysis of lung ultrasonography and ICU mortality

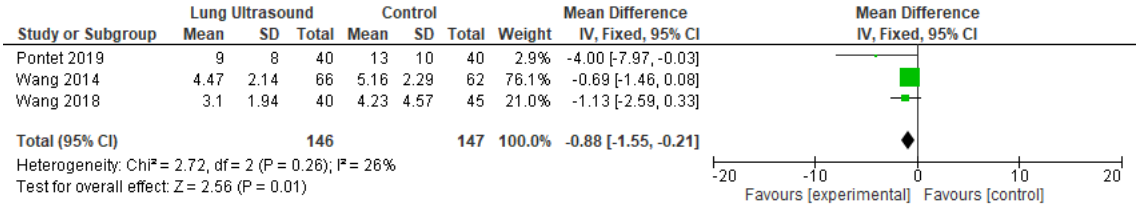

Figure 3. Fixed-effects meta-analysis of lung ultrasonography and ICU length of stay

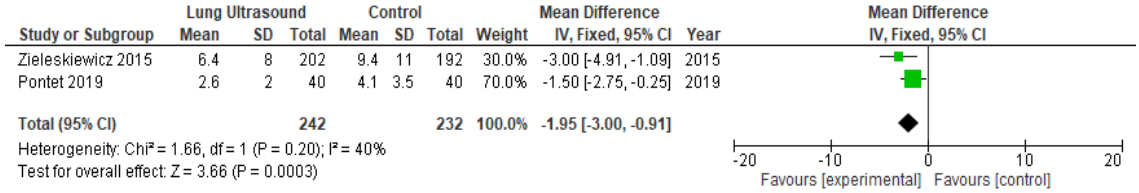

Figure 4. Fixed-effects meta-analysis of lung ultrasonography and number of chest radiographs

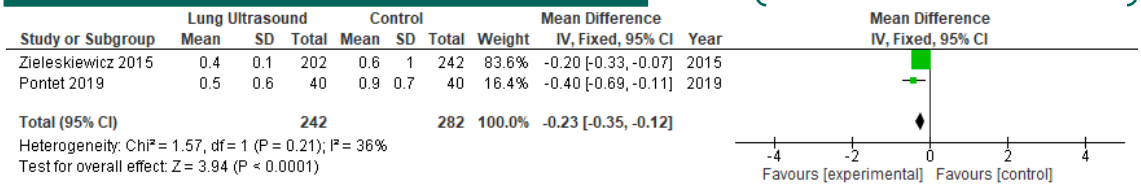

Figure 5. Fixed-effects meta-analysis of lung ultrasonography and number of chest CT scans

Three studies reported the association of lung ultrasonography with mechanical ventilation duration.[8,9,10] However, only two studies[8,10] reported ICU length of stay as medians and quartile ranges. In both studies, the duration of mechanical ventilation was not statistically significant in the treatment arms (p = 0.274 for Peris 2010, p = 0.09 for Zieleskiewicz 2015). In the third study[9], ultrasonography was associated with decreased duration of mechanical ventilation (5.1±5.7 days vs. 8.8±9.4 days, p= 0.03).

DISCUSSION

Based on the included studies, the use of lung ultrasound was associated with a decrease in the ICU length of stay and use of additional radiologic imaging. It is highly efficient, being able to provide real-time assessment of the patient's status and the evaluation of intervention in the dynamically changing ICU patient. In addition, it avoids the issues of transferring the critically ill patient out of the ICU and avoids overexposure to ionizing radiation provided by the lung CT scan and chest radiograph.[2,5-7]

All the included studies[8-12] highlighted the importance of lung ultrasound in the clinical-decision making. In the ICU, problems arise in identifying the etiology of shock, as etiologies often differ in approach to management.[5] The included studies show that the primary use of this modality is in the diagnosis of the type of shock and guidance in volume management, including the early identification of pulmonary edema caused by fluid overload. This results in the timely removal of fluids, thereby reducing the side effects of fluid overload in the critically ill patient. In addition, the studies emphasized that the use of lung ultrasound resulted in an individualized approach because of the robust information one can get based on a simple, safe, and repeatable lung imaging technique.[8-12] These factors led to the decrease in the ICU length of stay and use of additional radiologic imaging.

On the other hand, the study showed that lung ultrasound has no significant benefit in terms of ICU mortality and mechanical ventilation use. ICU mortality and mechanical ventilation use was no different between the standard of care and the addition of lung ultrasound to the standard of care despite the improved ICU length of stay. Reasons for this includes the heterogenous population of ICU admissions in the included studies which could have affected the underlying cause and prognosis of the critically ill patient. The studies also highlighted that the lack of a standardized protocol and inter-observer variability could have possibly affected the outcomes of these patients.

At present, lung ultrasound has been recognized by the American Thoracic Society[13] as an important diagnostic modality in the critically ill patient. It can provide a direct visualization of the normally aerated lung and it can also detect consolidation, effusion, pneumothorax and pulmonary edema with increased specificity and sensitivity versus a conventional chest radiograph and it is more readily available than a CT scan.[14] It also has other clinical utility in an intubated patient including assessment of endotracheal tube placing and assessing gastric contents for risk of aspiration.[14]

CONCLUSION

Lung ultrasound has no significant benefit in terms of ICU mortality and mechanical ventilation use but it is associated with decrease in the ICU length of stay and use of additional radiologic imaging. The primary utility of this modality is in the diagnosis of the type of shock and guidance in volume management including the early identification of pulmonary edema caused by fluid overload. Despite the limitations of interobserver variability, it remains an important adjunct in the current standard of care in the ICU.

DISCLOSURE

The authors have no conflict of interest and this study was self-funded by the authors and did not receive any grant from any institution or pharmaceutical company.

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Philippine Journal of Chest Diseases

Systematic Review

Local Pulmonary Administration of Tranexamic Acid as Inhalational or Nebulized for the Control of Hemoptysis

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ABSTRACT

BACKGROUND: Hemoptysis is defined as the expectoration of blood from the respiratory tract. It has various and broad etiologies for which the mainstay of treatment is addressing the underlying cause of bleeding. Current definitive management of pulmonary hemorrhage (i.e., bronchoscopy and surgical interventions), are not readily available particularly in rural settings and not all referral centers can do such interventions.

OBJECTIVE: To describe the use of nebulized tranexamic acid (nTXA) and to assess its effects on the control of hemoptysis among adults with hemoptysis due to any cause.

METHODS: The authors reviewed case reports, case series of patients and one available randomized controlled trial (RCT) for which tranexamic acid was used through nebulization for the treatment of hemoptysis to describe the potential use and the effect of nTXA in the control of hemoptysis. The NIH Quality Assessment Tool and the Joanna Briggs Institute (JBI) Critical Appraisal Tool were used in the appraisal of available data.

RESULTS: There is limited and paucity of data describing the use of nTXA as an agent for the control of hemoptysis, wherein only limited case reports, case series and one RCT were available. The review suggests that local administration of tranexamic acid through nebulization has the potential to be an alternative mode of administration to control the hemoptysis of various etiologies.

CONCLUSION: Tranexamic acid delivered through direct inhalation or nebulization can be a viable option for the control of hemoptysis in emergency rooms and hospitals. It can be a potential bridging agent in the control hemoptysis in low resource setting. However, due to limitation of available data, we recommended that more studies be conducted in the potential use of nTXA to determine its effects.

KEYWORDS: *tranexamic acid, inhalational, hemoptysis*

INTRODUCTION

Description of the condition

Hemoptysis is defined as the expectoration of blood from the respiratory tract.[1] It commonly results from infection, malignancy, or vascular disease; however, the differentials for bleeding from the respiratory tract are varied and broad.[2] It is imperative to determine the amount of blood expectorated - whether it is mild, moderate or massive. The severity of hemoptysis varies because of the dual blood supply of the lung—the pulmonary and bronchial circulations.[1]

Bleeding usually arises from the bronchi or medium sized airways which are under systemic pressure which makes it more challenging to address the bleeding. A blood loss of 400 mL in 24 hours or 100-150 ml/bout is considered massive hemoptysis.[1] This determination is important as patients are at risk of death due to asphyxiation from blood filling the airways.

Description of the intervention

Sequential management of massive hemoptysis involves protection of the non-bleeding lung and locating the site of bleeding and controlling it. Both surgical and medical management are applied to the affected blood vessel/s to control the bleed. Bronchoscopy may allow therapeutic interventions through photocoagulation and cautery, for which bronchial artery embolization is the procedure of choice.[1] However, bronchoscopy is not readily available in all medical institutions. Hence, it is prudent to determine ways to control the hemoptysis until the patient receives definitive management.

One of the medical interventions to control hemoptysis is through the use of TXA, a synthetic lysine analogue with antifibrinolytic activity.[2] TXA inhibits the activation of plasminogen to plasmin and by blocking the action of plasmin on fibrin.[3] Systemic administration of TXA may reduce surgical blood loss, improve abnormal uterine bleeding, and control traumatic hemorrhage.[4]

Nebulization facilitates the delivery of drug directly to the site of its intended effect. A machine converts a liquid of solution to fine droplets (in aerosol or mist form) that is intended to be inhaled into the lower respiratory tract. It is commonly used in delivering drugs on patients with asthma and chronic obstructive pulmonary diseases (COPD). nTXA solution is described in the reports and case series as intravenous TXA given as pure or diluted with normal saline.

How the intervention might work

The anti-fibrinolytic factors of TXA are depleted in sites of continuous bleeding[5], which is why several studies indicate that TXA is more effective when administered locally rather than systemically. Nebulization converts the TXA solution to aerosol or mist form that is delivered directly to the site of bleeding in the lower respiratory tract.

There are already published case series, case reports, and one RCT which describe nTXA as an initial treatment for hemoptysis. However, collected data and information are still limited for its benefit especially in a country like the Philippines wherein pulmonary tuberculosis is highly prevalent.[6]

This systematic review describes the local application of TXA by nebulization or inhalational for the control of hemoptysis. It is a potential bridging agent in controlling hemoptysis or pulmonary hemorrhage toward a more definitive management in areas with limited resources.

OBJECTIVE

We aim to describe the use of nebulized tranexamic acid (nTXA) and to assess its effects on the control of hemoptysis among adults with hemoptysis due to any cause.

METHODS

Search methods and identification of studies

The researchers searched Google Scholar and PubMed using the keywords "tranexamic," "hemoptysis," and "nebulize." The search yielded 275 and 10 citations respectively. Other online international and local journals were also utilized. The ancestry approach in the searched literature review was also applied. The researchers limited the inclusion to studies carried out in humans and with restriction to English language only. Commentaries or articles describing the published studies were excluded to avoid duplication. Studies included in this review are those which TXA were given either as inhalational or nebulization.

Inclusion Criteria

1. Studies which utilized nebulized or inhalational TXA for hemoptysis.
2. Studies with adult (18 years old and above) index cases or patients who presented with hemoptysis regardless of underlying etiology
3. Studies published within 2000 – 2021

Exclusion Criteria

1. Studies with pediatric (17 years old and below) index cases or patients who presented with hemoptysis
2. Studies wherein index patients were given other therapeutics or interventions aside from inhalational TXA to manage the hemoptysis
3. Studies wherein index patients were given bronchoscopic interventions concurrently with inhalational TXA to manage the hemoptysis
4. Studies wherein index patients were given inhalational TXA but did not present with hemoptysis

Risk of bias of included studies

The NIH Quality Assessment Tool was used to assess the Randomized Controlled Trial[33]. The Joanna Briggs Institute (JBI) Critical Appraisal Tool was used to assess the quality of case series and case reports (Annex C and D).[34,35] The JBI Appraisal Tool includes a set of questions that were answerable with yes, no, unclear and not applicable. Risk of bias was scored accordingly in each criterion wherein Yes=1, No=0, and U=Unclear. The criteria used to rank the risk of bias were set at >70% for Low, 50%-69% for Moderate and ≤ 49% for High. Two authors independently reviewed the articles and decided based on inclusion/exclusion criteria and the risk of bias using the mentioned tools. When conflict arise, the third author reviews the article in question and will make a consensus.

Selected Studies

The authors reviewed all the case reports and case series that satisfied the inclusion/exclusion criteria. An RCT was also included in the review. See Supplementary Table 1, which can be accessed through this link: https://bit.ly/nTXASuppTable, for the summary of selected studies.

Data extraction and management

Each patient's data were retrieved and handled individually within a case series/ report whenever possible. No authors from these studies were contacted to retrieve any missing data. For each case reported, the authors extracted the following data: (1) age, (2) gender, (3) diagnosis, (4) route of administration of TXA (5) the outcome of hemoptysis, and, (6) presence/absence of adverse effects. The availability of the data named earlier varied widely among the studies identified, and data were analyzed as reported. The RCT and prospective observational studies were critically appraised and the absolute risk reduction (ARR) and numbers needed to treat (NNT) were computed using the reported data.

Measures of treatment effect

Data analyses were performed to identify the effectiveness of direct application of tranexamic acid in the control of hemoptysis, either as inhalational or as

nebulization. Side effects, if any, were also summarized and reported. Continuous data were summarized as mean ± standard deviation (SD), and range. The researchers categorized the data, such as the time interval of resolution of hemoptysis from the start of administration as immediate (<12 hours), Day 1, Day 2, and Day 3. Studies which reported resolution of hemoptysis as 'immediate' after administration were labeled as such and those who reported resolution of fewer than 12 hours. Those who reported resolution of 12 hours or more but not more than 48 hours are classified as Day 1.

RESULTS

After thorough review, 21 publications which satisfied the inclusion and exclusion criteria were appraised and evaluated. Among these, six were case series,[9,11,12,18,21,30] fourteen were case reports,[7,8,10,19,20,22-29] and one was a RCT.[2] Further, there were a total of 30 patients in the reviewed case reports and series (Table 1) and 47 participants in the RCT. Identified cases in the reviewed reports and series who did not satisfy the inclusion and exclusion criteria were excluded in this review.

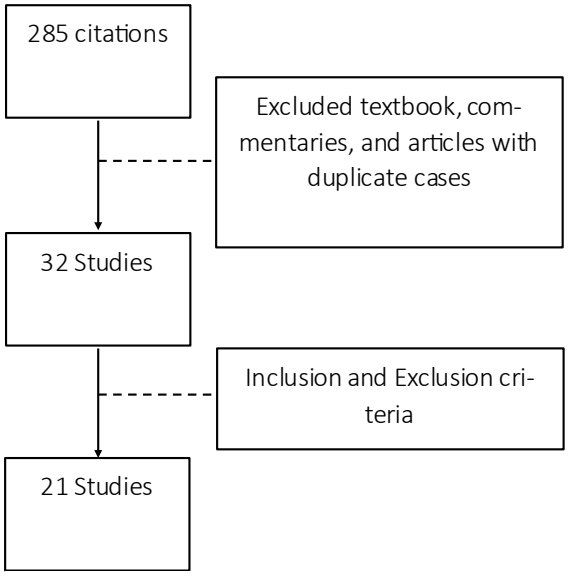

Figure 1. Study flowchart

Effects of interventions

Control of hemoptysis

SAlthough there is still limited data, existing reports suggest that hemoptysis can occur anytime in one's lifetime with no predilection to any age group. The mean age of the occurrence of hemoptysis in adults is 58 years old with majority of cases given with nTXA were males.

Table 1 depicts the age distribution of the cases. Mean age at the time of nTXA treatment was 58 (median age, 59 years), with a very wide range of 18 to 84 years old. The causes of hemoptysis of index cases included in the reviewed case reports and series were broad. Lung malignancy is the leading cause of hemoptysis accounting to 33% of index cases, followed by bronchiectasis all causes, diffuse alveolar hemorrhage all causes, coagulopathy all forms, and lung infection all causes. Other causes were acute respiratory distress syndrome, iatrogenic all causes, vasculitis, pulmonary embolism, and pulmonary hemosiderosis.

Table 1. Demographic of Index Cases Included in Case Series and Case Reports

Age		
Mean	58	
Range	18-84	
GENDER		
Male	22	73%
Female	8	27%

Resolution of hemoptysis

All 30 cases that were reviewed had noted complete resolution of hemoptysis after using nTXA. One reported case noted a recurrence of hemoptysis but was controlled with regular dosing. There was varying time interval to which the resolution of hemoptysis was reported from the time the treatment was initiated. Most of the index cases had resolution of hemoptysis on the first day of administration of the nTXA wherein 14 cases were reported with immediate

resolution (<12H) and 6 were resolved within the day. Data is not sufficient to compare each case because of varying causes, comorbidities, nTXA dosing, and the manners of administration.

Table 2. Duration of the Resolution of Hemoptysis from the Time of Local Pulmonary Application

Time interval from nTXA to Complete Resolution of	Number
Immediate	14
Day 1	6
Day 2	4
Day 3	1
Day 5	2
No Report	3

Majority of the reviewed studies described the nebulizer used were standard and Jet Nebulizer. Some reported the brand of machine such as the 22m Cirrus®2 nebulizer breathing kit and the Hudson PCI Micro Mist Nebulizer. Most studies also reported that nTXA was delivered with oxygen with varied flow rate.

It had been reported by Dempsey et. al., that there is crystallization when undiluted tranexamic acid was given through nebulization. Crystallization was resolved when tranexamic acid was diluted with 3mL of normal saline.[28] However, the report states that they used a Hudson PCI Micro Mist Nebulizer, unlike the other case studies which reported using standard and or jet nebulizer, which may have been the cause of the crystallization. Hence, it is suggested that tranexamic acid should be diluted with plain normal saline solution (PNSS) regardless of the nebulization machine.

The reviewed case series and reports had reported dosing with variable formulation/concentration by which all had concluded positive outcome. As seen in Table 3, most of the available studies had used a concentration of *500 mg/5 ml* by dissolving tranexamic acid 1000mg/vial in 10 ml of PNSS. Due to limited data, it is inconclusive if one formulation is superior to the other.

Table 3. Formulation of Nebulized Tranexamic Acid in Case Series and Case Reports

Concentration	Number
1000 mg/20 ml	1
500 mg/5 ml	17
500 mg/3 ml	1
250 mg/5 ml	1
No report of concentration	10

As seen on Table 4, there were also noted variations in terms of dosing schedule. Majority of the reported cases had been given a schedule of thrice a day until the control of hemoptysis. More so, most of the cases were treated with a dosage of 500 mg per dose. All reported a positive outcome regardless of the dosage and dosing interval, however, data was not sufficient to suggest if one interval or dosage is more effective than the other due to limited and heterogeneity of existing cases.

Table 4. Dosing Schedule of Nebulized Tranexamic Acid in Case Series and Case Reports

Dosing schedule	Number
Single dose	8
2x a day or every 12H	1
3x a day or every 8H	13
4x a day or every 6H	5
No report of dosing interval	3

Limited RCT of nTXA

Wand et. al. (2018) conducted a double-blinded RCT using nTXA 500mg 3x a day (vs. placebo) for patients with non-massive hemoptysis regardless of cause. Results showed a significant reduction in expectorated blood volume from the second day of admission with further resolution of hemoptysis within five days of hospital stay in the

treatment group. Moreover, nTXA shortened the length of hospital stay and reduced the need for invasive procedures to control bleeding.[2] The participants in the RCT were followed-up at 30 days and 1-year interval for evaluation for recurrence of hemoptysis. Results revealed an improved 30-day outcome in the treatment group with a significantly lower recurrence rate at 1-year follow up on the treatment group.[2]

Nonetheless, some limitations were noted in the study such as the exclusion of patients with critical and life-threatening hemoptysis and a relatively small study population. These limitations made it difficult to completely assess the efficacy of nTXA for hemoptysis and thus, prevented the researchers from forming definite conclusions.[31] Despite these, the participants who had various etiologies of hemoptysis made the study more inclusive of various subsets of patients.[31,32] In conclusion, the trial supported the previously published case series and reports with regards to the efficacy and benefit of nTXA for non-massive hemoptysis. nTXA can be used as a sole therapy, as well as an adjunct to other interventions in patients with hemoptysis of various causes.

The ARR was computed by the researchers of this systematic review at 0.46 or 46% which means that for every 100 patients treated with nTXA, about 46 bad outcomes would be averted. The computed NNT was 2.17, which means on average, only 2 patients would have to receive the nTXA for one additional patient to control the hemoptysis.

Adverse events

Majority of the cases and the RCT reviewed reported no significant adverse effect. It was described by Wood et. al. in their report of a patient with high thrombotic risk who developed left bundle branch block when using nTXA with cessation of the effect after discontinuation of the drug.[24] There is also a report of bronchospasm following nTXA in a patient with lung malignancy which was managed effectively with administration of a bronchodilator.[9]

It is also interesting that there had been reports describing the effectiveness of nTXA in the control of hemoptysis in patient with coagulopathy and patients on veno-venous- extracorporeal membrane oxygenation (vv-ECMO) needing heparinization.[17] Furthermore, nTXA reported lesser incidence of thrombosis[30] and other minor side effects such as gastrointenstinal disturbance, allergic skin reaction, and visual disturbance[7] by bypassing the first pass metabolism.[31]

DISCUSSION

In hemoptysis, determining the source of bleeding is of vital importance. Preferably, both bronchoscopy and chest CT Scan be performed in the first 12 - 24 hours to provide supportive diagnostic information.[36] Meanwhile, bronchoscopy can also be utilized as both a diagnostic and interventional tool (e.g., saline lavage, application of topical vasoconstrictive agents, guided balloon occlusion, photocoagulation and cautery, local thermal ablative therapies, etc.) to control the bleeding. However, such interventions are not always available, especially in areas with low resources.

Medical management with Tranexamic Acid (TXA), either through intravenous or oral route, is being used to augment any bleeding. However, a 2016 Cochrane pooled review of 2 RCTs revealed that while there was a decrease in the incidence of bleeding between oral and intravenous TXA, there was no substantial difference in the resolution of hemoptysis at 7 days.[31] Hence, this systematic review gathered multiple data and evidence from various studies for the use of inhalational TXA as an adjunct and/or initial treatment for hemoptysis.

The data collated suggests that giving inhalational or nebulized tranexamic acid

has a positive effect on the control of hemoptysis and is safe and easy to formulate. It can be a potential new option in the management and a potential temporizing agent in controlling hemoptysis or pulmonary hemorrhage in low-resource setting areas. Also, nTXA can be used as a noninvasive treatment for both palliative therapies in chronic hemoptysis and most commonly in the acute care setting.[7]

Majority of the reviewed studies described the nebulizer used were standard and Jet Nebulizer. It has been reported that undiluted TXA will result in crystallization and will result in hindering the delivery of the drug through micro mist inhalation. We suggest that tranexamic acid should be diluted with PNSS regardless of the nebulization machine.

There were also noted variations in terms of dose, dosing interval, and formulation of nTXA. However, regardless of these variations, all cases reported resolution of hemoptysis. Data is still inconclusive if one variation is more effective than the other due to limited and heterogeneity of existing cases. The authors suggest further studies to determine the most efficient dose, formulation, and standard procedure of delivering nTXA.

CONCLUSION

Implications for practice

The review suggests that local administration of tranexamic acid, either through direct inhalation or nebulization, can be an effective, safe, and easy-to-formulate mode of administration to control the hemoptysis of various etiologies. The treatment can be utilized in institutions with limited resources to alleviate patient's symptoms and can serve as an adjunct while awaiting a more definitive management when necessary.

Implications for research

Due to limited data, no cause-and-effect relationship can be concluded. It is recommended that more studies be conducted in the potential use of nTXA.

DISCLOSURE

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