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AN OFFICIAL PUBLICATION OF THE PHILIPPINE COLLEGE OF CHEST PHYSICIANS

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EDITORIAL

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

Moving On To The Next Level of Life

"Coronavirus also introduces us to a completely new world of life, to move on from our struggles and enjoy Next Level of Life." — Srinivas Mishra [1]

It has been over two years since the declaration of the COVID-19 Pandemic by the World Health Organization (WHO) in March 2020. While the medical community and scientists struggled against time to understand the novel virus, the ensuing months saw the rapid development of diagnostic tests, vaccine development and trials of therapeutic drugs for COVID-19 infection. With the decreasing number of cases over the last several months, the world is moving on from the struggles in combatting the coronavirus. We are now looking forward what our lives will be post-pandemic.

For us in the medical community, hopefully we have gained learnings from pandemic-related research studies that have been generated over the last two years. In the opinion article by Oviedo DC et al.[2] the role of clinical researchers during COVID-19 was aptly described as follows:

"At a scientific level, due to the complexity, novelty and unexpectedness of COVID-19, we as other researchers around the world, have urgently responded by rapidly generating data while maintaining scientific validity and replicability. Researchers and work groups have had to generate multiple therapeutic strategies, prevention mechanisms and diagnostic tests to tackle this new disease. Moreover, the COVID-19 pandemic has exposed the importance of research's social benefits. Knowledge cannot be limited to a laboratory or to a publication. It is mandatory that research in this health emergency has practical applications that rapidly reaches all countries affected by the virus."

EDITORIAL

Like other researchers around the world, our country's clinicians and researchers have also generated COVID-19 scientific researches. In this issue of the PJCD, three original researches and one case series tackled varied aspects of the COVID-19 infection. The study by De Vera et al. determined the risk factors for mortality of COVID-19 patients hospitalized in a referral tertiary hospital. The data from this study can help clinicians identify patients who need more close monitoring and allocate care accordingly. The retrospective, cross- sectional study by Morrell et al. reported the clinical, laboratory and radiological characteristics and outcomes of SARS-CoV-2 patients in critical care units. The utility of high flow nasal cannula (HFNC) in COVID-19 associated acute hypoxemic respiratory failure was determined in the study by Mariano and Lao. The case series by Dimabuyu and Chua evaluated the feasibility of applying airway pressure release ventilation (APRV) as rescue ventilation for refractory ARDS in COVID-19 patients.

Included in this issue are research articles about two common pulmonary diseases, namely COPD and TB. The observational cross-sectional questionnaire-based study by Villamonte et al. determined the knowledge, attitude and practice of non-pulmonary medicine specialists in the diagnosis of COPD. The results of this study will help design educational modules for non-pulmonary specialists in diagnosing COPD. A systematic review and meta-analysis conducted by Feraren et al. evaluated the effectiveness of remote TB-DOT (virtual) compared to conventional TB-DOT (in-person) in the management of drug-susceptible TB. This study explored TB DOT using telemedicine technology as alternative for treatment adherence and completion.

While the WHO has yet to officially declare the end of the pandemic, we have to prepare ourselves to a new world of life equipped with the knowledge gained from researches both local and international. May we see the end of this pandemic soon and the transition to the "Next Level of Life".

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2. Oviedo DC, Perez-Lao AR, Villarreal AE, Carreira MB and Britton GB. The Role of Clinical Researchers During COVID-19: Balancing Individual, Scientific, and Social Benefits of Research. Frontiers in Public Health. April 2021 Volume 9, Article 638964

Philippine Journal of Chest Diseases

Original Research

Clinical Characteristics and Outcomes of Patients With Laboratory-confirmed and Probable Critical Severe Acute Respiratory Syndrome Coronavirus-2 Infection Admitted To Critical Care Units at St. Luke's Medical Center Quezon City

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PAPER AWARDED IN THE FOLLOWING CONTEST: Philippine College of Chest Physicians (PCCP) Research Contest for Original Research Category 2020-2021 (2nd Place Winner)

ABSTRACT

BACKGROUND: The novel coronavirus (SARS-CoV-2) caused an outbreak in Wuhan, China in December 2019 and eventually emerged as a major global pandemic. The first identified case in the Philippines was documented last January 30, 2020. The subsequent spread was rapid in development, with 868 deaths, 3,249 recoveries and 9,918 active cases, as of this writing.

OBJECTIVE: To report the clinical, laboratory and radiological characteristics, treatment, respiratory parameters and outcomes of patients with laboratory-confirmed and probable critical SARS-CoV-2 infection among survivors vs. non-survivors; younger vs older and hypertensive vs. non-hypertensives.

METHODS: We conducted a single-center, retrospective, cross-sectional study of 122 patients, with 76 laboratory-confirmed and 46 probable critical SARS-CoV-2 infection, who were admitted to critical care units at St. Luke's Medical Center, Quezon City from March 1, 2020 to July 31, 2020. The primary outcome was in-hospital mortality. Secondary outcomes were clinical and laboratory characteristics of SARS-CoV-2 survivors vs. non-survivors, younger vs. older, and hypertensive vs. non-hypertensive patients; the proportion of patients developing acute respiratory distress syndrome (ARDS) and other complications; the mean number of ventilator and hospital days; and, the comparison of treatment modalities and interventions of survivors vs. non-survivors.

RESULTS: The mean age of the patients was 64.1 years (SD ± 13.67) with most being males (62.3%). Comorbidities were present in more than half of patients, with hypertension (76.2%) being the most common. The most frequent symptom on admission was shortness of breath (76.2%), with chest x-ray findings revealing bilateral infiltrates (77.9%). In non-survivors, prothrombin time and BUN were significantly elevated. The most frequently observed complication was ARDS (72.1%). Overall, in-hospital mortality was 53.3%.

CONCLUSION: Patients admitted for critical SARS-CoV-2 infection in this study were predominantly males, requiring mechanical ventilation and developed complications like acute kidney injury, septic shock and ARDS.

KEYWORDS: *SARS-CoV-2, critical COVID-19, ARDS*

INTRODUCTION

The novel coronavirus (SARS-Cov-2) caused an outbreak in Wuhan, China in December 2019 and eventually emerged as a major global pandemic evolving in real time.[1,8,9] Epidemiological evidence suggested that the cases had a history of exposure to a large seafood market in Wuhan City, China. It was confirmed to be an acute respiratory infection caused by a novel coronavirus and since then, the disease has promptly spread from Wuhan and to other 66 countries.[1,4] As of May 25, 2020, there are over 5.5 million cases worldwide [48], and more than 14,000 cases in the Philippines alone. [49] The estimated case fatality rate was calculated to be 2.2-7.2%.[2,3] The first identified case in the Philippines was documented last January 30, 2020. The subsequent spread was rapid in development, with 868 deaths, 3,249 recoveries and 9,918 active cases as of this writing.[49] These figures are updated daily and are expected to increase further.

Coronaviruses are enveloped non-segmented positive-sense RNA viruses belonging to the family Coronaviridae and the order Nidovirales and broadly distributed in humans and other mammals.[1,5] Its reproduction number was estimated to range between 2.2 to 3.5, ensuing threat to public health as the virus is spreading rapidly around the world.[5,6]

The SARS-CoV-2 is spread predominantly via respiratory droplets and its clinical presentation ranges from asymptomatic to a mild common flu-like illness to a potentially fatal severe pneumonia, with acute respiratory distress syndrome (ARDS) as its sequelae. Acute respiratory distress syndrome (ARDS) occurs within 1 week of a known clinical insult or as a new or worsening of respiratory symptoms, with chest imaging showing bilateral opacities, not fully explained by effusions, lobar or lung collapse, or nodules, with respiratory failure not fully explained by cardiac failure or fluid overload.[19]. It may be classified as mild (200 mmHg < Pao2/Fio2 ≤ 300 mmHg with PEEP or CPAP ≥5 cmH20); moderate (100 mm Hg < Pao2/Fio2 ≤ 200 mmHg with PEEP or CPAP ≥ 5 cmH20) or severe (PaO2/FiO2 ≤ 100 mm Hg with PEEP ≥ 5 cmH20).

Some recent studies have found that the most common symptoms were fever (45-98%), cough (67-76%), myalgia or fatigue (44%), headache (85%), hemoptysis (5%) and diarrhea (3%).[1,5,7] About half of the patients had dyspnea and lymphocytopenia and was observed in 68-83% of the patients.[1,7] Moreover, the current literature from studies conducted in Italy and Wuhan, China have noted that the elderly, and those with comorbidities are the most at risk for acquiring the disease.[11] The most common comorbidities reported were hypertension (30%), diabetes (19%), and coronary heart disease (8%).[10] Among patients who underwent respiratory failure, comorbidities were similarly prevalent: hypertension (27%), diabetes (19%) and cardiovascular disease (6%).[13] The frequency with which SARS-CoV-2 patients are hypertensive may not necessarily imply a causal relationship between hypertension and SARS-CoV-2 infection severity since based on reports, hypertension is highly frequent in those with advancing age and functionally impaired immune system.[1,11,13,16,17] However, it is uncertain whether uncontrolled blood pressure is a risk factor for getting infected with SARS-CoV-2, or whether controlled blood pressure among hypertensive patients is or is not less of a risk factor.[16]

Treatment is supportive at best and several regimens and protocols have been suggested, though none have been recommended as standard or with proven clinical efficacy to date. Some of these include the use of off-label drugs such as hydroxychloroquine, lopinavir/ritonavir, tocilizumab and remdesivir, convalescent plasma infusion, and hemoperfusion among others.

In a previous study conducted among critically-ill patients with COVID-19 infection, outcomes were as follows: mechanical ventilation was initiated in 71% of the patients,

while acute ARDS was observed in all patients requiring mechanical ventilation and 53% developed severe ARDS by 72 hours. In the same study, patients did not initially manifest with shock, however, vasopressors were used for 67% of patients during the course of illness. Cardiomyopathy developed in 7 patients (33%) and mortality was 67%, while 24% of patients have remained critically ill and 9.5% have been discharged from the ICU.[21] In another study done in Lombardy, the majority of the patients (58%) were still in the ICU 5 weeks after the first admission, 16% of the patients had been discharged from the ICU, and 26% had died in the ICU. The death rate was higher among those who were older.[11]

The SARS-Cov-2 outbreak has been a major challenge for clinicians and has caused concern to the medical community. With limited data available at the time of its outbreak in 2020, its epidemiology, clinical features, course and complications remain to be fully characterized. This study aims to describe the baseline characteristics and clinical outcomes of Filipino patients suffering from critical COVID-19 infection and to supplement the data provided by earlier foreign and local journals.

OBJECTIVES

To describe the baseline characteristics and outcome of patients with laboratory -confirmed and probable critical SARS-CoV-2 infection admitted to the critical care units at St. Luke's Medical Center, Quezon City. Specifically, to (1) compare the clinical and laboratory characteristics of critical SARS-CoV2 patients who survived vs. those who did not survive, younger vs. older patients, hypertensive vs. non-hypertensive; (2) compare the treatment modalities and interventions of survivors vs. non-survivors; (3) determine the respiratory parameters of survivors and non-survivors that include PaO2/FiO2 ratio, mean positive end-expiratory pressure (PEEP), and ventilator days; (4) determine the hospital days and complications of patients with COVID-19 who survived and did not survive; and, (5) determine the proportion of patients who expired and those who recovered or were discharged among laboratory-confirmed and probable critical SARS-CoV2 infected patients.

METHODS

Study Design

This is a single center, retrospective, cross-sectional study of patients admitted at the critical care units at St. Luke's Medical Center (SLMC), Quezon City from March 1, 2020 to July 31, 2020.

Ethical Consideration

The study was conducted in accordance with the International Conference on Harmonization-Good Clinical Practice (ICH-GCP) and the Principles of the Declaration of Helsinki (2013). The clinical protocol and all other related documents were carefully reviewed and approved by the SLMC Institutional Ethics Review Committee. Confidentiality was strongly upheld in the data collection process and throughout the entire duration of the study. Codes were assigned to each patient's documents and were accessible only to the principal investigators. Furthermore, all study-related documents such as versions of the protocol, ethical clearance, data collection forms and hard copies of the source documents will be kept and stored by the principal investigators in strict confidentiality for at least 5 years and will later be discarded by shredding of all aforementioned documents.

Inclusion Criteria

Included patients were aged 18 and above who went into acute respiratory failure and eventually admitted to critical care units at SLMC, Quezon City and who were either laboratory-confirmed SARS CoV-2 or Probable SARS-CoV-2 and classified to have Critical SARS-CoV-2 infection, defined as follows:

- Acute respiratory failure (ARF) – failure of the respiratory system mainly due to either

lung failure resulting in hypoxemia or pump failure resulting in alveolar hypoventilation and hypercapnia; defined by any one of the following: pO2 <60mmHg or spO2 pulse oximetry) <91% breathing room air, pCO2 >50 and pH <7.35, PF ratio (PO2/FiO2) of <300, pO2 decrease or CO2 increase by 10mmHg from baseline (if known). [17,18,24]

- Laboratory-confirmed SARS CoV -2 - a positive result of real-time reverse transcriptase–polymerase chain reaction (RT-PCR) assay of nasal and pharyngeal swabs.[15]
- Probable SARS-CoV-2 - a suspect case who fulfills any one of the following: (a) suspect case whom testing for COVID-19 is inconclusive, (b) suspect who underwent testing for COVID-19 but not conducted in a national or subnational reference laboratory or officially accredited laboratory for COVID-19 confirmatory testing, and (c) suspect case for whom testing could not be performed for any reason.[15]
- Critical SARS-CoV-2 - a patient with probable or confirmed SARS-CoV-2 infection who develops any of the following: RR >30/min or SpO2 <93% on room air; need for mechanical ventilation of high flow nasal cannula (HFNC); PaO2/FiO2 ≤ 300 mmHg; shock or multiorgan failure.[15]

Exclusion Criteria

- All patients below 18 years old
- Eighteen years old and above without any signs and symptoms of respiratory failure and failed to meet the criteria for probable critical SARS CoV-2 infection or tested negative for SARS CoV-2 on RT-PCR nasopharyngeal swab

Data Gathered

Source documents used were patients' electronic charts. All collected data were written in the data collection form by the investigators themselves. A standardized data collection form was created for this study and used for all patients whose medical records were reviewed. Epidemiological, clinical, and laboratory data were recorded and retrieved from the hospital charts of patients included in the study. This included the following:

- Baseline demographic data (i.e.,age, sex, date admitted and travel history)
- Patient symptoms (i.e., fever, cough, dyspnea, hemoptysis, sore throat, myalgia, headache, anosmia, rhinorrhea, headache, alteration of sensorium, skin rash, nausea and vomiting, diarrhea, abdominal pain and chest pain)
- Comorbidities (i.e., hypertension, chronic pulmonary obstructive disease (COPD), bronchial asthma, chronic kidney disease, chronic liver disease, diabetes mellitus, tuberculosis, asplenia, coronary artery disease, cerebrovascular disease, malignancy and HIV)
- Smoking history
- Baseline laboratory values (i.e., hemoglobin, white blood cell (WBC) count, absolute lymphocyte count, prothrombin time, SGPT (ALT or Alanine Aminotransferase), SGOT (AST or Aspartate Aminotransferase), creatinine, blood urea nitrogen (BUN), serum albumin, C-reactive protein (CRP), procalcitonin, ferritin, lactate dehydrogenase (LDH), D-dimer, chest X-ray and chest CT scan findings)
- Physical examination findings on admission (i.e., systolic blood

pressure (SBP), respiratory rate, temperature, baseline oxygen saturation, level of sensorium, baseline PaO2/FiO2 ratio, lowest PaO2/FiO2 ratio and qSOFA score)

- Medications and interventions given during course of admission (i.e.,vitamins and or supplements, statins, antiretroviral agents, antimalarial drugs, antibiotics, antifungals, tocilizumab, remdesivir, dexamethasone, convalescent plasma infusion, hemoperfusion, use of HFNC, from non-invasive mechanical ventilation to invasive mechanical ventilation, invasive mechanical ventilation and prone positioning)
- Complications (i.e., sepsis, septic shock, bacteremia, fungemia, acute kidney injury (AKI), acute liver injury, pneumothorax, myocarditis, gastrointestinal bleeding, acute coronary syndrome, cerebrovascular injury, venous thromboembolism (VTEs) and ARDS)

Sample Size Estimation

No statistical sample size calculation was performed a priori, and sample size was based on convenience sampling, wherein all charts of patients that fulfilled the inclusion criteria were included in the study, from March 1, 2020 to July 31, 2020.

Statistical Analysis

The clinical and laboratory characteristics of patients with critical SARS-CoV-2 infection among those who (1) survived versus those who did not survive, (2) among the younger and older patients and among those who are (3) hypertensive and non-hypertensive patients was compared. Chi Square test was used for clinical and laboratory characteristics that were qualitative and T-test or Mann-Whitney U-test for quantitative clinical and laboratory characteristics. Furthermore, determination of respiratory parameters (i.e., PaO2/FiO2 ratio, PEEP, number of ventilator days), number of hospital days, complications, treatment modalities and interventions among the survivors and non-survivors was analyzed using Chi Square test for qualitative variables and T-test or Mann-Whitney U test for quantitative variables. Lastly, comparison of the proportion of patients who expired among laboratory confirmed and probable critical SARS-CoV-2 patients was done using frequency and percentages. A 95% confidence interval of the percentage was also calculated. Level of significance was set at α less than 0·05.

RESULTS

A total of 136 patients were admitted to critical care units at SLMC, Quezon City with laboratory-confirmed and probable critical SARS-CoV-2 infection between March to July 2020. Fourteen patients were excluded due to the absence of signs and symptoms of respiratory failure or were unable to meet the criteria for probable critical SARS-CoV-2 infection. From a total of 122 patients included in the study, 76 were laboratory-confirmed and 46 were probable critical SARS -CoV-2 infection (Figure 1).

Clinical and laboratory characteristics and respiratory parameters of survivors and non-survivors

The mean age of the patients was 64.1 years (SD ± 13.67) and were predominantly males (62.3%). Comorbidities were present in more than half of the patients with hypertension (76.2%) being the most common, followed by diabetes mellitus (41%) and at least one other coexisting illness like atrial fibrillation, dyslipidemia, or thyroid disease (34%). The most common symptoms on admission were shortness of breath (76.2%) followed by cough (62.3%) and fever (61.5%). The majority of patients on admission presented with tachypnea with a mean respiratory rate of 25.8 (SD ± 6.81) cycles per minute and oxygen saturation level of 92.4% (SD ± 9.27).

There was no statistically significant difference in the computed p-values of the

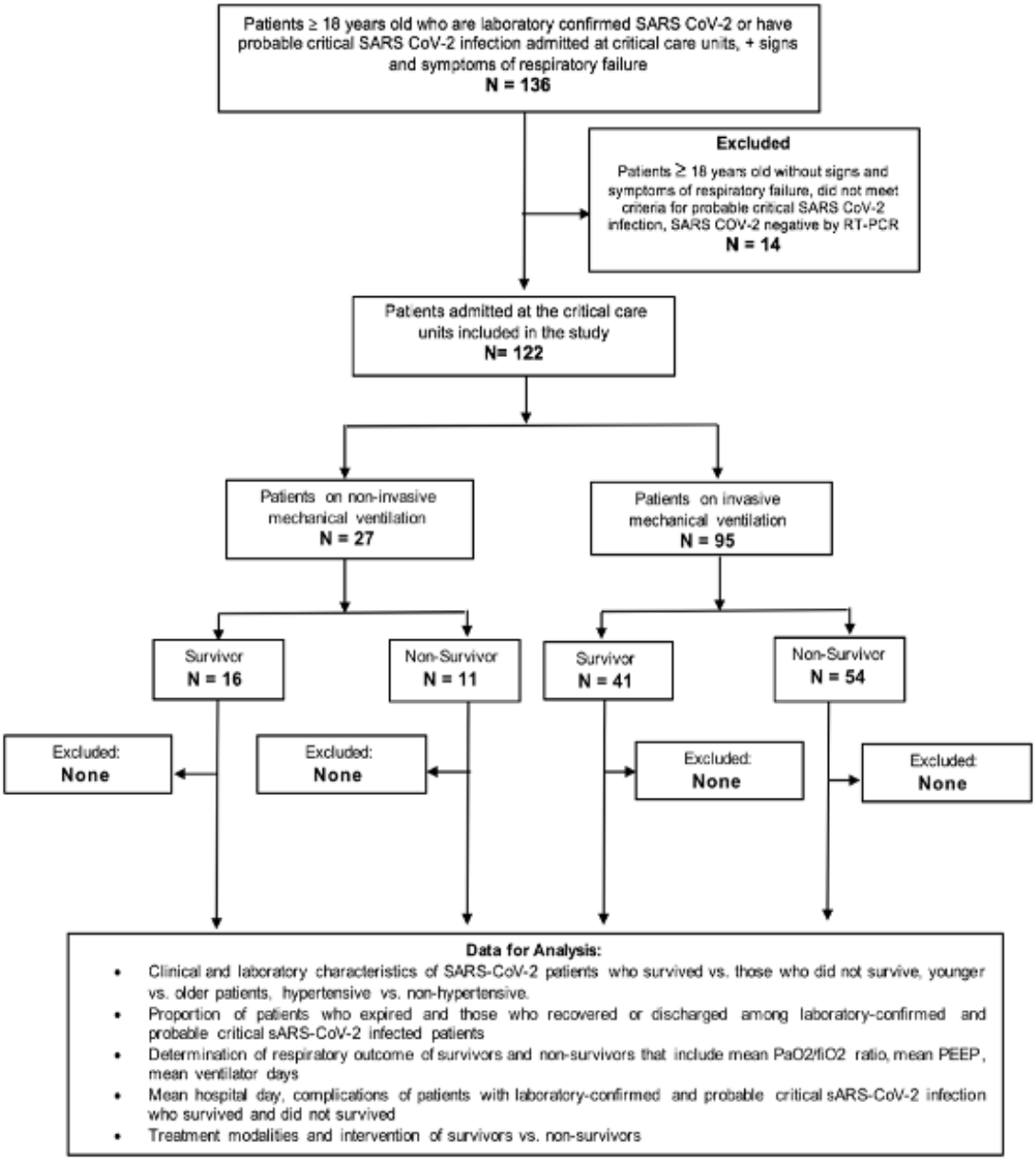

Figure 1. Flowchart of included patients in the study

baseline characteristics among survivors and non-survivors of this study (Supplementary Table 1: http://philchest.org/publications/Supplementary_Table_Manuscript29.pdf).

Lymphocytopenia with mean absolute lymphocyte count of 1,265.6 cells/mm3 (SD ± 867.66) was noted on admission, however, this was not found to be significantly lower among non-survivors (Supplementary Table 2).

Elevated mean serum CRP, procalcitonin, LDH, ferritin, D-dimer, SGOT, SGPT, creatinine, BUN and prothrombin time were observed, while mean serum albumin was low across both groups on baseline evaluation. All patients had chest x-ray done and majority of the findings revealed bilateral infiltrates (77.9%). Twelve patients underwent further imaging with chest CT scan, 25% of which showed features consistent with SARS-CoV-2 infection.

Ninety-five patients (77.9%) underwent

invasive mechanical ventilation on admission, while 27 patients (22.1%) were started on HFNC support, however, 16 of these patients initially on non-invasive mechanical ventilation were subsequently intubated. Baseline mean PaO2/FiO2 ratio on admission was low at 200.4 mmHg. The lowest PaO2/FiO2 ratio throughout the course of hospital stay was also reviewed and non-survivors were noted to have a significantly lower mean PaO2/FiO2 ratio compared with survivors (Supplementary Table 2)

Treatment modalities, interventions and complications of survivors and non-survivors

Almost all patients received empirical antibiotic treatment, 38 were given dexamethasone, 35 received 1 to 2 doses of tocilizumab, 34 were started on antimalarial drugs (i.e., hydroxychloroquine) and 22 were on remdesivir. Hemoperfusion was performed in 62 patients, convalescent plasma transfusion was given to 25 patients and prone positioning was done in 21 patients. Other treatments given are listed on Supplementary Table 3. ARDS (72.1%, OR 2.33, p 0.038) was the most frequently observed complication, followed by septic shock (70.5%, OR 5.6, p <0.001) and AKI (68%, OR 2.85, p 0.008), all of which occurring significantly in the non-survivor group (Supplementary Table 3).

Laboratory findings, respiratory outcomes and complications among younger and older patients, hypertensive and non-hypertensive patients

Comparisons between the younger and older, as well as, among hypertensive and non-hypertensive patients were also done, in terms of laboratory findings, respiratory parameters, oxygen support, outcomes and complications (Supplementary Tables 4 and 5, respectively).

Mean baseline BUN was significantly higher in the older (32.2 mg/dL SD ± 30.95) and hypertensive (29.7 mg/dL ± 31.22) patients while serum albumin was lower in the non-hypertensive group (2.2 g/dL ± 0.61). Acute kidney injury (AKI) was significantly higher among hypertensive patients (75.3% vs 44.8%) while other complications such as myocarditis and VTE were more evident in the non-hypertensive group.

Ventilator days and number of hospital days of survivors and non-survivors

The mean length of hospital stay was 25.7 days (SD ± 26.39), this was notably longer in the survivor group at 35.1 days (SD ± 26.54) compared to 17.6 days (SD ± 23.61) in non-survivors. The mean length of ventilator use was 13.9 days (SD ± 15.65). The duration of mechanical ventilation was not significantly different among the survivors and non-survivors (Table 1).

Outcomes of laboratory-confirmed and probable SARS-CoV-2 infection

From March to July 2020, the overall mortality rate of patients with critical SARS-CoV-2 infection was 53.3%. Sixty three percent of which were laboratory-confirmed while 37% were probable cases. Fifty-seven patients (46.7%) were eventually transferred out of critical units and/or discharged from the hospital (Table 2).

Table 1. Ventilator days, number of hospital days of survivors and non-survivors

	Total (N = 122)	Survivor (n = 57)	Non-survivor (n = 65)	p
Ventilator days	13.9 ± 15.65	15.1 ± 13.16	13.1 ± 17.22	0.512
Hospital days	25.7 ± 26.39	35.1 ± 26.54	17.6 ± 23.61	<0.001

Data are mean (±SD). p values were calculated by Pearson Chi-Square, or Fisher's exact test, as appropriate.

Table 2. Outcomes of laboratory confirmed and probable SARS-CoV-2 infection

Outcomes	Total (N= 122)	Confirmed SARS-CoV-2 Infection (n = 76)	Probable SARS-CoV-2 Infection (n = 46)	p value
Transferred/ Discharged	57/122 (46.7%)	35 (61.4%)	22 (38.6%)	0.849
Expired	65/122 (53.3%)	41(63.1%)	24(36.9%)	0.849
No aggressive measures (DNR, limit labs and medications)	21(17.2%)	11 (52.4%)	10 (47.6%)	0.303

Data are mean (±SD), n (%), or n/N (%). p values were calculated by Pearson Chi-Square, or Fisher's exact test, as appropriate. DNR = do not resuscitate

DISCUSSION

Clinical and laboratory characteristics of survivors and non-survivors

According to this study, among patients admitted at the ICU for critical SARS-CoV-2 infection, the majority were older men, hypertensive and with no significant travel history. These patients presented with shortness of breath, cough and fever, as reflected in studies by Guan et al. and Huang et al. in Wuhan, China.[1] Mean laboratory findings on baseline evaluation showed lymphocytopenia, elevated inflammatory markers, prolonged prothrombin time, elevated BUN, creatinine and liver enzymes. In a meta-analysis by Shao et al., higher levels of serum creatinine and BUN were associated with a significant increase in fatality in COVID-19 patients.[30] BUN is a nitrogenous end-product of protein metabolism and has been observed to be associated with mortality in various diseases and may indicate the presence of organ damage in addition to its role in the estimation of renal function. A multicenter review by Wernly et al. reported that BUN can independently predict mortality in critically ill patients admitted to the intensive care unit (ICU), while a study by Cheng et al. identified that the combination of BUN ≥4.6 mmol/L and D-dimer ≥ 0.845 µg/mL in COVID-19 patients were high risk for in-hospital mortality.[35] Coagulopathy was also reported by studies from Wuhan last January 2020, suggesting that elevated D-dimers and prolonged prothrombin time were among the baseline characteristics of patients critically ill with COVID-19.[1,4,7,10] Non-survivors in this study were observed to have significantly higher levels of BUN and prolonged prothrombin time consistent with earlier reports. As for imaging features, abnormal chest x-rays particularly bilateral infiltrates were noted in our population. This was congruent with a study by Cleverley et al., which emphasized that no single feature on a chest radiograph was specific or diagnostic for COVID-19 pneumonia, but a combination of multifocal peripheral ground glass opacities and/or consolidation, which were most commonly bilateral, were present in most reviewed cases.[31]

Laboratory characteristics and complications among younger and older patients, hypertensive and non-hypertensive patients

In this study, comparisons between the younger and older population, as well as, among hypertensives and non-hypertensives were done. Earlier reports conducted in Italy and Wuhan, China have noted that the elderly, and those with comorbidities are the most at risk for acquiring the disease, consisting primarily of hypertension (30%), diabetes (19%), and coronary heart disease (8%). Hypertension rates were particularly high in the severely ill, which was consistent with results of this study. This comorbidity is highly frequent in those with advancing age and func-

tionally impaired immune systems. A clear link has yet to be established with regards to survival and a causal relationship is yet to be found.[1,11,13,16,17] Significantly higher BUN levels were observed in the older patients which may be attributed to the age-related decline in renal function, as well as the increased vulnerability of AKI in the elderly.[25] Over time, uncontrolled high blood pressure can cause arteries around the kidneys to narrow, weaken or harden, thus disrupting the blood flow to the kidney tissue, causing decline in renal function.[26] In relation to this, the hypertensive population in this study was found to have a significantly higher mean BUN on admission and noted to develop more cases of AKI. Literature has also shown hypoalbuminemia to be an independent predictive factor for mortality.[1] The mean baseline serum albumin was low (2.4 g/dL ± 0.62) upon review, although this did not show major difference with patient outcome. Hypertensive patients had significantly higher mean serum albumin levels, consistent with results from Hostmark et al., which revealed a positive association between serum albumin and blood pressure. This could be attributed to albumin's role in keeping the colloid osmotic pressure in blood. Myocarditis was also one of the complications and found more frequently among the non-hypertensive group according to the data of this study, along with the occurrence of venous thromboembolism. Critically ill patients are generally predisposed to thromboembolism due to the combination of immobility, systemic inflammation, platelet activation, endothelial dysfunction, and stasis of blood flow.[27] Inflammation and coagulopathy have been associated with morbidity and increased mortality in hospitalized patients with COVID-19, suggesting that either the viral infection itself or the cytokine storm produced by the hyperinflammatory state induces a prothrombotic state predisposing these patients to thromboembolic events. As for viral myocarditis, the proposed pathophysiology is a combination of direct cell injury and T-lymphocyte–mediated cytotoxicity, which was also found to be augmented by the cytokine storm syndrome.[28] Though myocarditis and venous thromboembolism were more frequently observed in patients without hypertension in this study, limited data have shown any association between developing such complications in the non-hypertensive population, hence this should be interpreted carefully. Based on some literature, the prevalence of myocarditis among COVID-19 patients particularly in the early stages of this pandemic was unclear, if not underreported.[28,36-39] This may be attributed to its heterogeneous clinical presentations especially in the critically ill with SARS-CoV-2 infection and partly from the lack of specific diagnostic modalities to determine the features of myocardial injuries in these patients.[1,28,38]

Complications in survivors and non-survivors

The most common complication observed was ARDS (72.1%), followed by septic shock (70.5%) and AKI (68%). These findings occurred more frequently among the non-survivor group and may indicate poor prognosis. In a large meta-analysis[40], it was shown that the incidence of ARDS was 14.8%. Likewise, three studies [1,41,42] in Wuhan, China reported that among patients with SARS-CoV-2 infection and those transferred to ICU, most of the patients developed ARDS (17-61%). Critical cases of SARS-CoV-2 infection can also be complicated by sepsis and/or septic shock and multiorgan failure including acute kidney injury.[46] According to Huang et al., 20% of SARS-CoV-2 infection patients developed sepsis and/or septic shock and were admitted to ICU. A review of research data reported that prevalence of septic shock in SARS-CoV-2 infection is variable, ranging from 4-28.9%.[47] Growing evidence also has demonstrated that AKI is prevalent among patients with SARS-CoV-2 infection, particularly among patients in the ICU.[43,44] A recent study from Yang et al. suggested that the incidence of AKI is quite high at 29% while in a retrospective study by Diao et al., 27.06% of the patients had AKI, and showed that elderly patients (aged 60 years and above) had much higher incidence (70%). Similar to AKI from other causes, SARS-CoV-2 infection-associated AKI is found to

have more adverse outcomes which is consistent with the findings in this study. AKI secondary to sepsis and development of ARDS lead to greater derangement of vital signs and laboratory examination with higher need for ventilatory and inotropic support. These can be attributed to global tissue hypoxia brought about by the disparity between oxygen demand and delivery to tissues resulting in multiple organ failure and increased mortality rate.[29] The elderly and in individuals with at least one comorbidity have higher odds of in-hospital death amongst the reported cases, to date. Compared with other studies, a higher prevalence of ARDS, septic shock and AKI were noted in the results, which could be due to the severity of infection included in this study, consisting only of critical SARS-CoV-2 cases admitted to the ICU.

Treatment modalities and interventions of survivors and non-survivors

According to Wang et al., a standard treatment protocol has yet to be made and the main approach still remains as supportive for patients with COVID-19 infection. An update of the Solidarity Trial found that the following treatment: remdesivir, hydroxychloroquine, lopinavir/ritonavir and interferon had little or no effect on mortality, initiation of ventilation and duration of hospital stay. As of this writing, only corticosteroids have been proven as beneficial for severe and critical cases. The main approach is still primarily supportive in nature. Antibiotic therapy was initiated in 21 patients with 31% receiving dexamethasone, 29% receiving tocilizumab and 18% receiving antiretroviral treatment and remdesivir. Other interventions included hemoperfusion (51%), convalescent plasma infusion (20%) and prone positioning (17%). Based on this study, the treatment and interventions given showed no significant difference in the outcome of patients in terms of mortality, consistent with reports from earlier studies. In contrast, dexamethasone failed to show any benefit on survival, but it should be noted that use of corticosteroids was not in the initial treatment regimen and was added on later in the course of this study.

Respiratory parameters of survivors and non-survivors and mortality

For critically ill patients admitted to the ICU in this study, a large proportion required mechanical ventilator support (77.9%), slightly lower than that observed in the Lombardy trial (88%). In the same review, PEEP was 14 mmHg (12-16 mm Hg) compared to the mean PEEP level of 9mmHg in this study population. Mean duration of mechanical ventilation was 13.9 days (SD ± 15.65) and mean hospital stay was 25.7 days (SD ± 26.39). The latter was significantly longer in survivors (35.1 days ± 26.54) in contrast with non-survivors (17.6 days ± 23.61). Baseline PaO2/FiO2 ratio was low at 200.4 mm Hg, with the lowest PaO2/FiO2 ratio noted among non-survivors at 104.7 mm Hg being statistically significant.

Overall, there was a 53.3% mortality rate for laboratory-confirmed and probable SARS-CoV-2 infected patients admitted at the ICU, in comparison to 67% in the Washington study, 61% in Wuhan Study [46] and only 26% in the Lombardy study. This discrepancy may be attributed to the difference in severity of respiratory failure in the given populations.

SCOPE AND LIMITATIONS

This study has some notable limitations. Primarily, it was conducted in a single tertiary institution which only included ICU patients. It was difficult to assess various host risk factors that may have been related to disease severity and mortality due to the short time period allotted for data collection, thus limiting the generalizability of the given results. At the same time, statistical analysis and p-values should be interpreted with caution, and non-significant p-values do not necessarily reflect the exact situation of the general population. Another limitation is its retrospective approach, which may contribute to inherent biases. For this reason, not all laboratory tests were performed on all patients (particularly inflammatory markers and albumin) which may have led to the underes-

timation of their relation with hospital death. It is recommended that patients with laboratory-confirmed and probable acute SARS-CoV -2 infection admitted at progressive care units and non-ICU settings be included in further studies, as well as the distinction between confirmed and probable cases of COVID-19 into separate groups in the analysis of data to give a better comparison between the two discrete populations. Narrowing the range between age groups among the participants of the study would also be more appropriate. Likewise, a prospective and multicenter study with larger sample size is needed to deduce the full picture of the spectrum of the epidemiology, clinical characteristics, severity and prognostic factors associated with SARS-CoV-2 infection.

CONCLUSION

Critically-ill patients admitted at the ICU for SARS-CoV-2 infection were predominantly older men, hypertensive and with a large proportion requiring mechanical ventilation. In non-survivors, there were noted elevated levels of prothrombin and BUN, which were neither considered as risk factors for poor outcome in previous studies. Observed complications such as ARDS, AKI and septic shock were also significantly higher. Overall, in-hospital mortality was 53.3%. The COVID-19 pandemic continues to cause concern to both the medical and non-medical community, hence, this aims to supplement the data provided by earlier foreign and local journals regarding patients suffering from critical SARS -CoV-2 infection.

DISCLAIMER

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Original Research

Risk Factors for Mortality of COVID-19 Confirmed Patients Admitted at the Lung Center of the Philippines

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ABSTRACT

BACKGROUND: COVID-19 is an emerging infection that has reached pandemic levels with a reported fatality rate of 3%-4%. As the knowledge about COVID-19 is still evolving, local data tackling disease characteristics and outcomes has yet to be published. Local studies on outcomes of COVID-19 in-patients and predictors of mortality are lacking as well.

OBJECTIVE: To determine the risk factors at baseline that predicts in-hospital death due to COVID-19 for patients admitted at Lung Center of the Philippines.

METHODS: We conducted a retrospective cohort, observational, and analytical study that used chart review for data collection. The study subjects included cases of confirmed COVID-19 patients that were either admitted and/or discharged, or expired at the Lung Center of the Philippines (LCP) from March 7 to August 31, 2020. Patients who were less than 19 years old, with missing data or information, and who opted for advance directives (i.e., do not intubate, do not resuscitate), or discharged against medical advice, and transferred to another hospital were excluded.

RESULTS: Only 258 out of the 531 admitted patients were included in this study. There were 84 non-survivors, and 174 survivors. Non-survivors were older and had more than one co-morbidity, particularly, chronic kidney disease (CKD). Fever, cough, and dyspnea were the most common symptoms of disease onset. The inflammatory markers that were significantly elevated among non-survivors were aspartate aminotransferase (AST), C-reactive protein (CRP), lactate dehydrogenase (LDH), procalcitonin, and troponin I. Multivariate analysis showed that, low oxygen saturation (OR 0.952 CI 0.92-0.99 p 0.015), low Glasgow Coma Scale (GCS) score (OR 0.4722 CI 0.27 – 0.83), estimated glomerular filtration rate (eGFR) (OR 0.9681 CI 0.95-0.98 p<0.001), neutrophilia (OR 1.0485 p 0.036), and increased LDH (OR 1.0038 CI 1.002 – 1.006 p<0.001) correlates with mortality.

CONCLUSION: Physical findings of decreased oxygen saturation, low GCS score, as well as baseline laboratory findings of increased neutrophils, increased LDH, and decreased eGFR may warrant more aggressive management on COVID-19 inpatients as they confer increased risk for mortality.

KEYWORDS: *COVID-19, SARS-CoV-2, mortality, risk factors*

INTRODUCTION

The latter part of 2019 saw the emergence of a novel coronavirus and was later termed SARS-CoV-2 or COVID-19. It was first reported in Wuhan City, the province of Hubei, China. The has reached pandemic proportions – affecting 58 million people in 218 countries and killing more than 1,392,000 to date.[1] The Philippines was not exempted from this global pandemic with over 400,000 cases by November 2020 and over 8,000 deaths due to this disease.[3] With the ease of lockdowns both locally and internationally, the number of COVID-19 cases continues to rise.

SARS-CoV-2 hails from a family of *Coronaviridae*, a zoonotic infection known to infect both humans and animals.[4] The majority of people that were infected developed mild-to-moderate flu-like symptoms or respiratory illness, while the vulnerable portion of the population such as the elderly and those who have underlying chronic conditions developed serious illnesses.[5] Person-to-person transmission through respiratory droplets and infected surfaces has been the most documented modes of transmission.[5] The incubation period of the virus is within 2-14 days of exposure. One infected person has the capacity to infect 6-14 other people. Countries have adopted several measures to mitigate the spread of the virus and infection which forced several industries as well as local and international travels to shut down.[6]

Several foreign studies show that different demographic, clinical, laboratory, and radiographic findings were found to influence mortality, wherein self-reported dyspnea, tachypnea, and elevated inflammatory markers conferred greater risk of mortality.[8,9-12,14,22] Baseline chest X-ray and chest CT-scan findings were not found to be associated with greater mortality risk.[12]

As the knowledge about COVID-19 is still evolving, local data tackling disease characteristics and outcomes has yet to be published. Local studies on outcomes of COVID-19 in-patients and predictors of mortality are still lacking.

OBJECTIVES

To determine the risk factors associated with mortality in COVID-19 confirmed cases admitted at the Lung Center of the Philippines (LCP). Specifically, this study aimed to: (1) determine and compare the baseline demographic, epidemiologic, and clinical characteristics, disease severity, and time from onset of illness to hospital admission among survivors and non-survivors; (2) to determine and compare baseline inflammatory and infection markers of patients who recovered and died; and (3) to determine and compare the initial radiologic and CT scan findings among survivors and non-survivors. This will help identify preventable causes of death among patients with COVID-19 and also prognosticate patients with advanced disease.

METHODS

Study Subjects and Design

This research was a retrospective cohort, observational, and analytical study using chart review for data collection. The study subjects included patients with COVID-19 confirmed by RT-PCR testing or SARS-CoV-2 GeneXpert who were admitted and/or discharged or expired at the LCP from March 7 to August 31, 2020. Patients who were less than 19 years old, with missing data or information, and who opted for advance directives, or discharged against medical advice, and transferred to another hospital were excluded.

Data Collection and Processing

A pooled patient master list from the Hospital Epidemiologic Surveillance Unit and Admissions and Records section of LCP was obtained to identify subjects. Demographic and clinical characteristics, baseline radiologic and laboratory parameters of the identified patients were extracted through chart review using a standard data collection tool (Supplementary Data 1&2:http://philchest.org/publications Supplementary_Tables_Manuscript_No9.pdf)

Based on the current observed case fatality rate in the Philippines of 4.3% from the Department of Health, a minimum sample size of 253 confirmed COVID-19 patients satisfying the inclusion/exclusion criteria were required to have an 80% chance of describing the clinical course and determining the risk factors of mortality among confirmed COVID-19 patients at 2.5% margin of error.[16] A total of 531 closed confirmed COVID-19 cases were recorded during the specified study period. Simple random sampling was done using a random number generator to retrieve the charts. A total of 270 charts were pulled out – 6 patients were excluded due to age, while another 6 patients had advanced directives. Descriptive statistics was used to summarize the demographic and clinical characteristics of the patients. Frequency and proportion was used for categorical variables, median and inter-quartile range for non-normally distributed continuous variables, and mean and SD for normally distributed continuous variables. Independent sample T-test, Mann-Whitney U test, and Fisher's Exact/Chi-square test was used to determine the difference of mean, rank, and frequency, respectively, between alive and expired patients. Odds ratio and corresponding 95% confidence intervals from binary logistic regression were computed to determine significant predictors for mortality. Stepwise method was utilized to determine the final multivariate model. All statistical tests were two-tailed test. Shapiro-Wilks test was used to test the normality of the continuous variables. Missing variables were neither replaced nor estimated. Null hypotheses were rejected at 0.05 α-level of significance. STATA 13.1 was used for data analysis.

Ethical Considerations

The study protocol was approved by the LCP Institutional Ethics Review Board. Data from this study was utilized solely for academic purposes. Patient names were initially used to retrieve medical records but were eventually coded and deleted from the data collection tool. Raw data from the study will be disposed after two years.

RESULTS

Out of the 531 identified subjects, 270 charts were retrieved using a random number generator for data extraction and analysis. Twelve subjects were excluded due to age limitation of less than 19 years old (n=6) and presence of advanced directives (n=6). From the analyzed charts, 174 subjects survived and 84 did not – putting the crude mortality rate at 33%. Supplementary Table 3 summarizes the demographic, clinical, baseline physical, laboratory and radiographic findings of admitted patients. The mean age of admitted patients was 57 years old (56.83 + 14.4, p<0.001), with majority having no known exposure to COVID-19 (n=118, 47.01%, p 0.273). The mean age of non-survivors was significantly higher as compared to survivors at 62 years old (61.82 + 12.6 vs 54.43 + 14.66, p<0.001). Most of the admitted patients were male but differences in sex distribution and time of illness onset to hospital admission were not significant. The most common reported symptoms upon admission were fever, cough, and dyspnea. However, more survivors reported dyspnea and sore throat as their presenting symptoms. Hypertension and type 2 diabetes mellitus were the most common comorbidity among COVID-19 inpatients. Non-survivors reported having two or more comorbidities with the prevalence of CKD as compared to patient survivors. Smoking status and pack year history did not significantly differ between the two groups.

Most of the admitted patients were classified as moderate (n=157, 61.81% p<0.001), followed by critical (n=45, 17.72% p<0.001), and severe (n=44, 17.32% p<0.001) in terms of disease severity on admission. Majority of the patients with moderate COVID-19 on admission survived (n=132, 77.65% p<0.001), while those classified as critical did not (n=37, 44.05% p<0.001). There were significantly more survivors as compared to non-survivors (n=24 vs 20, p<0.001) among patients with severe COVID-19.

Physical examination during admission showed that the patients in the non-survivor cohort were more tachycardic, tachypneic, and desaturated at room air thereby requiring a significantly higher oxygen support on admission as compared to survivors. Baseline arterial blood gases showed a more decreased mean pH and metabolic acidosis in non-survivors. PO2/FiO2 (PF) ratio was lower in non-survivors (n=162.2, range 91-265.7 p<0.001). Complete blood count (CBC) among non-survivors during admission revealed an increase in white blood cell count (WBC) and neutrophil fraction. CRP, LDH, procalcitonin, troponin I, and AST levels were found to be significantly elevated among non-survivors. Conversely, higher eGFR, and a lower baseline creatinine was observed in survivors. No electrolyte abnormality was noted to be significantly present in either cohort. Bacteremia and consolidation on baseline chest X-ray were more prevalent in non-survivors (n=7, 20% p 0.011 and n=21, 25% p<0.001) than survivors (n=2, 3.28% p 0.011 and n=14, 8.05% p<0.001).

Table 1 summarizes the treatment that was initiated on patients upon admission. Most patients received non-invasive forms of ventilation, with the majority belonging to the survivor cohort. Invasive ventilation on admission was seen more among non-survivors (n=34 vs 12, p<0.001), while non-invasive ventilation via nasal cannula (n=109 vs 28, p<0.001) and at room air (n=28 vs 2, p<0.001) was seen in patients who survived. Hemoperfusion and hemodialysis on admission were required more by non-survivors (n=26 vs 21, p 0.006).

Table 1. Treatment Initiated on Admission

	Total (n=258)	Non-Survivors (n=84, 33%)	Survivors (n=174, 67%)	P-value
	Frequency (%)			
Invasive ventilatory support No Yes upon admission	169 (65.5) 46 (17.83)	13 (15.48) 34 (40.48)	156 (89.66) 12 (6.9)	<0.001
Non-invasive ventilatory support (n=201) Room air Hi Flow BIPAP CPAP NC Face Mask NRM	30 (14.91) 20 (9.95) 1 (0.5) 1 (0.5) 137 (68.16) 8 (3.98) 4 (1.99)	2 (4.35) 10 (21.74) 0 0 28 (60.87) 2 (4.35) 4 (8.7)	28 (18.06) 10 (6.45) 1 (0.65) 1 (0.65) 109 (70.32) 6 (3.87) 0	<0.001
Hemoperfusion	47 (50.54)	26 (68.42)	21 (38.18)	0.006
Hemodialysis				
Status (n=77) Done	27 (35.06)	21 (60)	6 (14.29)	<0.001

Table 2 shows the significant risk factors for mortality which was determined after logistic regression and multivariate analysis. Oxygen saturation (OR 0.952 CI 0.92-0.99 p 0.015), GCS score (OR 0.4722 CI 0.27 – 0.83), and baseline eGFR (OR 0.9681 CI 0.95-0.98 p<0.001) were found to decrease mortality. Factors that conferred increased mortality were neutrophilic ratio (OR 1.0485 p 0.036) and LDH (OR 1.0038 CI 1.002 – 1.006 p<0.001) – increasing mortality odds by 4.85% and 0.38%, respectively per unit increase.

Table 2. Multivariate Odds Ratio of the Significant Risk Factors for Mortality of COVID-19 Patients

Parameters	Adjusted Odds ratio	95% CI	P-value
Oxygen Saturation (O2sat)	0.9520	0.92 to 0.99	**0.015**
GCS Scoring	0.4722	0.27 to 0.83	**0.010**
Neutrophils (multiply by 100)	1.0485	0.27 to 0.84	**0.036**
EGFR (by EPI)	0.9681	0.95 to 0.98	**<0.001**
LDH	1.0038	1.002 to 1.006	**<0.001**

DISCUSSION

The initial results of this retrospective cohort on COVID-19 mortality was the first among all the designated referral centers in the country. Mortality rate was 33% and consistent with the other studies which ranged between 20%-44%.[26-28] We found through multivariate logistic regression that lower baseline oxygen saturation, eGFR and GCS, neutrophilic predominance on CBC, and high LDH levels conferred an increased mortality rate.

A lower baseline oxygen saturation could correlate to increased disease severity on admission. A retrospective cohort study by Wang et. al showed that low oxygen saturation on admission was largely attributed to disease severity and impending acute lung injury through cytokine storm.[11] This was also found on a recent study by Bahl et. al which showed that low oxygen saturation on admission is a risk factor for in-hospital death.[25] Xie et. al stated that it is the most powerful predictor of death among the multiple variables that was measured and that severe hypoxia was associated with elevation of inflammatory markers, which is also consistent with our study.[29]

A low GCS score in association with increased mortality was seen on a study of COVID-19 patients in Italy and on COVID-19 patients with pre-existing stroke.[30,31] It was regarded as part of the Sequential Organ Failure Assessment (SOFA) score in the retrospective cohort done by Zhou et. al wherein an increased SOFA score conferred a 5x higher risk of mortality.[12] A low GCS score can therefore be seen as part of an advanced end-organ damage associated with sepsis syndrome. GCS score is also part of the Modified Early Warning Score (MEWS) and Rapid Emergency Medicine Score (REMS) where it established high predictive values for mortality of admitted critically-ill patients with COVID-19.[32]

A study by Lin et. al showed that the mechanism of kidney injury in COVID-19 involves direct attack to the intrinsic renal cells and that high Angiotensin Converting Enzyme-2 (ACE2) on the proximal tubular epithelial cells are targets of SARS-COV-2 thereby induces decreased eGFR.[33] There is 30% prevalence of kidney disease on admission which was associated with greater in-hospital mortality according to an international registry in Europe and America.[34] Chronic kidney disease, which can also yield a decreased eGFR at baseline, has also been found in our univariate analysis as a comorbidity with significant effect on mortality. The study by Uribarri et. al also stated that patients with low eGFR conferred greater risk of mortality when CKD patients were excluded from the analysis.[34] Decreased eGFR at baseline can likewise be a manifestation of end organ damage due to

sepsis which is usually present in COVID-19 patients admitted in our institution.

Increased neutrophilic ratio was found in this study to confer increased mortality. This finding was also found in other cohorts and descriptive studies that specifically looked at neutrophil to lymphocyte ratio (NLR) as a novel biomarker for the dysregulated immune response seen in more severe COVID-19 infections as well as for non-refractoriness of the disease.[11,24,25] The pathophysiology of increased neutrophils is theorized to be in direct correlation to the proinflammatory response – leading to preferential production of neutrophils and subsequent apoptosis of lymphocytes. A study in Wuhan University, China found that neutrophilia is significantly associated with greater risk of developing acute respiratory distress syndrome (ARDS) and it can lead to severe pneumonia and death. [35]

LDH, a housekeeping enzyme present in various tissue types including the cardiomyocytes, pneumocytes, kidneys, liver, and striated muscle is another proinflammatory marker found in this study that increases the odds for mortality.[12,22] As such, the release/increased levels of LDH in the circulation often heralds cytokine-mediated tissue damage and/or injury. Increased LDH levels in COVID-19 often correlate with acute lung injury from severe interstitial pneumonia often culminating in ARDS.

Other inflammatory markers such as ferritin, troponin I, D-dimer, and CRP were not seen to be significantly elevated in non-survivors in this study unlike what was seen in cohorts done earlier which may be due to the limited availability of these laboratory exams during the initial months of the pandemic.[9,11,12] The utility of these inflammatory markers can therefore be realized by doing a prospective cohort study in the future.

The 4C (Coronavirus Clinical Characterization Consortium) mortality score developed by the World Health Organization-International Severe Acute Respiratory and Emerging Infections Consortium predicts in-hospital mortality for admitted COVID-19 patients.[36] Included in this scoring are the oxygen saturation, GCS score, kidney function, and inflammatory markers which are consistent with our study. Thus, the combination of the physical examination findings and laboratory values deemed to be significant predictors of mortality elicited in this retrospective cohort and can be used as a guide among patients who has poorer prognosis at baseline and warrants a more aggressive management. Although no treatment regimen has yet been identified to significantly alter mortality, risk factors for mortality can help clinicians identify patients who needs more close monitoring and allocate care accordingly.

Since the development of vaccines against COVID-19, more recent studies have emerged that investigated the impact of the vaccine rollout and on the risk factors for severe COVID-19 outcomes.[37] In the study done by CDC, immunosuppression, pulmonary disease, liver disease chronic kidney disease, and neurologic diseases were found to be risk factors for either respiratory failure, ICU admission and/or death.[37] Age, chronic kidney disease, and neurologic disease were also risk factors identified in this study.

LIMITATIONS AND STUDY RECOMMENDATIONS

The study having a retrospective design has several limitations, namely: (1) incompleteness of some of the data gathered (i.e., BMI and other inflammatory markers); (2) non-uniformity of some laboratory values due to their initial unavailability in-house; (3) lack of specific data in some of the subjects may underestimate their role in COVID-19 mortality; and, (4) findings in this study is also limited by number of subjects analyzed compared to the target population identified. A more comprehensive analysis can be obtained after all eligible study subjects are included. An update to this study is warranted to capture the effect of vaccination in the local setting as well as the emergence of novel variants.

CONCLUSION

Oxygen desaturation, low GCS score, decreased eGFR, increased LDH, and neutrophilia were found to increase the risk of mortality for COVID-19 inpatients. Invasive ventilator support, other clinical and laboratory findings, hemoperfusion, and hemodialysis were not found to significantly affect mortality for COVID-19 after adjusting for confounders. Predictors for greater risk of mortality whether clinical or laboratory findings will guide the healthcare team to allocate more aggressive management to which patients accordingly.

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Original Research

Utility of High Flow Nasal Cannula and its Predictors of Failure in COVID-19 Associated Acute Hypoxemic Respiratory Failure

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ABSTRACT

BACKGROUND: The use of high flow nasal cannula (HFNC) among patients with severe COVID-19 associated hypoxemic respiratory failure especially in resource-limited institutions is uncertain. HFNC was extensively used in different countries with limited access to intensive care unit (ICU) resources. However, only few data exist regarding its use among COVID-19 patients in general wards and predictors of failure are still being studied until now.

OBJECTIVE: To determine the HFNC use among COVID-19 patients including the predictors of HFNC failure in a non-ICU setting.

METHODS: We conducted a descriptive-retrospective study of 71 patients with acute hypoxic respiratory failure due to COVID-19 pneumonia admitted at Vicente Sotto Memorial Medical Center from March 1, 2020 to September 30, 2020. Patient's, age, gender, comorbidities, vital signs, arterial blood gas results, and Respiratory Rate-Oxygenation (ROX) indices were determined and correlated with HFNC failure.

RESULTS: Among the 71 severe COVID-19 patients who received HFNC, 36 (51%) were successfully weaned while 35 (49%) failed and were intubated. The mean age (in years) of intubated patients is higher (58.14 + 13.7) than those weaned ((57.5 + 11.6), p =0.832). Hypertension is the most common comorbidity in both groups. Tachycardia was slightly associated with HFNC failure (p=0.097). Intubated patients have shorter HFNC duration with mean of 35.7 hours than those weaned with 53.1 hours (p=0.000) and they also have shorter hospital days with mean of 5.5 days while 14.5 days for those weaned (p=0.000). Patient's disposition and HFNC therapy are significantly related (p=0.000). Use of the ROX index to determine HFNC success is statistically significant (p=0.000). ROX-2 of 4.85 can classify 97.1% of those who will be weaned and 85.7% of false positives. Thirty-three (94%) out of 35 intubated patients died while 1 (1.4%) out of 36 weaned patients died. ROX-2 score is an important predictor of HFNC failure.

CONCLUSION: HFNC provides respiratory support among severe COVID 19 patients and successful weaning can be done on more than half of those who received it even in a non-ICU set-up.

KEYWORDS: *COVID-19, acute hypoxemic respiratory failure, high flow nasal cannula, ROX index*

INTRODUCTION

The current COVID-19 pandemic, caused by SARS-CoV-2 tragically infected 110,224,709 people in across 219 countries with 2,441,901 mortalities as of February 20, 2021.[1] Majority (81%) have mild respiratory symptoms, while 19% progress to severe to critically–ill pneumonia thereby increasing the burden on healthcare systems especially among the world's least developed countries.[2-3] Shortages of ICU beds and mechanical ventilators among hospitals were reported during the peak of the pandemic that compromised care.[4,5,6]

Acute hypoxemic respiratory failure (AHRF) is the most concerning complication of severe COVID-19 patients with numerous mechanisms that includes pulmonary edema, hemoglobinopathies, vascular occlusion, and ventilation and perfusion (V/Q) mismatch.[7] It requires a high fractional concentration of inspired oxygen (FiO2) since the variable pulmonary compliance related to severe COVID-19 is comparable to pulmonary compliance reported for acute respiratory distress syndrome (ARDS).[8]

High flow nasal cannula (HFNC) is a non-invasive respiratory modality that improves oxygenation by providing humidified and heated gas up to 60 L·min−1 with an FiO2 up to 1.0 that washes out pharyngeal dead space (CO_2 removal), reduces labored breathing, provides continuous fraction of inspired oxygen with a positive end expiratory pressure, and attains 100% humidification.[9-10] Its use in wards could be a lifesaving modality for patients suffering from severe respiratory compromise awaiting ICU care especially in hospitals with high influx of COVID-19 admissions and overburdened critical care units.[6,11] Evidence-based guidelines on HFNC use in a non-ICU setting and its use in infected patients with other corona viruses are still limited especially during the start of pandemic.[11-12] In the Philippines, local guidelines from the Philippine College of Chest Physicians (PCCP) and Philippine Society for Microbiology and Infectious Diseases (PSMID) were used as references as to when HFNC can be safely used among COVID-19 patients and when endotracheal intubation is deemed necessary.[13-14]

Vicente Sotto Memorial Medical Center (VSMMC), is among the active government hospitals in Cebu that catered the majority of severe to critical COVID-19 patients. Out of the total 1,133 admitted COVID-19 patients from March 1, 2020 to September 30, 2020, 96 (0.08%) received HFNC. This study will serve to corroborate the utility of HFNC among COVID-19 patients in a resource limited center particularly in non-ICU-setting and identify possible factors that will predict HFNC failure.

OBJECTIVES

To ascertain the utility of high-flow nasal oxygenation via HFNC for severe COVID-19 associated hypoxemic respiratory failure. Specifically, we aim to determine the (1) age, gender and co-morbidities of admitted COVID-19 patients on HFNC; (2) proportion of patients with hypoxic respiratory failure successfully weaned off from HFNC; and, (3) factors that predict HFNC failure.

METHODS

Study Design

This is a descriptive, retrospective, and single-center records review study of severe COVID-19 patients who received HFNC to determine its use and its predictors of failure.

Study Setting

This study was a medical chart review from March 1, 2020 to September 30, 2020 conducted at Vicente Sotto Memorial Medical Center.

Population and Sampling Technique

The study involved a total enumeration of medical records of patients who received HFNC from the mentioned dates, hence, no sample size was calculated. The data collection ran for a period of 6 months.

Inclusion Criteria

All confirmed severe COVID-19 (laboratory confirmed SARS-CoV-2 positive via PCR with SpO2 <90, RR >30) patients admitted from March 1, 2020 to September 30, 2020 who received oxygenation via HFNC aged 18 years old and above; with or without diagnosed co-morbidities, with Glasgow Coma Scale (GCS) of >8, stable vital signs (i.e., no paradoxical breathing, no need of vasopressors, no fatal arrhythmias, not in cardiac or respiratory arrest) and no recent facial or neck trauma, either discharged or died during their stay at the COVID-19 ward of Vicente Sotto Memorial Medical Center were included in the study.

Exclusion Criteria

Excluded from the study are patients who received intubation prior to HFNC therapy, less than 18 years old, with poor sensorium (GCS<8), with cardiac or respiratory arrest that necessitates immediate intubation, and those with recent facial or neck trauma.

Figure 1 shows the conceptual framework of the study. Severe COVID-19 patients with acute hypoxic respiratory failure with good sensorium (GCS >8), stable vital signs (i.e., no paradoxical breathing, no need for vasopressors, no fatal arrhythmia, not in cardiac and respiratory arrest), and no trauma on the face and neck were identified. The severity of hypoxia were classified based on their ABG results as mild (Pao2/FiO2 of 200-300), moderate (Pao2/Fio2 of 100- 200), or severe (Pao2/Fio2 of <100). These patients were attached to HFNC and their condition was assessed whether there is improvement based on their sensorium, vital signs and oxygenation as to their respiratory rates, ROX index and ABG results. Weaning off from HFNC implies improvement of condition or HFNC success regardless if the patient died from other causes while endotracheal intubation denotes HFNC failure.

Patients who were weaned off from HFNC were either directly discharged from the hospital or transferred to regular IM ward but their course in the ward were not followed up.

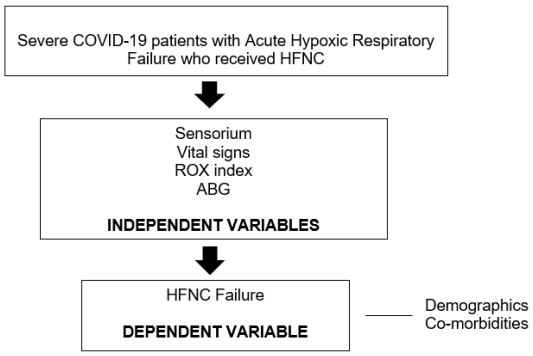

Figure 1. Conceptual Framework

Data Collection Procedure

All data using data collection form (Supplementary Data: http://philchest.org/publications/Supplemetary_Tables_Manuscript_No10.pdf) was taken from a retrospective medical records review. Demographic data, medical history, clinical characteristics that include vital signs (i.e., body temperature, respiratory rates, heart rates, and blood pressures), oxygen saturations, ABG results and clinical outcomes were gathered and analyzed. ROX indices (oxygen saturation/fraction of inspired oxygen to respiratory rate) at 2, 6 and 12 hours post-HFNC attachment for each patient were also computed to predict HFNC failure (need to intubate), based on the algorithm on the respiratory management of COVID-19 by the PCCP. Patients who were weaned off HFNC are considered to have HFNC success while those intubated patients have HFNC failure. These data were treated with statistical analyses suited for the objectives declared in the study.

Statistical Analysis

The clinico-demographic characteristics of the subjects were summarized using descriptive statistics. Qualitative variables were expressed as frequency and percentage

while quantitative variables as mean + standard deviation. Variables were compared among patients with different severity of hypoxemia, with successful (weaned) and failed (intubated) HFNC treatment, as well as between survivors and non-survivors. Binary logistic regression was used to ascertain the effects: ROX index 2 hours after HFNC attachment, respiratory rates prior HFNC, elevated blood pressure (>/= 140/90mmHg) and PF ratio 1 day after HFNC attachment on the success of therapy, with 0.05 level of significance. Prediction of HFNC failure was gauged using the area under the receiving operating characteristic curve (AUROC) plus cut-offs. SPSS software for statistical analyses was done.

Ethical Consideration

This study was conducted upon approval of the research protocol by the Ethics Review Board (ERB). Hospital permission was sought and review of medical records was granted. As a retrospective type of study without patient intervention, informed consent was waived. The investigator will suit the moral doctrines established within the National Ethical Guideline for Health and Health-related Research (2017) and in the Declaration of Helsinki. Important information innate to patients such as names and other identifying features will be kept confidential and all results will not be disclosed elsewhere except for future publications, in observance with the Data Privacy Act of 2012.

RESULTS

During the study period we identified 96 subjects with AHRF who received HFNC, 71 of which fit the inclusion criteria as shown in Figure 2. Majority (51%) had a successful outcome of which most of them were directly discharged (22.5%). Among those with failed (49%) HFNC therapy, 94% died.

Baseline characteristics of the subjects are presented in Table 1. Patients with severe hypoxemia are older with a mean age of 58 (s.d. = 12.4) compared to those who have mild and moderate hypoxemia. Majority of those with severe hypoxemia are males (53.5%), afebrile (66.2%), and with comorbidities including hypertension (52.1%) and diabetes (33.5%). Two patients (2.8%) had an arterial partial pressure of oxygen <60mmHg and SpO2 <90 but with PF ratio > 300 thus, severity of hypoxemia was classified as very mild.

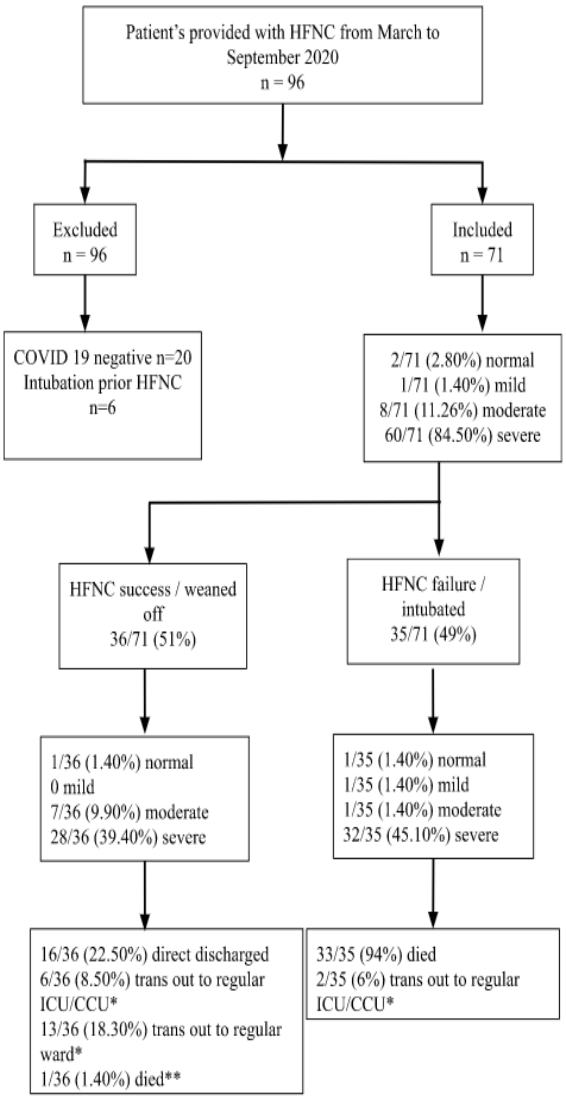

Figure 2. Diagram of HFNC outcomes and survival
*Recovered = IgG positive patients
**Sudden death = weaned off from HFNC but died from other causes

Table 1. Baseline Characteristics and Severity of Hypoxemia

Characteristics	Severity of Hypoxemia			
	Very Mild (n=2)	**Mild** (n=1)	**Moderate** (n=8)	**Severe** (n=60)
Age, years (mean±s.d.)	56.5±13.4	73.00	52.5±14.0	58.3±12.4
Gender				
Male	2 (2.8%)		5 (7.1%)	38 (53.5%)
Female		1 (1.4%)	3 (4.2%)	22 (31.0%)
Blood Pressure n (%)				
Hypertensive	1 (1.4%)	1 (1.4%)	6 (8.5%)	37 (52.1%)
Normal	1 (1.4%)		2 (2.8%)	23 (32.4%)
Heart rate n (%)				
Tachycardic	1 (1.4%)	1 (1.4%)	4 (5.6%)	26 (36.6)
Normal	1 (1.4%)		4 (5.6%)	34 (47.9%)
Temperature n (%)				
Febrile			1 (1.4%)	13 (18.3%)
Afebrile	2 (2.8%)	1 (1.4%)	7 (9.9%)	47 (66.2%)
Comorbidities n (%)				
Hypertension	2 (2.8%)	1 (1.4%)	7 (9.9%)	37 (52.1%)
Diabetes Mellitus	1 (1.4%)		3 (4.2%)	24 (33.8%)
PTB (ongoing treatment)	1 (1.4%)			4 (5.6%)
Bronchial Asthma				2 (2.8%)
CKD (ongoing hemodialysis)	1 (1.4%)			2 (2.8%)
Hepatitis				2 (2.8%)

Patients requiring intubation (HFNC failure) are older (mean=58.14,s.d.=13.7) than those who had successful HFNC therapy (mean=57.5,s.d.=11.6) as seen on Table 2. Most of those who required intubation are males (28.2%), hypertensive (31.0%), tachycardic (26.8%), afebrile (38.0%), with pre-existing hypertension (33.8%), and has diabe-

Table 2. Baseline Characteristics and HFNC Therapy Outcome

Characteristics	HFNC Outcome		Odds Ratio (95% CI for OR)	P-value
	Failed n=35	**Success** n=36		
Age, years (mean±s.d.)	58.14±13.7	57.5±11.6		0.832
Gender				
Male	20 (28.2%)	25 (35.2%)		0.282
Female	15 (21.1%)	11 (15.5%)		
Blood Pressure n (%)				
Hypertensive	22 (31.0%)	23 (32.4%)		0.928
Normal	13 (18.3%)	13 (18.3%)		
Heart rate n (%)				
Tachycardic	19 (26.8%)	13 (18.3%)	2.101 (.812-5.439)	**0.097
Normal	16 (22.5%)	23 (32.4%)		
Temperature n (%)				
Febrile	8 (11.3%)	6 (8.5%)		0.361
Afebrile	27 (38.0%)	30 (42.3%)		
Comorbidities n (%)				
Hypertension	24 (33.8%)	23 (32.4%)		0.434
Diabetes Mellitus	13 (18.3%)	15 (21.1%)		0.442
PTB (ongoing treatment)	3 (4.2%)	2 (2.8%)		0.486
Bronchial Asthma	2 (2.8%)			0.146
CKD (ongoing hemodialysis)	2 (2.8%)	1 (1.4%)		0.539
Hepatitis	1 (1.4%)	1 (1.4%)		0.984

*** significant at 0.10 level of significance; all other comorbidities such as COPD, malignancy, Thyroid, HIV, Valvular disease and myasthenia have only one case*

Table 3. Clinical Outcomes and Severity of Hypoxemia

Clinical Outcomes	Severity of Hypoxemia				P-value
	Very Mild (n=2)	Mild (n=1)	Moderate (n=8)	Severe (n=60)	
Length of Hospital stay (mean±s.d.)	6.0±7.1	3.00	15.4±8.2	9.6±8.0	0.172
Hours prior to HFNC (mean±s.d.)	73.5±100	6.00	104.9±85.5	36.1±104.2	0.331
Duration of HFNC (mean±s.d.)	17.0±9.9	38.00	121.3±61.5	110.9±119.7	0.618
HFNC outcome n(%)					
Success	1 (1.4%)		7 (9.9%)	28 (39.4%)	0.124
Failure	1 (1.4%)	1 (1.4%)	1 (1.4%)	32 (45.1%)	
Disposition n(%)					
Expired	2 (2.8%)	1 (1.4%)	1 (1.4%)	30 (42.3%)	**0.096
Discharged			5 (7.0%)	11 (15.5%)	
Trans out to ICU/CCU			2 (2.8%)	6 (8.5%)	
Trans out to regular ward				13 (18.3%)	

*** significant at 0.10 level of significance*

Patients with severe hypoxemia did not stay long in the hospital with a mean hospital day of 9.6 (s.d = 8.0) unlike those who were moderately hypoxemic with a mean hospital day of 15.4 (s.d=8.2) as seen in Table 3 above. Those patients with severe hypoxemia were started HFNC early on, within 36 hours after admission but attached longer to HFNC with a mean duration of 110.9 hours (s.d=119.7). HFNC therapy is successful in 51% of the subjects while 49% required intubation (HFNC failure). Moreover, among those with severe hypoxemia, HFNC was successful on 47% of them although 50% of the severely hypoxemic expired.

Those who were successfully weaned from HFNC therapy stayed longer in the hospital (mean=14.5, s.d=5.8) while those who were intubated stayed less than a week (mean=5.5, s.d=7.4), and this difference in the number of hospital days is significant (t(69)=-5.76, p=0.000) (see Table 4). The shorter hospital stay among those who were intubated is attributed to the increased mortality rate among them. Understandably, the duration of HFNC therapy is longer (in terms of hours) for those who were weaned (mean=53.1, s.d=59.1), than those who are intubated (mean=35.7, s.d=134.1) and this is statistically significant (t(69)=-4.91, p=0.000). The number of hours prior to HFNC therapy do not significantly differ between those who were weaned against those who were intubated. However, disposition of the patients and HFNC therapy are significantly related (x2= 61.116, p=0.000).

Table 4. Clinical Outcomes and HFNC Therapy

Clinical Outcomes	HFNC		P-value
	Failed n=35	Success n=36	
Length of Hospital stay, days (mean±s.d.)	5.5±7.4	14.5±5.8	*<0.005
Hours prior to HFNC (mean±s.d.)	58.14±13.7	57.5±11.6	0.480
Duration of HFNC, hrs. (mean±s.d.)	35.7±134.1	53.1±59.1	*<0.005
Disposition n (%)			
Expired	33 (46.5%)	1 (1.4%)	*<0.005
Discharged		16 (22.5%)	
Trans out to ICU/CCU	2 (2.8%)	6 (8.5%)	
Trans to regular ward		13 (18.3%)	

*** significant at 0.10 level of significance*

Among the different models considered, the only factor which is deemed to be significant in predicting the likelihood of

success (i.e., being weaned) is ROX-2. Taken as a single predictor, using ROX-6 or ROX-12 also serve as significant predictors but their predictive ability is deemed insignificant if taken together in a single model (i.e., with ROX- 2, ROX - 6, and ROX-12 as predictors in one logistic model).

A binary logistic regression was done to ascertain the effects of ROX-2, respiratory rate (RR) prior to using HFNC, Pao2/FiO2 (PF) ratio 1 day after HFNC attachment, and elevated blood pressure on the success of therapy, as shown in Table 5. The logistic regression model was statistically significant, $\chi^2(4) = 20.225$, p =0.000. It explained 34% (Nagelkerke R^2) *of the variance in HFNC therapy success and correctly classified 71.4% of cases. Those with lower ROX-2 have a 3.470 times higher chance of intubation.*

Prediction of HFNC failure or the need for mechanical ventilation was assessed using AUROC and cut-offs. It was found out that the use of ROX index to determine success of HFNC is statistically significant, p=0.000 and it is fair enough predictor (AUC=0.768, 95% C.I. 0.655 – 0.881). The corresponding Receiver Operator Characteristic Curve (ROC Curve) is shown in Figure 3.

A cut-off ROX index two hours after HFNC attachment of 4.85 can correctly classify 97.1% of those who will be weaned and can correctly classify 85.7% of false positives. The ROX index of 4.85 after the HFNC attachment is already a good cut-off score.

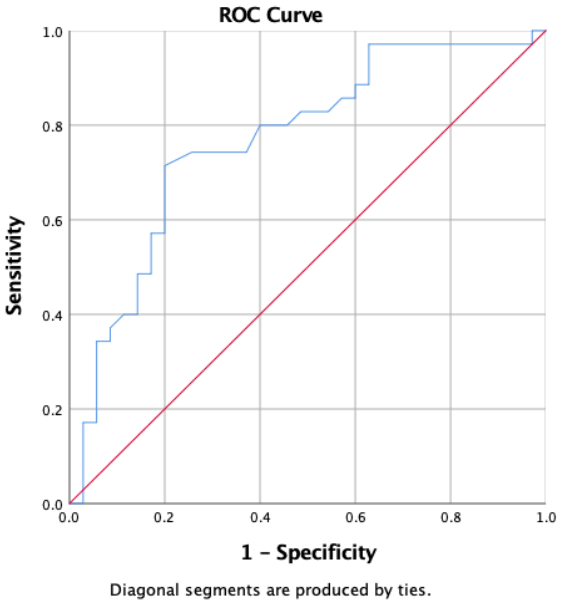

Figure 3. ROC Curve

Table 5. Logistic Regression Analysis of HFNC failure

Variables included in the Analysis	B	S.E	Sig	Odds	95% C.I. for odds	
					Lower	Upper
ROX 2 hours post HFNC attachment	1.244	0.522	0.017	3.470	1.25	9.65
RR prior HFNC attachment	-0.173	0.121	0.154	0.841	0.664	1.07
PF Ratio HFNC Day 1	0.004	0.006	0.505	1.004	0.993	1.02
Elevated Blood Pressure (1)	0.249	0.582	0.669	1.282	0.410	4.01
Constant	0.269	4.178	0.949	1.308		

df=1

DISCUSSION

COVID-19 has devastated the healthcare system worldwide. Burden of the disease has compromised the level of care significantly. Much has been done to augment the shortage of ventilatory support for severely hypoxemic patients, including the use of high flow nasal oxygenation via HFNC. HFNC is an easy to set, non-invasive and can be used outside the ICU setting.

Severe COVID-19 as defined by the World Health Organization is SARS-CoV-2 positive via reverse transcription polymerase chain reaction (rt-PCR) with either respiratory rate of >30 breaths/minute and oxygen saturation

of <90%.[15] Increasing age, especially older adults, having cardiovascular disease and diabetes mellitus, and male gender are risk factors for severe illness, [16] which also characterize the majority of the study population.

Age is a crucial risk factor for COVID-19 morbidity and mortality. Advanced age is related to a decline in respiratory function, weaker immune reaction, frailty, and comorbidities that increases the risk of getting complications.[17-22] Within the study, the mean age of intubated patients with 94% mortality is above than those weaned (58.14 $\pm$ 13.7 vs. 57.5 $\pm$ 11.6) but not significant (p=0.832). This is in contrast with a retrospective study of Hu et al., where age is significantly associated to HFNC outcome (p <0.001).[23] Mortality rate of COVID-19 is 8.1 times higher among those who are aged 55-64 years old compared with individuals who are $\leq$ 54 years old and more than 62 times higher among those $\geq$65 years old.[24] Men have 70% higher death rates in COVID-19 than women and is taken into account as a possible aspect for poor outcomes in other studies.[25] In the study, 28.2% of these intubated were males while 21.1% were females but no significance noted (p = 0.282) which is not concordant with study of Hu et al., where gender is significantly associated with HFNC outcome (p=0.025).[25] Men have more angiotensin converting enzyme-2 (ACE) receptors than women, which is the entry point of SARSCoV-2 into host cells, and would explain why men are more vulnerable to infection and its consequences, although other psychosocial, biological, and behavioral factors play a part.[24,25] These receptors act on the renin-angiotensin-aldosterone system (RAAS) which controls blood pressure, thus hypertension was linked to COVID-19,[26] with a two-fold increased risk of dying from it.[27] In the study, hypertension is the most common comorbidity in both failed and successful HFNC groups but no significance in HFNC outcome (p= 0.928) which is comparable in previous HFNC studies.[22,27,28]

This study showed that HFNC provided respiratory aid to severe COVID-19 patients who had hypoxic respiratory failure, and prevented most of them (51%) from being intubated and attached to mechanical ventilators. Major benefits of HFNC include giving patients with continuous positive airway pressure decreasing airway collapse, constant alveolar recruitment and more comfortable means improving compliance.[29] During a prospective randomized crossover study from Italy, researchers examined HFNC to oxygen therapy by face mask at approximately the same FiO_2 settings and their findings showed that HFNC significantly enhanced oxygenation, reduced respiratory rate and work of breathing, improved dynamic compliance, lung volume, transpulmonary pressures, and consistency.[30] Consistent with the study of Soffler et al., intubation rates were decreased in patients who received HFNC (55% vs. 72%) but mortality rates were similar.[31]

HFNC failed in almost half (49%) of the study population, with high mortality among this group who received mechanical ventilation which is analogous to the outcomes of a prospective multi-center observational study conducted in Cape Town, South Africa.[32] Within the latter study, high prevalence of HIV and tuberculosis, multiple comorbidities, and socioeconomic deprivation attributed to poor ventilation outcome which differs during this study since among the physiological parameters, increase in heart rate slightly affected HFNC success.[32] A prospective observational cohort study done in China wherein 145 patients were given HFNC, it concluded that tachycardia is related to HFNC failure reflecting decompensation of the cardiopulmonary system or increase in sympathetic drive resulting to poor outcomes.[32] The diagnostic accuracy of the ROX index could be intensified by incorporating the heart rates within the index (ROX-index/heart rate x 100) with a ROX-HR index of < 6.80 signifying HFNC failure.[33] Tachycardia as early as 1 hour after HFNC attachment was associated to HFNC failure as observed by Frat et al., during a multicenter analysis. [34]

The ratio of arterial oxygen partial pressure to fractional inspired oxygen (PF ratio) is used to measure respiratory efficiency and indicates degree of hypoxemia, with normal value of >400 mmHg at sea level.[35] A value of <100mmHg is classified as severe hypoxemia in Berlin's definition of ARDS with 45% death rate.[36] Within the study, the majority (85.7%) of the subjects have severe hypoxemia of which 45.1% among them had failed HFNC (p=0.124) and 42.3% of them died (p=0.096) as explained by its accompanying high mortality rate. No significant relationship between PF ratio, 1 day post HFNC attachment, and HFNC failure was found within the study which is similar in the study of Hu et al. (p= 0.722).[22] However, a significant relationship, (p=<0.001) was noted between PF ratio at HFNC initiation to HFNC outcome in a study done by Calligaro et. al. [9] Moreover, no association between respiratory rate prior HFNC attachment and HFNC failure was noted in the study which differs from the study of Park et al. (p=0.04).[31] The study shows that respiratory rate alone does not predict failure but when incorporated to ROX calculation, shows a relationship.

Majority (94%) of the intubated patients stayed less than a week (mean= 5.5, s.d = 7.4) and its difference on the length of hospital stay among those who were weaned is statistically significant (t(69) = -5.76, p=0.000). In addition, the duration of HFNC therapy is shorter than those who were weaned and is also statistically significant (t(69) =-4.91, p = 0.000). Both of these can be explained by the high mortality of intubated patients in the study, entailing HFNC failure as a poor prognosis. This is comparable with the multicenter retrospective cohort study done by Xia et al. in Wuhan China, where patients who received endotracheal intubation after failed HFNO showed a mortality rate as high as 75%.[36] Moreover, majority (80%) of COVID-19 patients who were intubated died which is consistent with the reports during the early outbreak in China.[37-38]

Shortage of ICU beds and ventilators due to the imposed severe strain of COVID-19 associate AHRF caused variation in the invasive mechanical ventilation rate among hospitals worldwide.[4,9, 39] Mechanical ventilation is an invasive vital breathing assistance provided among severe COVID-19 patients with unacceptable ROX-index and ideally done by rapid sequence intubation using a video laryngoscope, [8] which is being done in VSMMC. Algorithm in its initiation and settings set by the PCCP is being followed in VSMMC. Yet, it may result in airway injury, ventilator-induced lung injury promoting lung damage and introduces pneumonia which increases the chance of non-survival.[40-41] Once intubation is done, the patient must be monitored closely for accompanying risks involved.

HFNC failure may delay intubation thereby increasing mortality risk.[42] Survival and timing of intubation had a little but important relationship with one other, having a 1.001 (95% CI, 1.001–1.002) hazard ratio for every additional hour between admission and intubation during a large multihospital, retrospective cohort study done in New York City.[43] Delayed intubation results to self-induced lung injury that causes more severe ARDS causing death.[43] In relation with the study, patients with severe hypoxemia (85% of the entire study population) were started HFNC early on, within 36 hours after admission but attached longer to HFNC (mean=110.9, s.d=119.7) with 45% mortality. In a study done by Hyman et al., intubation increased the in-hospital mortality rate by 1.03-fold per day of delay among the retrospectively analyzed 755 intubated patients with COVID-19 pneumonia.[44] This emphasizes the importance of timely distinction of patients who would need mechanical ventilation from patients who may benefit from HFNC, [45] and once HFNC unsuccessfully improve gas exchange and ventilatory function, delaying tracheal intubation should be avoided.[46]

The use of ROX index to determine success of HFNC is statistically significant (p=0.000) and is fair enough predictor

(95%C.I., 0.655 – 0.881) as shown in the study. Using ROX two hours post HFNC attachment (ROX-2) provides early prediction of HFNC failure with a cut off ROX - 2 of 4.85 classifying 97.1% of those who will be weaned and 85% of false positives. Those with lower ROX-2 have a 3.470 times higher chance of intubation. This result differ from a 2-year multicenter prospective observational cohort study done by Roca et al. which is also being followed by the PCCP, where identified predictors of HFNC failure include a ROX< 2.85, <3.47, and < 3.85 at 2, 6, and 12 hours of HFNC initiation, respectively. Meanwhile, ROX – 2, 6 and 12 of >4.88 determine HFNC success.[48-49] Monitoring the patients' overall condition including hemodynamic stability and alteration in mental status must be considered also rather than ROX index alone when deciding for intubation.

Mortality in COVID-19 can also be attributed to its other complications. Severe COVID-19 may lead to cardiac arrhythmias, coagulopathy, rhabdomyolysis, acute cardiac, liver and kidney injury and shock[49] which may be related to high markers of inflammation like elevations in C-reactive protein and interleukin-6, hyperferritinemia, thrombocytopenia, lymphopenia and high procalcitonin and D -dimer levels[50]. However, these complications are beyond the scope of the study but can be included in future studies.

Caring for severe hypoxemic COVID-19 patients in a regular ward or a non- standard ICU setting with limited manpower and resources occurred in other countries like South Africa and Italy, but still cared for by intensivists.[30, 52] Like VSMMC, a tertiary government hospital in Cebu, admitted COVID-19 patients were provided respiratory support non-invasively in a non- ICU setting and multidisciplinary approach was undertaken. HFNC use in out-ICU-setting was successful in managing more than two-thirds of severe COVID-19 patients failing standard oxygen therapy in a study done in India.[53] Moreover, 9 ICU's in Philadelphia recorded a high endotracheal intubation rate of 69.9% among severe COVID 19 patients who received HFNC. [54] Results proved to show that severe COVID-19 patients with acute hypoxic respiratory failure managed in a resource limited institution specifically in regular ward did not portend worse outcome as compared to those admitted in ICU. [30 , 54 , 56] HFNC is thus a viable option with failure rates similar to those of ICU settings , [53, 54, 55] which is contrary in the study of Calligaro et al where HFNC failure rate experienced in ICU (44/105, 41.9%) was lower than in wards (76/188, 59.6%). [9]

Various studies suggested that HFNC use is associated with proven bio-aerosol dispersion of viable particles around the patient's room because of high gas flow used, but still unable to relate it clearly with the increased number of health care workers being infected.[56] Putting a surgical mask on top of HFNC among patients considerably lessens dispersion distance and the patients should be placed in an airborne isolation rooms with staffs wearing complete level 4 PPE while in the room, as advised also by the local guidelines. [12,14,52]

CONCLUSION

Providing severe COVID-19 patients with respiratory support through HFNC was deliverable and feasible even in a ward-based non-ICU setting in a tertiary government hospital. HFNC use improved oxygenation and reduced the rate and workload of breathing. It can be successfully weaned off on more than half of those who received it and conversely, there is a high mortality rate in patients who were intubated from failed HFNC. Success rate of HFNC use between ICU and non-ICU setting did not differ significantly compared to other studies.[53,54,56] ROX-2 score is an important predictor of HFNC failure.

Increase in heart rate slightly affected HFNC outcome and can be studied further as a predictor of HFNC failure. Future studies may also consider Sequential Organ Failure Assessment (SOFA) scoring, inflammatory bio-

markers (D-dimer, serum ferritin, LDH, procalcitonin) chest X- ray results, concomitant bacterial pneumonia as factors that might foresee HFNC outcome. Lastly, treatment regimens given to COVID-19 patients may also be pondered.

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Philippine Journal of Chest Diseases

Original Research

Non-Pulmonary Medicine Specialists' Knowledge, Attitude and Practice in the Diagnosis of Chronic Obstructive Pulmonary Disease in a Tertiary Hospital in Manila, Philippines

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ABSTRACT

BACKGROUND: Underdiagnosis of chronic obstructive pulmonary disease (COPD) in the Philippines has become one of the driving forces of medical organizations such as the Philippine College of Chest Physicians (PCCP) to increase awareness about COPD. According to the 2009 Philippine Clinical Practice Guidelines on COPD, several reasons for underdiagnoses are physician's lack of knowledge, poor attitude, and lack of practice regarding screening, diagnosis and management of populations at risk.

OBJECTIVE: To determine the knowledge, attitude and practice of non-pulmonary medical specialists in COPD diagnosis.

METHODS: We conducted an observational cross-sectional online questionnaire-based study. Non-pulmonary medical specialist consultants from the Departments of Internal Medicine and Family Medicine were recruited. A validated questionnaire was used to measure outcomes of the study.

RESULTS: Eighty-two (82) respondents participated in the study that was conducted from May to August 2020. Majority of the respondents were aware of the COPD Global Initiative for Chronic Obstructive Lung Disease (GOLD) guideline. Forty-five respondents (54.88%) knew how to interpret spirometry. Thirty-four (41.46%) were somewhat confident in diagnosing COPD based on GOLD. Almost all (97.56%) recognized that spirometry is essential in diagnosing COPD, however, only 8 (9.76%) always requested spirometry for COPD patients.

CONCLUSION: Majority of the respondents recognize the importance of spirometry in the diagnosis of COPD and are aware of the GOLD guidelines. However, its implementation and accurate interpretation is considerably lacking. Knowledge gaps were recognized but most of the respondents expressed their willingness to learn spirometry. The results of this study will help design educational modules for non-pulmonary specialists in diagnosing COPD which will improve physicians' awareness and knowledge on COPD diagnosis.

KEYWORDS: *COPD, diagnosis, spirometry*

INTRODUCTION

COPD is currently the 3rd leading cause of death according to the World Health Organization. More than 3 million people died of COPD in 2012, accounting for 6% of all deaths globally. Despite being a preventable and treatable disease, COPD is a major cause of mortality and morbidity.[1]

The Burden for Obstructive Lung Disease (BOLD) study showed that the prevalence of COPD among people aged 40 years old and above in Manila and two rural towns in Nueva Ecija are 13.9% and 21.8%, respectively.[4] These rates are relatively high compared to other countries.[3] An important observation in the BOLD study was that only 2% of the subjects were diagnosed by a physician.[2] This degree of underdiagnosis is one of the driving forces of medical organizations such as the PCCP to increase awareness about COPD in the country.[2]

One of the possible reasons for the underdiagnosis of COPD in the Philippines is due to the physician's lack of knowledge, poor attitude, and lack of practice regarding screening, diagnosis, and management of populations at risk of COPD.[2] The role of non-pulmonary specialists, particularly those who practice Internal Medicine and Family Medicine, is considered substantial because they attend to a significant number of patients who are at risk of developing COPD. Hence, determining the knowledge, attitude, and practices of non-pulmonary specialists in diagnosing COPD will help formulate the necessary education modules needed to facilitate their diagnosis of this disease.

OBJECTIVES

To determine the knowledge, attitude and practice of non-pulmonary medical specialists in COPD diagnosis. Specifically, we aimed to determine the (1) characteristics of non-pulmonary specialists in terms of age, gender, specialty, years of practice, and type of practice at USTH; (2) prevalence of non-pulmonary specialists adhering to the GOLD document; (3) prevalence of non-pulmonary specialists who utilize spirometry in the diagnosis of COPD and their confidence in interpreting its results; and, (4) describe how a non-pulmonary specialist screens a patient for possible COPD.

METHODS

Sample Size

The sample size of the study is 92 non-pulmonary medical specialists in order to detect power of 80% with an alpha level of 5%. Sample size computation was done online via OpenEpi (http://www.openepi.com). Non-response rates of at least 10% were taken into consideration in order for the study to be significant.

Research Setting

The study was conducted at the University of Santo Tomas (UST) Hospital from May to August 2020. A Knowledge, Attitudes, and Practices questionnaire was formulated by the investigators. Questions were based on and patterned after the available GOLD Clinical Practice Guideline regarding the diagnosis of COPD. Content validity of the questionnaire was done by three pulmonologists who are experts in the field. The questionnaire was reproduced after Research Ethics Committee (REC) approval was obtained. A pilot study was conducted among 10% of the total population. The questionnaire was finalized after modifying the questions based on the pilot study. We obtained permission from the Hospital Medical Director to distribute the questionnaires to the different Section Heads of the population to be included in the study. Thereafter, the Google form link of the online questionnaires and consent forms were sent through the e-mail of the participants. The questionnaire included details of the respondents. Refer to Figure 1 for the study's flow chart.

Statistical Analysis

Descriptive statistics was used to describe the baseline characteristics of the respondents whereas summary statistics was used to report the knowledge, attitude, and

practices of non-pulmonary specialists. All of the analysis was done using STATA1C 16 software.

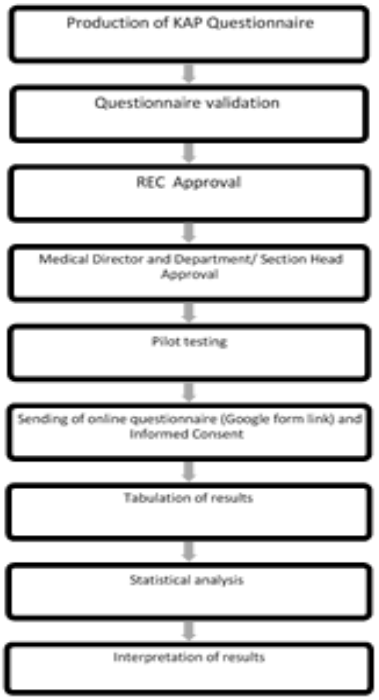

Figure 1. Study Flowchart

Ethical Consideration

The study was done in observance of healthcare practitioners' right in accordance to the Helsinki Declaration. The study adhered to the principles set by the 2017 National Ethical Guidelines for Health and Health Related Research (NEGHHRR). The approval of the UST Hospital Research Ethics Committee was obtained prior to the initiation of the research study. All non-pulmonary medical specialists of UST Hospital had an equal chance of being chosen in the study. The identity of each participant was kept anonymous and was identified using code numbers. Informed written consent was obtained from the respondent prior to giving the questionnaire. Joining in the study entailed no risk and no undue influence, coercion, or manipulation to participate.

The summary of their response to the questionnaire was sent back to each participant and kept confidential. Data obtained were kept confidential in compliance to the Data Privacy Act of 2012 and its Implementing Rules and Regulations. Google form was used for the online questionnaire and all tabulated answers were stored in a password-protected data file using Microsoft Excel (v13.64, 2020) in observance with privacy and confidentiality. Research data will be stored up to a period of one year after the conduct of the study and will be permanently deleted thereafter. The Google forms online questionnaires were deleted after the completion of the study.

We addressed questions pertaining to the study and appropriate contact numbers were given for reference should there be any questions or clarification from the participants. Subjects who felt uncomfortable answering the questionnaire were given permission to withdraw from the study. No compensation was given to any of the respondents and we shouldered all the expenses in the conduct of the study.

RESULTS

Table 1 below shows the demographic profile of the respondents. There were 82 non-pulmonary medicine specialists who participated in the research study. Mean age of respondents was 49.13 years (30,70) with the majority (30.49%) belonging to the 51-60 years' age group. Among the participants, forty-four (53.66%) were male and 38 (46.34%) were female. Majority (95.12%) of the respondents were from the Department of Internal Medicine. Sixty-seven percent were active consultants. Mean years in practice was 15.82 (1,40) years. Question 1, 7, 8, and 9 were questions on knowledge and summarized in Table 2. For question number 1, 64 participants (78.05%) are aware of the COPD GOLD guideline. Majority (67.01%) of the respondents knew which clinical scenario wherein they will consider COPD. Furthermore, 45 participants (54.88%) knew how to interpret a spirometry result and nearly half (45.12%) does not. Most of the respondents (48.78%) correctly answered the spirometry parameter cut-off value of FEV1/FVC <0.70 as diagnostic of COPD.

Table 1. Demographic Data

Variables		N=82	Percentage
Age		49.13 years (30,70)	
	30-40	21	*25.61%*
	41-50	24	*29.27%*
	51-60	25	*30.49%*
	61-70	12	*14.63%*
Gender			
	Male	44	*53.66%*
	Female	38	*46.34%*
Subspecialty *(Non-Pulmonary)*			
	Internal Medicine	78	*95.12%*
	Family Medicine	4	*4.88%*
Hospital Status			
	Active Consultant	55	*67.07%*
	Visiting Consultant	27	*32.93%*
Years in Practice		15.82 years (1,40)	
	1-10	28	*34.15%*
	11-20	33	*40.24%*
	21-30	14	*17.07%*
	31-40	7	*8.54%*

Table 2. Questions on Knowledge

	YES		NO		A (%)	B (%)	C (%)	D(%)
	N	%	N	%				
Are you aware of the GOLD document					(Yes) 64 *(78.05)*	(No, but I am aware of other COPD clinical practice guideline) 9 *(10.98)*	(No, I don't know any other COPD clinical practice guideline) 9 *(10.98)*	
In which clinical scenario will you consider COPD?					(Risk Factors Present; Symptoms Present) 55 *(67.01)*	(Risk Factors Present; Symptoms Absent) 21 *(25.61)*	(Risk Factors Absent; Symptoms Present) 5 *(6.10)*	(Risk Factors Absent; Symptoms Absent) 1 *(1.22)*
Do you know how to interpret a spirometry result	45	*54.88*	37	*45.12*				
What is the spirometry parameter cut-off value diagnostic of COPD?					(FEV1/FVC <0.50) 11 *(13.41)*	(FEV1/FVC <0.60) 19 *(23.17)*	(FEV1/FVC <0.70) 40 *(48.78)*	(FEV1/FVC <0.80) 12 *(14.63)*

Table 3 below shows the response of non-pulmonary specialists to questions on attitude towards COPD diagnosis. Thirty-seven (45.12%) were somewhat confident and 24 (29.27%) were neutral when asked about how confident they are in understanding the GOLD guideline. Likewise, when asked about their confidence in diagnosing COPD based on GOLD, 34 (41.46%) were somewhat confident and 21 (25.61%) were neutral. Majority (95.12%) were willing to learn how to interpret a spirometry report. Almost all (97.56%) of the respondents thinks that spirometry is essential for diagnosing COPD. Thirty-one (37.80%) respondents do not request for spirometry among COPD suspect patients because they think that it is too expensive for their patients. Eighteen (21.95%) respondents thinks that clinical diagnosis is reliable enough and 7 (8.54%) said that it is not readily available in their place of practice. Eighteen out of 26 non-pulmonary specialists who answered "Others" stated that their reason for not requesting spirometry was they refer these patients to pulmonary specialists.

Table 3. Attitudes of non-pulmonary specialist medical consultants toward COPD diagnosis

	YES		NO		A (%)	B (%)	C (%)	D (%)	E (%)
	N	%	N	%					
How confident are you in understanding GOLD guidelines					(Not confident at all) 4 *(4.88)*	(Not very confident) 15 *(18.29)*	(Neutral) 24 *(29.27)*	(Somewhat confident) 37 *(45.12)*	(Very confident) 2 *(2.44)*
How confident are you in diagnosing COPD based on GOLD?					(Not confident at all) 5 *(6.10)*	(Not very confident) 20 *(24.39)*	(Neutral) 21 *(25.61)*	(Somewhat confident) 34 *(41.46)*	(Very confident) 2 *(2.44)*
Are you willing to learn how to interpret a spirometry report?	78	*95.12*	4	*4.88*					
Do you think spirometry is essential for diagnosis of COPD?	80	*97.56*	2	*2.44*					
Among your COPD suspect patients, what is/are your reason/s for not requesting a spirometry test?					(It is not available in my place of practice) 7 *(8.54)*	(It is too expensive for my patient) 31 *(37.80)*	(Signs and symptoms (clinical diagnosis) are reliable enough) 18 *(21.95)*	(Others) 26 *(31.71)*	

Questions regarding the practices of non-pulmonary medical specialists on COPD diagnosis are question numbers 4, 5, 6, and 12. Their responses are summarized in Table 4 below. Fifty-two (63.41%) consultants sometimes implement the recommendations of the GOLD document and only 11 (13.41%) always implement it. Most of the respondents (47.56%) start screening a patient for possible COPD only at the age 50 years. According to GOLD 2018 and 2009 Philippine CPG, prevalence of COPD is higher in those > 40 years old, hence the recommendation to start screening for COPD in this age group. Fifty-five (67.07%) respondents answered that they always obtained smoking history and exposure. Only 8 (9.76%) of the clinicians always request spirometry for COPD patients.

DISCUSSION

COPD is a common, preventable, and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases.[1] Currently, there is no national COPD prevalence study in the Philippines. The most reliable data on the burden of COPD in the Philippines is the BOLD study. The prevalence of COPD in Manila and

Table 4. Practices of non-pulmonary specialist medical consultant regarding COPD diagnosis

	YES		NO		A (%)	B (%)	C (%)	D(%)
	N	%	N	%				
Do you implement the recommendations of the GOLD document?					(Yes, all the time) 11 *(13.41)*	(Yes, sometimes) 52 *(63.41)*	(No, not at all) 19 *(23.17)*	
In your practice at what age do you start screening a patient for possible COPD					(30 years old) 5 *(6.10)*	(40 years old) 35 *(42.68)*	(50 years old) 39 *(47.56)*	(60 years old) 3 *(3.66)*
In your practice, do you get the smoking history and exposure of your patients?					(Yes, all the time) 55 *(67.07)*	(Yes, sometimes) 27 *(32.93)*	(No, not at all) 0 *(0)*	
Among your COPD patients, how often do you request for spirometry					(Always; ≥ 90%) 8 *(9.76)*	Often;> 50% to 89%) 34 *(41.46)*	Occasionally; ≥ 20% to 49%) 22 *(26.83)*	(Hardly; less than 20%) 18 *(21.95)*

two rural towns in Nueva Ecija is 14% and 21%, respectively. Aside from the high rate, it is unfortunate that only 2% of these cases were diagnosed by doctors practicing as internists, family physicians, and general physicians. Thus, there is a 12% to 21% under diagnosis of COPD with a concomitant reason to believe that there is a high prevalence of under treatment as well.[5]

In this study, it is noteworthy that despite the fact that 97.56% of the respondents think that spirometry is essential in the diagnosis of COPD, only 9.76% always request it. About 21.95% responded that they do not request for spirometry since clinical diagnosis is reliable enough. This reason was also reported in the survey by Chokhani et al. wherein 37% of general practitioners said that they only relied on the clinical features for the diagnosis of COPD.[10]

Similarly, 78.05% of the non-pulmonary specialists are aware of the GOLD guidelines but only 13.41% always implement the recommendations stated in the guidelines. This shows that there is divergence from what one knows to what one practices. It must be addressed as well that nearly half of the respondents who are in a teaching institution answered that they do not know how to interpret a spirometry result. GOLD is the guideline that has served as the major reference of the PCCP Council of COPD and Pulmonary Rehabilitation Summary Consensus Statements on the Diagnosis and Management of COP in the Philippines.[15]

The diagnosis of COPD in primary care has to be improved and it may require more than simple provision of spirometry equipment. Other barriers which potentially caused the under- and over diagnosis of COPD includes: (1) lack of time and training in interpreting the spirometry; (2) shortage of trained medical assistants to perform the test; and, (3) physicians' perception that having spirometry results will not add benefit. These barriers are potential areas that needs to be addressed to improve the use and quality of spirometry in primary care.[11]

A multi-center survey done from 2007-2014 in Chicago, California, North Carolina, and Florida assessed the knowledge and attitudes of family physicians attending COPD continuing medical education. It showed that their knowledge about COPD was based on GOLD and American Thoracic Society/ European Respiratory Society Guidelines.[9] The most common barrier they experienced in diagnosing COPD are due to patient's lack of symptoms, failure of patient to report symptoms, patient having multiple comorbidities, and underutilization of spirometry due to the lack of access and training with the use of spirometry.[9]

The role of primary care in COPD diagnosis is vital since misdiagnosis of COPD has been reported to occur in the primary care setting. Studies have shown that patients are often mislabeled and this may be attributed to the lack of awareness of and knowledge about COPD.[12] More importantly, included in the Philippine College of Physicians' terminal competencies for internists is interpretation of basic spirometry alongside electrocardiogram and other imaging modalities, hence, it must be given the same emphasis as the other diagnostic procedures.

This study included non-pulmonary medical specialists of the UST Hospital who belong to the Department of Family Medicine and Department of Internal Medicine. One major limitation of this study is the small number of participants. Other factors such as recall bias in this self-reporting study may affect the result as well.

After assessing the knowledge, attitude, and practice of non-pulmonary medical specialists in the diagnosis of COPD, this study recommends that in order to increase the confidence of non-pulmonary medical specialists in diagnosing COPD, lectures on the latest GOLD guideline especially on disease diagno-

sis must be conducted. Likewise, easily comprehensible modules for all non-pulmonary medical specialists must be designed so as to empower them and lessen the need for referral of all COPD suspects to pulmonologists. Further, the authors of the COPD guideline must assess if the guideline itself is too complicated for non-pulmonologists, or if there is possible lack of its dissemination. Finally, to improve the utilization of spirometry, regular programs such as free or low-cost spirometry must be conducted.

CONCLUSION

Diagnosis of COPD is as essential as its treatment since it considerably decreases productivity and quality of life of patients. Underdiagnosis of COPD arises from physician's inadequate knowledge and poor attitude and practice. It was shown in the results that awareness about the guidelines and recognition of the importance of spirometry are somewhat sufficient, however, its implementation and accurate diagnostic interpretation are considerably lacking.

Our role as physicians on timely screening, early diagnosis, and accurate interpretation of spirometry is important. Certain knowledge gaps were recognized as it was shown in the results that despite knowing the clinical scenario when to request for spirometry, nearly half do not know how to the results. However, most of the respondents positively responded by expressing their willingness to learn on how to interpret spirometry test results. We can also enhance the confidence of physicians in utilizing spirometry and GOLD recommendations by increasing their knowledge on COPD diagnosis. On the other hand, barriers to adhering to GOLD recommendations as non-pulmonary medical specialists were identified which includes the cost of spirometry and the referral system to specialists.

RECOMMENDATION

We recommend conducting further studies that will involve more respondents, preferably coming from different institutions, and include more Family Medicine specialists and statistically analyze if there will be differences in the knowledge, attitude and practice between them and the non-pulmonary Internal Medicine consultants. Finally, more COPD prevalence studies must be carried out to know the real burden of the disease in our country.

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AUTHOR DISCLOSURE

All the authors are under the Department of Internal Medicine in the University of Santo Tomas Hospital and were involved in the care of healthcare professionals included in this study.

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Philippine Journal of Chest Diseases

Systematic Review & Meta-analysis

A Systematic Review and Meta-Analysis of the Effectiveness of Remote Tuberculosis- Directly Observed Treatment (TB-DOT) (Video/Virtual) Compared with Conventional In-Person TB DOT In The Management of (Drug-Susceptible) Tuberculosis

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ABSTRACT

BACKGROUND: Tuberculosis is still a significant cause of death especially among developing countries like the Philippines despite the implementation of the widely studied Directly Observed Treatment Short Course program (DOTS). Several adherence interventions have been explored and one of them is the telemedicine application of DOT, which showed potential to be a more convenient, cost-effective and less laborious option for both patients and healthcare workers alike, and thereby improving treatment adherence and completion.

OBJECTIVE: To evaluate the effectiveness of remote TB DOT (Video/Virtual) compared with conventional in-person TB DOT in the management of drug-susceptible tuberculosis.

METHODS: We conducted a systematic review and meta-analysis on the effectiveness of remote TB DOT. We searched MEDLINE, the Cochrane Registry and ClinicalTrials.gov for the research and the primary outcome was treatment completion; other outcomes were treatment adherence and cost. The title and abstract of all identified papers that passed the title and abstract screening based on predefined eligibility criteria were independently assessed by the 2 investigators. Disagreements were resolved through a third party (research adviser). The following data were extracted from studies included in the review: study characteristics (study design, duration, sample size, setting), participants, intervention characteristics, and clinical outcomes. All 4 included studies reported the primary outcome of treatment completion which favors remote TB DOT.

RESULTS: There was no statistically significant difference in treatment completion, however, there was significant heterogeneity noted in the results. Two of the studies have shown that the population of patients enrolled in remote DOT resulted in better treatment adherence with less missed doses as opposed to conventional DOT and that the average cost of treatment is greater for conventional in-person TB DOT than for remote TB DOT (video/virtual).

CONCLUSION: The effectiveness of remote TB DOT is comparable with conventional TB DOT. Offering a remote TB DOT as an alternative improved treatment completion and adherence, and it is also more cost-effective.

KEYWORDS: *Remote TB DOT, Video DOT, Virtual DOT, In-Person DOT, Drug-susceptible TB*

INTRODUCTION

Tuberculosis caused by Mycobacterium tuberculosis has been a significant cause of death in adults worldwide, especially among developing countries like the Philippines.[1] The mode of transmission of M. tuberculosis is via the inhalation of aerosolized droplets, which may then lead to four possible outcomes: immediate clearance of the organism, primary disease, latent infection or reactivation disease.[2] According to the data of the World Health Organization (WHO), approximately 10 million people are infected with tuberculosis each year and despite being preventable and curable, about 1.5 million people die of tuberculosis each year. A timely diagnosis and full adherence to treatment results in successful management of the disease and the curtailment of further transmission. The geographic distribution of the disease points to the countries in Southeast Asia having the most cases (44%), followed by Africa (24%), and the Western Pacific (18%), cases from the Philippines alone account for 6% of the worldwide TB population.[1] United Nations member countries have intensified their initiatives in identifying and notifying infected individuals. The set target for notifying cases have been met for the year 2018, however, the gap between case notification and treatment is yet to be reduced. The Philippines has been identified as one of the countries with a huge gap between notification and treatment which is primarily due to inaccessibility to health care. The global strategies set to successfully eradicate TB can only be achieved if TB diagnosis, treatment and prevention services are provided within the context of progress towards universal health coverage and if there is multisectoral action to address the broader determinants that influence TB epidemics and their socioeconomic impact.[1]

Directly observed treatment, short-course (TB-DOTS) is the flagship TB control strategy of the WHO whose early development can be attributed to the International Union Against TB and Lung Disease. It was piloted between 1970 – 1980 in four African countries. Its initial success was noted to be responsible for the increase in cure rates to nearly 80%.[3] Currently, the five major components of DOTS, as described by the WHO are: (1) political commitment and resources, which must be the strongest link because TB is a public health responsibility and an epidemic in some countries; (2) accurate diagnosis through sputum smear microscopy among symptomatic patients; (3) standardized treatment regimens; (4) regular, uninterrupted supplies of effective anti-TB medications and assurance of full compliance; and, (5) standardized recording and reporting of patients' treatment and progress.[4] The implementation of DOTS is not without its challenges, among those identified in the Brazilian study were some patients' thoughts of DOTS as difficult, laborious, conflicting with work schedules, medications too numerous or large to swallow, and healthcare workers beset with managerial/administrative problems.[5] Despite these challenges, efforts have been made by the WHO to strengthen the DOTS programs, ensuring adequate supplies of medications, developing plans and strategies with global agencies and regional entities, mobilizing resources, and funding and providing technical and strategic support to countries.[1]

Telemedicine or Telehealth has been defined by the Health Resources Services Administration as the use of electronic information and telecommunications technologies to support long-distance clinical healthcare, patient and professional health-related education, public health and health administration. Technologies include videoconferencing, the Internet, store-and-forward imaging, streaming media, and terrestrial and wireless communications. Telemedicine refers specifically to remote clinical services, while telehealth can refer to remote non-clinical services, such as provider training, administrative meetings and continuing medical education, in addition to clinical services.[7] Video or Virtual TB DOT is the application of telehealth in the management of TB wherein patients record and transmit medication ingestion videos that are

watched by healthcare providers remotely to monitor treatment adherence.[10]

The Infectious Diseases Society of America published a position statement on the application of telemedicine to the practice of infectious diseases in 2019, the telemedicine management of TB was among them. Given that two of the reasons why DOTS is considered challenging by patients are the amount of time and distance required to travel to a DOTS clinic or facility, electronic DOT may reduce these burdens.[6] The CDC has released its toolkit for the implementation of an electronic DOT program as an alternative method to in-person or conventional DOT. This toolkit aims to assist TB programs in developing and implementing a TB eDOT program which may be tailor fit to meet their respective TB program's patient needs, utilize available resources, and meet management and regulation concerns. Depending on the resources of the program and the technology available, the electronic DOT may be implemented with the use of a smartphone, a tablet or a computer with a webcam. Just like any telemedicine or telehealth consultation, the health care worker and the patient can agree on an appointment, to meet virtually. During the session, the healthcare worker asks about the patients condition and well-being, any issues or side effects with the medications, any signs or symptoms and then watches the patient live as he or she takes the medications.[8]

The relevance of remote DOT is particularly important at this time when people are strongly advised to stay home, have limited mobility to essential travels, social distancing or avoidance of hospital or clinic visits to mitigate the spread of COVID-19. While the virtual consults are not a true replacement for actual patient-doctor interaction, patients can still avail of medical consultations in a safe, cost-effective and practical manner. In addition to the benefits of remote DOT to patients, it is also beneficial to health care workers that the DOTS facility may operate in a skeletal workforce schedule, thereby reducing staff travel cost and time.[8] On the other hand, identified challenges to remote or electronic DOT are the lack of a clinical evaluation for monitoring adverse events, the lost opportunity of building rapport and the legal, ethical and moral issues of patient privacy in the transmission of data through these devices.[8]

This meta-analysis aims to evaluate the effectiveness of remote TB DOT comparing it with conventional in-person TB DOT. It has been established previously that through conventional DOT, the WHO is able to improve the treatment of TB and curtail further infections, drug resistance, and disease recurrence. During this time of the COVID-19 pandemic in which there has been a noted increase in the utilization of telemedicine, it is deemed appropriate by the reviewers to seek out the possibility that remote DOT is an appropriate alternative to conventional DOT and that future recommendations may be made to improve the options available for the treatment of TB patients in the Philippines.

WHO conditionally recommended VDOT as an alternative to DOT in 2017, but the evidence was graded weak due to few randomized controlled trial available (RCT). In 2018, a WHO-funded systematic review and meta-analysis of trials and observational studies on adherence interventions and outcomes of tuberculosis reported successful treatment outcomes with VDOT based on two cohort studies.[11] This updated meta-analysis will include the most recent studies (RCTs and cohorts) available now.

OBJECTIVE

To evaluate the effectiveness of remote TB DOT (Video/Virtual) compared with conventional in-person TB DOT in the management of drug-susceptible tuberculosis. Specifically, to determine the effectiveness of remote TB DOT (Video/Virtual) versus conventional in-person TB DOT in improving treatment completion and in achieving treatment adherence and to assess the clinical cost benefit of remote TB DOT (Video/Virtual) com-

pared with conventional in-person TB DOT.

METHODS

Study Design

Studies included are RCTs, and cohort studies evaluating the effectiveness of remote TB DOT (Video/Virtual) compared with conventional in-person TB DOT in the management of tuberculosis.

Types of Participants

Studies involving patients with a TB diagnosis (bacteriologically confirmed or clinically diagnosed), aged 18 years old and above are included.

Types of Interventions

We looked into studies evaluating the effectiveness of remote TB DOT (Video/ Virtual) compared with conventional in-person TB DOT in the management of tuberculosis.

Types of Outcome Measures

Primary: Treatment Completion

Secondary: Treatment adherence and cost of treatment observation

Search Methods

An electronic search strategy was used to identify trials published in MEDLINE, the Cochrane Central Register of Controlled Trials as well as the clinicaltrials.gov. The search terms included the following intervention terms: Free Text: Tuberculosis, Telehealth, Remote TB DOTS, Video DOTS, Telemedicine General search strategy: Tuberculosis AND (Telehealth OR Remote TB DOTS or Video DOTS or Telemedicine)

Data Extraction and Management

The title and abstract of all identified papers that passed the title and abstract screening based on predefined eligibility criteria were independently assessed by the 2 investigators. Disagreements was resolved through a third party (research adviser). The following data were extracted from studies included in the review: Study characteristics (study design, duration, sample size, setting), participant and intervention characteristics and clinical outcomes. Studies that did not report any of the outcome measures enumerated above were excluded.

Assessment of risk of bias of included studies

The risk of bias was independently assessed by the two authors using the template from the Cochrane Handbook for Systematic Reviews of Interventions. Any disagreements between reviewers was resolved through third third party (research adviser).

Measures of treatment effect

We used relative risk for treatment completion with corresponding 95% confidence interval. Qualitative analysis was done for treatment adherence and cost of treatment observation.

Unit of analysis issues

Statistical analysis was performed using Review Manager version 5.4. Random effects model was used for the meta-analysis on the assumption that true size effect are similar but not identical among the studies included. This model represents the lack of knowledge about why real, or apparent, intervention effects differ by considering the differences as if they were random.

Assessment of heterogeneity

Clinical heterogeneity between studies was assessed by comparing the characteristics of the study populations, interventions and outcome measure. Statistical heterogeneity was assessed using the I2 statistic, chi-square p value, and visual inspection of Forest plot. Substantial heterogeneity is considered if the I2 is ≥ 50% or chi square p-value is <0.1.

Assessment of reporting biases

Reporting bias was planned to be reported using a funnel plot.

Data synthesis

Statistical analysis was done using Review Manager Version 5.4

Sensitivity analysis

Sensitivity analysis was done to try to remove the source of heterogeneity.

Ethical Considerations

The protocol for this study was reviewed by the Lung Center of the Philippines Institutional Ethics Review Board and has been qualified for exemption from review.

RESULTS

Description of Studies

MEDLINE, Cochrane library and clinicaltrials.gov website were used to search for possible studies. 61 studies were initially yielded by the search after the following filters were applied (english language, clinical trials and RCTs conducted in the last 5 years). Duplicates were then removed yielding 34 studies. The search was further narrowed down to 7 papers whose design was in accordance to the PICO format of our research question. Full text articles of the remaining 7 studies were retrieved. 3 studies were further excluded. Figure 1 illustrates the search and study selection process.

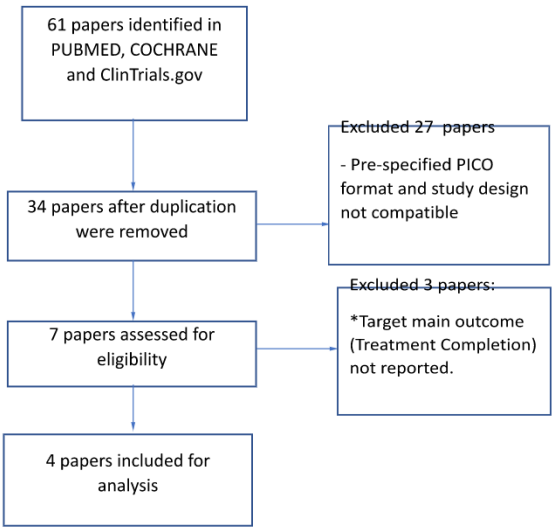

Figure 1. Flow diagram of the search and study selection process

We included 2 RCTs (n = 583) and 2 cohort studies (n = 709) in this systematic review and meta-analysis. The two RCTs and two cohort studies had two-arm trials (using remote DOT and in-Person DOT for the treatment of Tuberculosis). All studies were conducted among patients diagnosed with drug-susceptible tuberculosis. The 4 studies all included intervention of interest, remote DOT and in-person DOT as comparator group. All studies were conducted in developed countries and were done between year 2015 to 2020. Table 1 shows the summary of description of studies. Out of the 7 papers assessed for eligibility, 3 studies were excluded after full text articles were reviewed. The 3 studies did not report on the main outcome of interest (treatment completion).

Table 1. Summary of description of included studies

Author, Year, Location/ Setting	Study Design	Population	Intervention	Control	Outcome
Peng Guo, 2019 China	RCT	Adult diagnosed with Tuberculosis	Remote DOT: N= 203	In-Person TBDOT: N = 202	Treatment Completion, Treatment Cost
Ravenscroft, 2020 Moldova	RCT	Adult patients diagnosed with Tuberculosis	VDOT: N= 85	In-Person TBDOT: N = 93	Treatment Completion, Treatment Adherence, Treatment Cost
Xujun Guo, 2020 China	Cohort Study	Adult patients diagnosed with Tuberculosis	VDOT: N= 235	In-Person TBDOT: N = 158	Treatment Completion, Treatment Adherence, Treatment Cost
Chuck, 2015 USA	Cohort Study	Adult patients diagnosed with Tuberculosis	VDOT: N= 49	In-Person TBDOT: N = 267	Treatment Completion

Risk of Bias of Included Studies

The following were used to assess the risk of bias: random sequence generation and allocation concealment for selection bias, blinding of outcome assessment for detection bias, incomplete outcome data for attrition bias, and selective reporting for reporting bias. The two RCTs generally exhibited low risk of bias but due to the nature of the intervention, researchers, medical professionals and participants were not blinded to the allocation of trial group. Figure 2 shows the risk of bias graph while Figure 3 shows the risk of bias summary. A different instrument (Newcastle-Ottawa scale) was used to assess the risk of bias in the two cohort studies (Table 2).

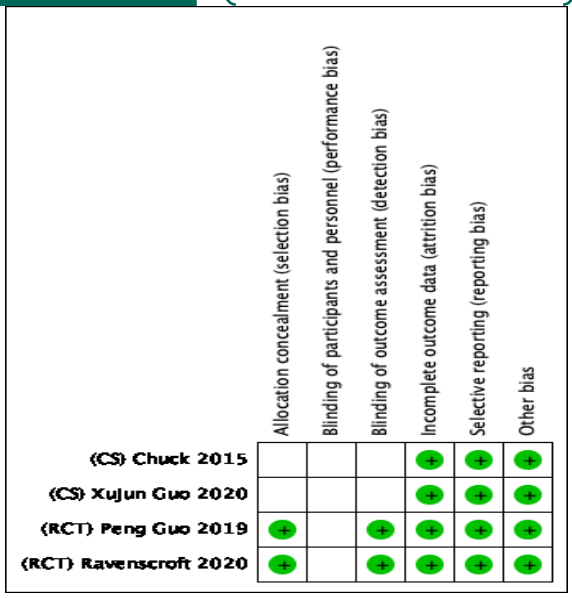

Figure 3. Risk of Bias Summary

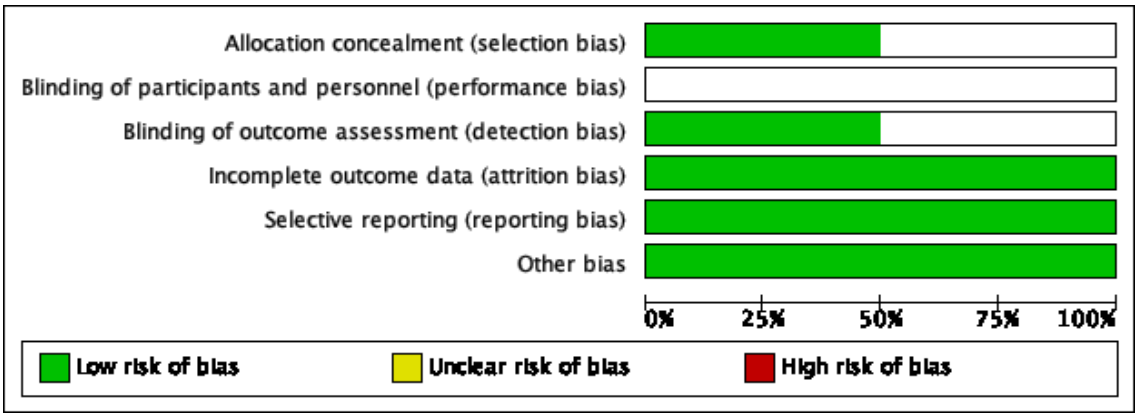

Figure 2. Risk of Bias

Table 2. Newcastle-Ottawa Quality Assessment Scale for Cohort Studies

Study	Xujun Guo, 2020 China	Chuck, 2015 USA
Representativeness of Export Cohort	★	★
Selection of Non-Exposed Cohort from same source as Exposed Cohort	★	★
Ascertainment of Exposure		
Outcome of interest was not present at start of study	★	★
Assessment of outcome	★	★
Follow-up long enough for outcome to occur	★	★
Adequacy of follow-up	★	★
Quality Score	*GOOD*	*GOOD*

Selection

All the RCTs used randomization during the selection of the patients, which minimized selection bias. The two RCTs used sealed envelopes as their way to ensure allocation concealment to minimize selection bias. It was impossible to blind both participants and outcome assessors to their treatment assignment. The four studies did not report significant dropouts, thus minimizing attrition bias. No reporting bias was noted.

Effects of Interventions

All four included studies reported the primary outcome of treatment completion which favors remote TB DOT. Three studies (Peng Guo 201913, Ravenscroft 202014 and Xujun Guo 202015) included treatment cost in their outcomes and have unanimously shown that remote DOT is more cost effective than conventional in-person DOT. Two studies (Ravenscroft 2020 and Xujun Guo 2020) have shown that the population of patients enrolled in remote DOT resulted in better treatment adherence with less missed doses as opposed to conventional DOT.

Primary Outcome: Treatment Completion

Four studies reported treatment completion (Figure 4). Remote DOT versus In-Person TB DOT showed no statistically significant difference in treatment completion (1.05 95% CI, 0.97 to 1.14; p = 0.19). However, there was significant heterogeneity noted in the results (I2: 89%).

Sensitivity Analysis

A sensitivity analysis was done to try to remove the source of heterogeneity for treatment completion (Figure 6). The exclusion of one study (Xujun Guo) significantly reduced the heterogeneity of the remaining studies (1.02, 95% CI, 0.99, 1.04, I2: 0%).

Secondary Outcome/s: Treatment Adherence and Treatment Cost

Treatment Adherence (No. of Patients with at least 80% Adherence)

Two studies (Table 3) have shown that the population of patients enrolled in remote DOT resulted in better treatment adherence with less missed doses as opposed to conventional DOT.

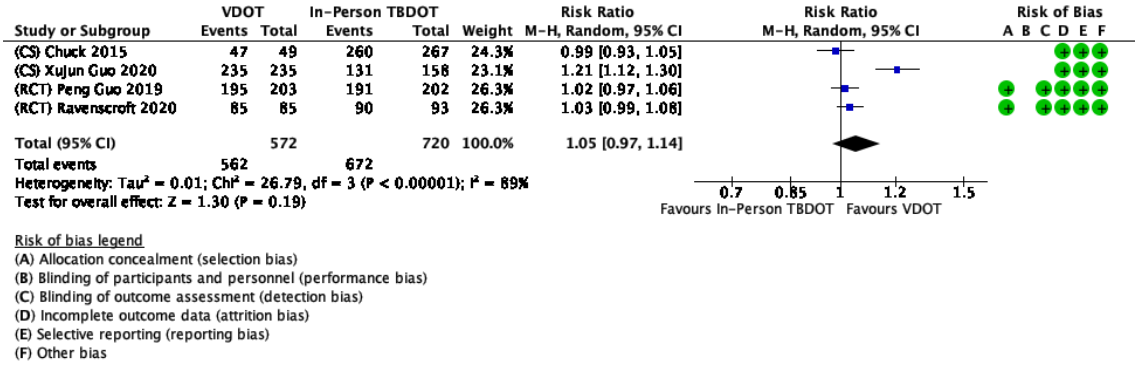

Figure 4. Remote DOT vs In-Person TB DOT: Treatment Completion

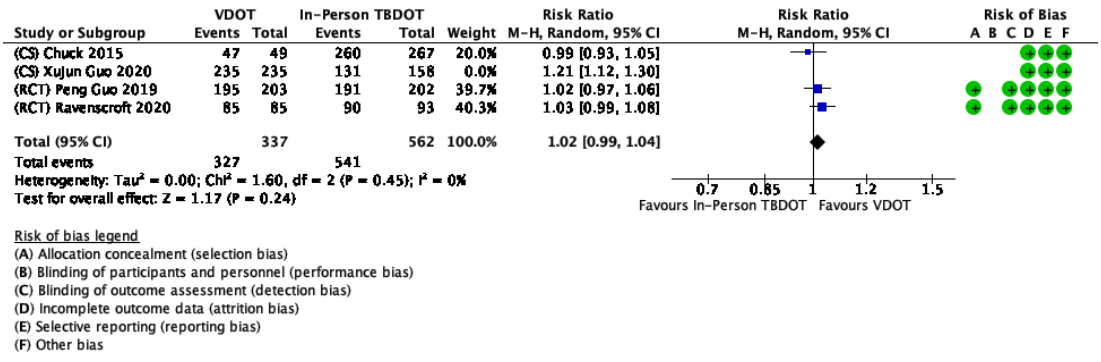

Figure 5. Remote DOT vs In-Person TB DOT: Treatment Completion Sensitivity Analysis

Table 3. VDOT vs In-Person TB DOT: Treatment Adherence

Author, Year, Design, n	VDOT	In-Person DOT
Ravenscroft 2020 Moldova RCT N=178	74.5% *80% adherence in any given two-week period	19.5% *80% adherence in any given two-week period
Xujun Guo, 2020 China CS N=393	88.9% *Adherence during the course of the treatment.	31.3% *Adherence during the course of the treatment.

Treatment Cost

Three of the studies (Table 4) took into consideration the average cost of both DOT modalities which showed that the average cost of treatment is greater for conventional in-person TB DOT than for remote TB DOTS (video/virtual).

Table 4. VDOT vs In-Person TB DOT: Treatment Cost

Author, Year, Design, n	VDOT	In-Person DOT
Peng Guo, 2019 China RCT N=405	34.3 Yuan *amount spent on every observed treatment	71.6 Yuan *amount spent on every observed treatment
Ravenscroft 2020 Moldova RCT N=178	187 Moldovan Leu *amount spent by patient over 4-month period	697 Moldovan Leu *amount spent by patient over 4-month period
Xujun Guo, 2020 China CS N=393	53 Yuan (USD 7.57) *amount spent on every observed treatment	276 Yuan (USD 39.94) *amount spent on every observed treatment

DISCUSSION

Summary of Findings

There is a limited number of studies comparing the effectiveness of VDOT versus in-person TB DOT. There was no significant difference in baseline characteristics of patients included in these studies. Significant heterogeneity was noted on the outcome of treatment completion among the studies included. Remote TB DOT (Video/Virtual) is comparable with conventional in-person TB DOT in the management of drug-susceptible tuberculosis. Remote TB DOT improved treatment completion, adherence and cost-effectiveness.

Overall Completeness and Applicability of Evidence

The strength of this study are the inclusion of RCTs to ensure methodological quality and that the patients randomized to either remote DOT or conventional in-person DOT already have basic knowledge on how DOT is conducted. Studies regarding remote DOT are few and thereby limits this study. Also, there is no uniform reporting of the currencies to evaluate cost-effectiveness.

Quality of Evidence

The GRADE methodology was used to assess for the quality of evidence (Table 5). The strength of evidence is moderate for treatment completion favoring remote TB DOT.

Potential Biases in the Review Process

The database search was limited to studies in English whose full texts were available online. Also, search was limited to the three databases previously mentioned.

Agreements and disagreements or reviews

The findings in this review, comparing the effectiveness of VDOT versus in-person DOT, is similar to the systematic review and meta-analysis done in 2018. The previous meta-analysis included only two cohort studies favoring remote TB DOT. With the addition of RCTs with low risk of bias, the strength of evidence for treatment completion is moderate in this review.

Table 5. Strength of Evidence

Outcome	Strength of Evidence Elements						Summary of Findings	
	No. of Studies	Risk of Bias	Consistency	Directness	Precision	Publication Bias	Description of Effect	Strength of Evidence
Treatment Completion	4 VDOT=572 In-Person DOT=720	Low	Inconsistent	Direct	Precise	None	Based on 2 RCT and 2 CS (n=1292) there was considerable heterogeneity of the results (1.05 95% CI, -0.97 to 1.14, I^2=89%, p=0.19).	Moderate

CONCLUSION

The effectiveness of remote TB DOT (Video/Virtual) is comparable with conventional in-person TB DOT in the management of drug-susceptible tuberculosis. Offering a remote TB DOT alternative improved treatment completion, adherence and cost-effectiveness. Patient satisfaction surveys conducted by the proponents of the studies included in this analysis have also shown that remote TB DOT is easy, convenient and advantageous to those enrolled. It is a welcome enhancement of the DOT program.

Due to the burden of TB in our country – worsened by challenges in delayed diagnosis and continued transmission, compounded by situations such as poverty, lack of transportation, an ongoing pandemic, frequent weather disturbances, and calamities that make conventional DOT difficult, it is recommended that adherence interventions such as remote TB DOTS should be appropriately explored and pilot tested in DOT centers. A significant number of Filipinos have access to a smartphone capable of receiving updates/reminders and videoconferencing. Although the quality of our internet connections leave a lot to be desired, the bare minimum of sending a video call to a DOTS worker/observer of a patient taking his meds can potentially improve treatment adherence and completion in a convenient and cost effective way. DOTS programs can also send text brigades akin to that of NDRRMC's to remind patients to take their medications and to report any adverse reaction or new symptoms. Based on the experience and available data of other DOT centers albeit in first world nations, exploring the possibility of remote TB DOT in our country shows promise. Historically, the successes and challenges of the original DOTS programs were documented in China and Brazil. Taking into consideration the feedback of patients and healthcare workers alike in most DOTS centers worldwide, policy makers were able to adjust, revise and improve into the program that we know today and several adherence interventions are still currently being explored. Filipino patients are not strangers to technological advancement. During the COVID-19 pandemic, service patients in government hospitals were able to communicate with their doctors and obtain their prescriptions through the Facebook Messenger platform – a simple, social messaging application with which millions of Filipinos have access to. In recent times, even those in lower economic households have relied on telecommunications and the internet to receive important news and announcements regarding calamities or disas-

ters, including TB notifications. Important announcements such as TB notifications necessitate a strong political commitment and allocation of resources and a working collaboration between the Department of Health and the Department of Information and Communications Technology. The Lung Center of the Philippines, being the apex center for lung and chest diseases in this country, can explore the feasibility of this adherence intervention in its TB DOTS clinic.

Future research may explore the possibility of using video/virtual means in other adherence interventions other than actual observation of medication administration and monitoring of adverse effects such as the conduct of a support group session through video conferencing (TB DOT equivalent of virtual asthma club). Providing incentives such as free cellphone load or mobile data through platforms like Gcash, reminders and tracers like text brigades from NDRRMC may also be explored to see whether these interventions will result in improved treatment adherence, treatment completion, more efficient follow-up, and monitoring of patients.

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Case Series

Airway Pressure Release Ventilation as Rescue Ventilatory Strategy for Refractory Acute Respiratory Distress Syndrome of Patients with COVID-19: A Case Series

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ABSTRACT

BACKGROUND: Tuberculosis One of the devastating consequences of COVID-19 is severe pneumonia leading to acute respiratory distress syndrome (ARDS). The standard of care is low tidal volume, individualized positive end-expiratory pressure (PEEP) and prone positioning. Question remains what can still be done for persistent hypoxemia due to refractory ARDS despite utilizing low tidal volume and optimal PEEP titration and if lack of manpower hinders us to do proning.

OBJECTIVE: To evaluate our experience and the feasibility of applying APRV as rescue ventilation and to present the challenges in the management of patients, including how to initiate, titrate and wean patients from APRV.

METHODS: We collected data of all adult patients admitted for critical COVID-19 pneumonia in ARDS who were ventilated using APRV and successfully weaned from March to November 2020. Data from these patients regarding baseline clinical status, initial APRV settings, their reported subsequent clinical course, and any recorded episodes of hemodynamic instability or adverse events attributable to the use of APRV were collected from each patient's health records.

RESULTS: Oxygenation markedly improved in patients managed with APRV. Most common effect noted was development of hypercapnia in all 4 cases due to prolonged inspiratory time (Thigh), hence ventilator settings were modified accordingly. There were no episodes of hemodynamic instability or major adverse events recorded. No one required neuromuscular blockade.

CONCLUSION: Although APRV may be useful in oxygenating COVID-19 patients, we still strongly recommend adhering to evidence-based management as suggested by international guidelines for ARDS before commencing APRV for severe hypoxemia where possible. Future research should aim to clarify which specific subgroups of patients, if any, would benefit from the use of APRV.

KEYWORDS: *COVID-19, Acute Respiratory Distress Syndrome, Airway Pressure Release Ventilation*

INTRODUCTION

One of the devastating consequences of COVID-19 is severe pneumonia leading to ARDS. ARDS as defined by the Berlin Criteria is an acute hypoxemic respiratory failure following an acute event, such as a respiratory viral infection, that presents as bilateral pulmonary infiltrates on lung imaging in the absence of a purely cardiogenic or hydrostatic etiology.[1]

The pathophysiology of ARDS results from an acute systemic inflammatory response affecting the lung's gas exchange surface, the alveolar-capillary membrane. Increased permeability of the membrane associated with the recruitment of neutrophils and other mediators of acute inflammation into the airspace manifests as high permeability pulmonary edema. The resulting acute inflammatory exudate inactivates surfactant leading to collapse and consolidation of distal airspaces with progressive loss of the lung's gas exchange surface area. This would be compensated for by hypoxic pulmonary vasoconstriction thereby allowing deoxygenated blood to cross unventilated lung units on its way to the left heart. This could lead to profound hypoxemia and eventually type 2 respiratory failure as hyperventilation fails to keep pace with carbon dioxide production.[2,3]

Management of ARDS is mainly supportive. Where mechanical ventilation is required, the use of low tidal volumes (<6 ml/kg ideal body weight) and airway pressures (plateau pressure <30 cmH_2O) was recommended. For patients with moderate/severe ARDS, prone positioning was recommended for at least 12 hours per day. By contrast, high frequency oscillation was not recommended and it was suggested that inhaled nitric oxide is not used. The use of a conservative fluid management strategy was suggested for all patients, whereas mechanical ventilation with high PEEP and the use of the neuromuscular blocking agent, cisatracurium, for 48 hours was suggested for patients with ARDS with ratio of arterial oxygen partial pressure to fractional inspired oxygen (PF) ratios less than or equal to 27 and 20 kPa, respectively.[4]

Prone positioning leads to a relief of severe hypoxemia due to reduction of overinflated lung areas, promotion of alveolar recruitment and decrease in ventilation/perfusion mismatch. The Proning Severe ARDS Patients (PROSEVA) trial, performed by Guerin et al. demonstrated a significant decrease in 28-day and 90-day mortality in patients with severe ARDS.[5] The main obstacle continues to be its implementation and generalization among each institution. Trained and qualified nursing and respiratory therapists are the most important factor to obtain successful results, as severe life-threatening events may occur at any given time (i.e., self-extubation, hemodynamic instability, lack of adequate sedation, pressure ulcers). Lack of manpower hinders us to do proning especially if the patient is obese.

COVID-19 has been known to be a heterogenous syndrome with reports of dichotomized L and H phenotypes: (1) Type L which is characterized by low elastance, low ventilation-to-perfusion ratio, low lung weight and low recruitability and (2) Type H which is characterized by high elastance, high right-to-left shunt, high lung weight and high recruitability. Despite falling in most of the circumstances under the Berlin definition of ARDS, whose distinctive features are severe hypoxemia often associated with near normal respiratory system compliance, some COVID-19 patients may exhibit profound hypoxia with relatively little dyspnea—"happy hypoxics." This raises numerous questions about the pathophysiology and treatment implications including ventilatory strategies.[6,7] Question remains what can we still do for persistent hypoxemia due to refractory ARDS. Various modes can be used, but there is increased interest in using APRV, which is a special mode characterized by two levels of pressure that invert by increasing inspiratory time.

APRV was originally described in 1987 by Downs and Stock as a means to oxygenate

the lungs. It prevents significant fluctuations in airway pressure (Paw) and thus is thought to decrease the risk of barotrauma.

The application of continuous positive airway pressure (CPAP/P_{high}) for a prolonged time (T_{high}) maintains adequate lung volume and alveolar recruitment. This results in persistent application of elevated mean airway pressure (MAP). This elevated MAP allows almost constant lung recruitment (open-lung approach) at lower peak and plateau pressures, in contrast to conventional invasive ventilation, in which a briefer period of recruitment is used followed by PEEP to prevent alveolar collapse. There is a time-cycled release phase to a lower set of pressure (P_{low}) for a short period of time (T_{low} or release time) where most of ventilation and carbon dioxide (CO_2) removal occurs. A patient is able to maintain spontaneous breathing throughout this mode and is not constrained by the traditional forms of ventilation, which can lead to dyssynchrony and a need for sedation. If the patient has no spontaneous respiratory effort, APRV becomes typical of inverse ratio whereby inspiratory time is longer than expiration.[8,9] This concept was illustrated by Yoshida in a retrospective analysis of 18 patients with ARDS. Patients who received APRV were found to have more dramatic improvements at follow up in PaO2/FiO2 (PF) ratio and percentage gains in lung aeration. Similar findings of improved oxygenation have been demonstrated in additional small retrospective series, although it should be noted that the majority of publications evaluating APRV versus conventional ventilation illustrates that oxygenation between the two modes is largely similar, albeit with the benefit of lower peak airway pressures. Only one trial has compared APRV with conventional low tidal volume ventilation for patients with ARDS. The single-centered, open-label study showed an increase in ventilator-free days with APRV but no mortality benefit.[8,9,10]

A retrospective analysis was done by Mahmoud et al. involving 60 patients with COVID-19 who developed refractory hypoxemia (PaO2/FIO2 ratio (P/F ratio) <200) while on mechanical ventilation and were treated with a trial of APRV for at least 8 hours. They found that APRV significantly improved the P/F ratio and decreased the FiO2 requirements. There was an increase in tidal volume per predicted body weight and decrease in total minute ventilation during the APRV trial. In their multivariate analysis, higher inspiratory rate and airway pressure were also seen.[11] Another single-centered, retrospective, observational study with 14 COVID-19 ARDS patients underwent mechanical ventilation with APRV showed significant improvement in oxygenation with an increase in mean P/F ratio from 62 to 110 after initiating APRV. It also showed an increase in the mean airway pressures ranging from 25-35 cmH_2O as compared to a range of 18-26 cmH_2O but no significant changes in peak airway pressures. Tidal volumes ranged from 5.4 -13.2 ml/kg. There was also a 41% decrease in vasopressor requirements with no significant changes in sedation and analgesic requirements.[12]

In this case series, we report the story of four patients hospitalized in our institution with refractory ARDS secondary to COVID-19 who utilized APRV and successfully weaned from mechanical ventilators.

METHODS

We reviewed the cases of all adult patients admitted for critical COVID-19 pneumonia in ARDS at Cardinal Santos Medical Center who were ventilated using APRV and successfully weaned from March 2020 to November 2020. APRV was delivered using the Draeger Infinity c500. We collected data on the patients' health records, specifically, their baseline clinical status, initial APRV settings, reported subsequent clinical course, and any recorded episodes of hemodynamic instability, air leaks or adverse events attributable to the use of APRV.

RESULTS

Out of the sixty-four invasively mechanically ventilated patients in our institution be-

tween March 2020 to November 2020, there were four patients who were ventilated using APRV and successfully weaned.

APRV was initiated primarily due to refractory hypoxemia despite low tidal volume and optimal PEEP titration while on assist control (AC) mode. Ventilator asynchrony was also reported while on AC mode, hence they were on sedation but no paralysis was done. These cases were described in detail and summarized in Supplementary Table 1 (http://philchest.org/publications/Supplementary_Table_Manuscrip22.pdf).

Case 1 (Male): He was admitted at day 6 of illness. Respiratory status deteriorated at day 10 of illness despite treatment. High flow nasal cannula (HFNC) was initially started with an increasing oxygen requirement up to 100%. He was subsequently intubated and AC mode was initiated. He was transitioned to APRV due to refractory hypoxemia and O2 saturation going down as low as 75%. Following 2 hours of APRV, his FiO2 requirements improved from 1.0 to 0.6 and was weaned further after 10 days. He tolerated APRV well and sedation was discontinued after 2 days on APRV. APRV was shifted to CPAP and extubated after 4 days and hooked to HFNC.

Case 2 (Female): She was admitted at day 4 of illness and intubated at day 8 of illness. She was initially set on AC mode and to be extubated after 6 days but after 48 hours, she developed respiratory acidosis. She was reintubated for respiratory failure secondary to bacterial infection. She was initially set on AC mode for 2 days to resolve the respiratory acidosis then switched to APRV due to refractory hypoxemia. She remained ventilator dependent for a prolonged period, hence underwent tracheostomy. APRV was applied for 11 days. After which, she was shifted to synchronized intermittent mandatory ventilation (SIMV) mode then CPAP prior to liberation to mechanical ventilator.

Case 3 (Male): He was admitted at day 7 of illness and hooked to HFNC and eventually reaching up to FiO2 100% after 4 days. There was a note of persistent desaturation and was intubated. He was initially set at AC mode but due to refractory hypoxemia, he was switched to APRV mode. Ventilation subsequently improved following APRV. He was transitioned to SIMV after 14 days of APRV then shifted to CPAP and successfully extubated 5 days later and hooked to HFNC.

Case 4 (Male): He was admitted last week of March 2020 where tocilizumab, convalescent plasma and hemoperfusion were not yet available at that time in our institution. He remained on APRV for 13 days and was switched to SIMV mode then T piece and eventually extubated after.

DISCUSSION

COVID-19 depends on the interaction of the following factors: the severity of the infection, the host response, physiological reserve and comorbidities, and the ventilatory responsiveness of the patient to hypoxemia. In this case series, oxygenation has markedly improved in our patients managed with APRV even after an hour. Repeat chest radiograph also showed a decrease in haziness on bilateral lung fields. Most common effect noted was development of hypercapnia (pCO2 range of 48-65 mmHg with pH >7.3) in all 4 cases due to prolonged T_{high}, hence, ventilator settings were modified accordingly. There were no recorded episodes of hemodynamic instability, episodes of air leaks or major adverse events attributable to the use of APRV in any of the four cases. No one required neuromuscular blockade.

Patients with COVID-19 and severe hypoxemia have a high in-hospital mortality. APRV may benefit these patients as it maximizes alveolar recruitment resulting in improved oxygenation, alveolar ventilation and CO2 clearance. These effects are more pronounced for increase in tidal volume, higher airway pressure and in-

spiratory to expiratory (IE) ratio. [11]

In contrast to conventional mechanical ventilator settings, the time spent at the higher pressure is generally 80-90% of the respiratory cycle in APRV. Alveolar collapse is typically prevented by keeping the time at the lower pressure very brief rather than by providing high positive end expiratory pressure. The higher CPAP level is known as Phigh and the lower pressure level as Plow. The time spent at high and low pressure is known as Thigh and Tlow, respectively.13 There are 5 key parameters to set in APRV14 (Figure 1):

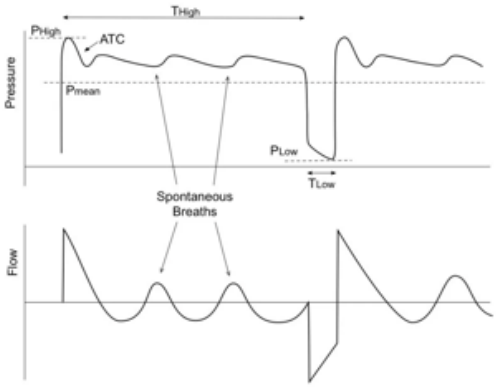

Figure 1. Key parameters in APRV Completion

1. P_{high}: P_{high} can be considered the target plateau pressure. P_{high} determines the mean airway pressure and the driving pressure of the released breath, depending on the degree of intrinsic PEEP. Excessive P_{high} can lead to alveolar overdistention and impair hemodynamics causing cor pulmonale. If P_{high} is too low, the patient may suffer from atelectrauma, increased work of breathing or derecruitment and hypoxemia.
2. T_{high}: T_{high} is the duration of time spent at P_{high} and is the driving factor for the respiratory rate. If the T_{high} is too short, derecruitment and hypoxemia can occur. If T_{high} is too long, the respiratory rate will decrease leading to hypercapnia.
3. P_{low}: P_{low} is the target pressure during the release phase. P_{low} is generally set at zero to maximize peak expiratory flow rate. However, a P_{low} of 0 cm H20 is never reached during expiration, if the T_{low} is sufficiently brief, generating intrinsic PEEP to stabilize the open lung. The exhaled tidal volume is determined by the pressure gradient between the P_{high} and P_{low} as well as the duration of T_{low}.
4. T_{low}: T_{low} is the time spent at P_{low} and is critical to control end-expiratory lung volume. It is very important to avoid setting a T_{low} that is too long, as it will lead to alveolar collapse, causing ventilator-induced lung injury via atelectrauma from repeated opening and closing of alveoli during each tidal breath. Conversely, if the T_{low} is too short, the volume of the release breath will not be adequate to clear CO_2.
5. FiO2: Fraction of inspired oxygen titrated to a target saturation of 88-94%.

When initiating APRV for hypoxemic respiratory failure, one method is to set the P_{High} at approximately the plateau pressure on conventional MV. Plateau pressure is the best clinical estimate of the average alveolar pressure. The P_{high} should then be increased as necessary in order to allow the FiO2 to be weaned to a less toxic level (a cutoff of 0.6 is often used). Our practice has been to keep the P_{low} at zero, as described by Frawley and Habashi, which facilitates maximum acceleration of expiratory gas flow and minimizes the time required for release ventilation.[15] We usually begin with a T_{high} of 3.5– 5.5 sec. The long T_{high} maintains the Paw and hence alveolar recruitment. The appropriate T_{low} depends on the expiratory time constants of the lungs. An optimal release time allows for adequate ventilation while minimizing lung volume loss. A short release time should impede complete exhalation in the slower compartments (i.e., areas of high compliance or resistance to exhalation) and generate regional intrinsic PEEP. Theoretically, this will enhance alveolar recruitment. Our practice is to adjust the T_{low} until the patient's expiratory flow during the release phase reaches approximately 50–75% of its peak value. Short cut method is to adjust the T-low to target a dumping breath volume of approximately 6-8 cc/kg. For patients who

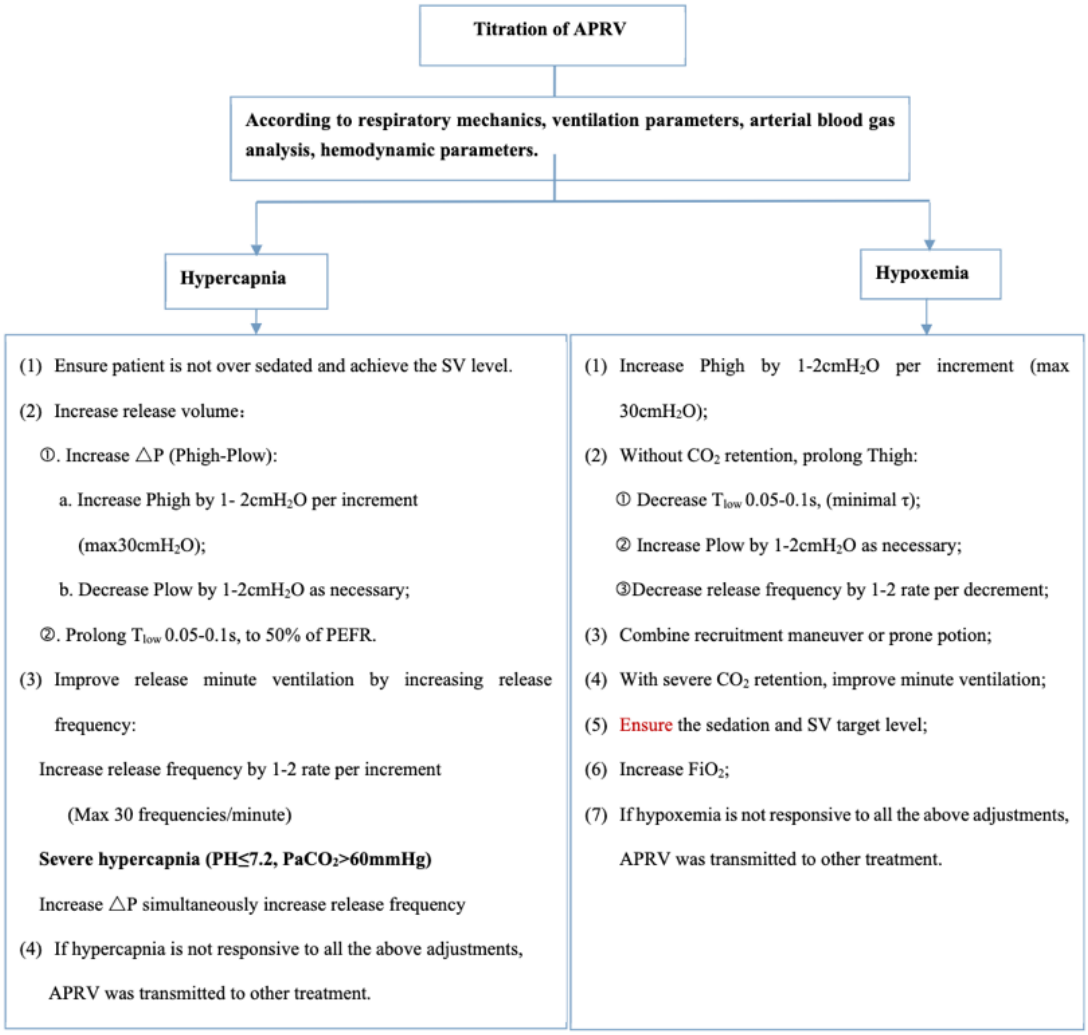

Figure 2. Titration of APRV

are actively breathing on the ventilator, this may be the only possible method to use.[16,17]

Figure 2 shows the algorithm for titrating or troubleshooting common problems using APRV as adopted from Zhou et al.[18] In our institution, there were 12 other patients who were ventilated using AC mode but developed persistent hypoxemia despite low tidal volume and optimal PEEP titration hence shifted to APRV. However, eight patients died and the other 4 patients reverted back to AC mode due to respiratory acidosis (pH <7.3, pCO2 >70).

Permissive hypercapnia during mechanical ventilation is a strategy that has been widely adopted to facilitate the benefits of lung-protective ventilation. The degree of hypercapnia and respiratory acidosis tolerated by each patient will differ, and although we have recommended a value of pH ≥7.25 or 7.3, many patients tolerate further decreases in pH to ≥7.2. Conversely, other groups of patients will not tolerate even moderate degrees of hypercapnia, particularly in neurocritical care, those with coronary artery disease, congestive cardiac failure, arrhythmias, pulmonary hypertension, right ventricular dysfunction and significant hypovolemia.[16, 18]

One method of weaning on APRV is the "drop and stretch technique." P_{high} was decreased in increments of 2 cm and T_{high} was prolonged by increments of 0.5-2 seconds. This may be done every 4-8 hours as tolerated. This was continued until the patient was

weaned down to a P_{high} of ~16 or18 cm and a T_{high} of more than 8-10 seconds. The Thigh is lengthened and the P_{high} is lowered in a stepwise fashion, thus allowing a slow, controlled wean of Paw, until a low enough level of CPAP (no release phase) is reached from which the patient can be extubated. Lengthening the Thigh in this fashion is usually only tolerated when the patient is breathing spontaneously.[17]

Increased intrathoracic pressure as a result of mechanical ventilation has many effects on the heart, both positive and negative. The negative effects are well known: decreased venous return to the right side of the heart, increased afterload, and increased pulmonary vascular resistance (which can be catastrophic in patients with right heart failure). However, the positive effects are often neglected: high intrathoracic pressure decreases the transmural left ventricular pressure thereby reducing the work of contraction and increasing cardiac output. In the context of hypoxemia, a mode of mechanical ventilation that improves arterial oxygenation will improve myocardial oxygen delivery, myocardial function, and cardiac output. As APRV is a spontaneous breathing mode, in addition to the benefits of spontaneous ventilation, reduced doses of sedative drugs can often be used, with subsequent reduction of requirement for vasoactive drugs and improvement in hemodynamic state.[19, 20]

Critics of APRV argue that spontaneous breathing during T_{high} can cause high local transpulmonary pressures and tachypnea, especially in the context of heterogeneous lung disease, which in turn may increase the risk of patient self-inflicted lung injury. They also warn that occult atelectrauma still occurs with APRV, as T_{low} times longer than 0.2 seconds could still result in collapse of injured alveoli, and many ventilators are unable to provide T_{low} times this short.[21]

One group of patients who might not benefit from APRV are patients with substantial obstructive lung disease (e.g., COPD or asthma). Such patients tend to accumulate excessive intra-thoracic pressures (autoPEEP) with any ventilator mode. APRV could potentially exacerbate this. APRV may be used cautiously in patients with mild or moderate obstructive lung disease, with the understanding that patients may require unusually long T_{low} and that careful monitoring is required to ensure adequate ventilation.[13]

Improvement in P/F ratio and vasopressor requirements was noted after the initiation of APRV in COVID-19 patients. However, patients on APRV had higher release volumes and mean airway pressures. Longer duration of APRV was associated with the incidence of barotrauma and volutrauma related complications like pneumothorax, pneumomediastinum and subcutaneous emphysema with higher mortality rate (52% vs 85.7%).[12] Chiumello et al. demonstrated that venous admixture and PaO_2/FiO_2 were not correlated to the fraction of non-aerated lung, suggesting a different mechanism of hypoxemia in their patients with COVID-19 pneumonia. The severity of hypoxemia appeared to be out of proportion to the impairment in lung mechanics. This conclusion agreed with the pathological findings revealing unusual involvement of the pulmonary microvasculature and associated coagulopathy.[22]

APRV may be considered in the course of intubated COVID-19 patients with severe ARDS, in order to provide adequate alveolar recruitment. The application of APRV continues to be limited, given that many providers are not familiar with this ventilation mode or its titration methodology, stemming from a lack of commonly accepted APRV protocols. The marked heterogeneity in APRV settings prohibits prospective evidence from a RCT and accurate meta-analyses of their outcomes.

CONCLUSION

When contemplating the heterogeneous nature of respiratory failure in critically ill COVID-19 patients, it is probable that one

mode of ventilation does not provide optimum support for every patient with respect to gas exchange or survival. In this paper, we have summarized the rationale for and against the use of APRV and explained how APRV can be initiated, titrated and weaned. While APRV has an attractive theoretical basis, there are no large multi-center RCTs supporting its use. Future research should aim to clarify which specific subgroups of patients, if any, would benefit from the use of APRV. Therefore, although APRV may be useful for oxygenating COVID-19 patients, judgment should be reserved when considering its use until it achieves the level of scientific evidence to improve outcomes in this challenging patient population.

LIMITATIONS

The limitations of our study are as follows (1) it is a case series with a large potential for bias; (2) there was no defined protocol for initiation of APRV or for consequent ventilator management as well as non uniform management for COVID-19 patients at that time; and, (3) patients included in this case series were also relatively young.

RECOMMENDATIONS

We strongly recommend adherence to evidence-based management as suggested by international guidelines for ARDS which includes lung-protective mechanical ventilation, individualized PEEP and prone positioning before commencing APRV for severe hypoxemia in ARDS. Safety and efficacy needs to be established by a large prospective observational trial or a randomized controlled trial.

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ERRATUM

Erratum to "*Effect of a Chronic Obstructive Pulmonary Disease Discharge Bundle on Re-Admission Outcomes*". Philippine Journal of Chest Diseases Vol. 20 No. 1, January-June 2022, Pages 28-36.

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On page 28, the hospital affiliation of the authors was written incorrectly and should read as "The Medical City, Pasig City, Metro Manila, Philippines".

The publisher would like to apologize for any inconvenience caused.

In addition, the authors would like to declare that the paper was presented in the following conference: Asian Pacific Society of Respirology Congress (November 2019).

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