LUNG CENTER OF THE PHILIPPINES

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Scientific Proceedings

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Vincent Balanag Jr., MD, MSc
Executive Director IV
Lung Center of the Philippines

This latest issue of the **Scientific Proceedings** features the experiences of our institution during the first 2 years of the COVID-19 pandemic in the country. The papers included in this issue would give us a general picture of the conditions present during this period. Although it should be also worth mentioning that there were distinct phases of the pandemic characterized by varying levels of preparedness among our health workers, the available types of medical interventions, as well the numbers and degree of severity of cases. Nevertheless, there are many new findings and conclusions that can be extracted from these papers that will be useful to clinicians in the management of COVID-19 cases in the present time and in the future.

Health workers are the frontliners in the fight against COVID-19. Keeping them healthy and safe is vital to ensure that our health system is not overwhelmed. Among health workers in LCP, sources of COVID-19 infection may come from patients, co-workers or the community. The majority (80%) of cases were mild, with more than half (56%) detected during routine screening of asymptomatic carriers, of which more than half eventually developed symptoms (Bautista, et al). The study highlights the importance of vigilance among health workers and to always follow standard health protocols wherever they are, perhaps especially when they are in the community in order to reduce the likelihood of infection.

COVID-19 infection may present without symptoms, or with symptoms ranging from mild to very severe, with increasing severity of illness predictive of higher mortality rates. Clinicians, therefore should be astute in eliciting signs and symptoms, and requesting diagnostic tests that are predictive of disease severity and adverse clinical outcomes, so that life-saving measures can be promptly instituted whenever available. Presence of dyspnea, tachypnea and high oxygen requirement on admissions likely indicate severe disease; while high oxygen saturations and PF ratio are good indicators of adequacy of oxygenation (Manuel, et al). Patient characteristics like age, sex and co-morbidities such as hypertension, heart disease, and diabetes contribute to the severity of illnesses as may be seen in COVID-19 cases who developed ARDS and acute coronary syndrome (de Guzman-Pamplona, et al).

Certain hematologic and biochemical markers may be useful in determining severity, risk of disease progression and even prognosis. These include LDH, CRP, ferritin and procalcitonin (Bulaclac, et al). Several patterns in CT scan of COVID-19 such as the extent of ground-glass opacities (GGO) and consolidation, and number of lobes involved, are also useful in determining duration and severity of illness (dela Pena, et al).

Several factors were identified that can affect survival in COVID-19 patients. Higher oxygen saturation, GCS score, eGRF associated with survival, but higher neutrophilic predominance and LDH may predict lower survival in COVID-19 patients (de Vera, et al). In severe to critically-ill cases, higher APACHE scores, lower PF ratios and need for mechanical ventilation are associated with increased mortality (Chan-Reyes, et al).

Numerous studies from here and abroad have identified several existing and novel interventions useful in improving outcomes in COVID-19, especially for severe to critically-ill cases, and these have been verified by studies done in LCP. Effective treatment which reduced mortality include a standard care regimen consisting of antibiotics, IV fluids, anticoagulant and steroids, together with high flow nasal cannula (HFNC), in combination with tocilizumab, remdesivir, hemoperfusion and proning (Cervales, et al; Chan-Reyes, et al). These are now considered part of best practices here in the Philippines.

Congratulations to the participating authors of this issue for providing these valuable information.

LUNG CENTER OF THE PHILIPPINES
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Jubert Benedicto, MD
Editor-in-Chief

To say that the past two years have been challenging will be an understatement. This I say because we were taught some hard lessons… we were tested to the limits in terms of resilience and strength… and certainly, the pandemic has uncovered certain things which we thought we never had. The past two years were a mix of roller coaster rides and tumultuous times especially for a designated COVID-19 referral institution like the Lung Center of the Philippines.

LCP had to adapt and evolve. In a lot of instances, the circumstances were beyond our control. External forces tend to exert significant pressures that influenced LCP's pandemic response. The hospital administration and staff had to be quick in their thinking and quicker in terms of decisive actions. COVID surges magnified these issues. However, these trying times also revealed what we knew all along: that as an institution with a proud history of excellence in lung health and delivery of specialized respiratory care, we had no choice but to be victorious amidst these unpredictable times.

I think one of the keys to our success was that *we let Science speak*. We insulated ourselves from the usual "noisy" debates and innuendos and just concentrated on the evidence (or lack thereof) in the scientific literature. If there was no "statistically significant difference" in terms of touted interventions, we concentrated on trends. We let Science arm us. Critical thinking prevailed. We were willing to collaborate, we accepted our limitations, and we were willing to change without holding on tightly to any pre-conceived ideas.

Such a demeanor resulted to policies, standards of care, and clinical pathways which were considered as "living documents." We expected that these may change and should not be automatically "cast in stone." That was indeed reflective of our humility. This was the context of what it was to be as a COVID-19 center. These concepts were tested through the process of research. We needed to see and examine what would work and what were feasible in our setting. We built on what we saw from existing literature but also considered the local landscape. That is an unquestionable attribute of a good researcher.

We are proud and honored to have a dedicated issue of the **Scientific Proceedings** focusing on COVID-19-related research outputs. This is the product of conscientious investigators who were able to churn out quality papers while being immersed at the frontlines at the same time. This is a product that is a testament to the unbridled spirit of steadfast learners who were able to find value in sharing their unique experience and perspectives. This amalgam of experiences will surely find relevance in the local scenario and possibly similar future circumstances.

I encourage the readers, policy makers, and other stakeholders to carefully go through each published article. Communicate with the authors if necessary. Scrutinize them well. Apply them to your hospital setting. Replicate them if applicable. Improve on them until they will be relevant and feasible in your practice.

We have high aspirations for our **Scientific Proceedings**. The editorial board has great plans in sustaining our LCP community's interest in research and readily offer this platform as a viable option for publication. Please do not let any interesting idea just die down. Act on them. Investigate. Write them up and more importantly, SHARE your findings with others. Your idea will lose its importance if not shared. This COVID-19 dedicated issue is a concrete attempt to do just this.

LCP humbly dedicates this issue to all frontliners and COVID-19 workers who continue to work tirelessly and unselfishly every single day. This is for all of you!

About the Journal

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

Focus and Scope

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

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LUNG CENTER OF THE PHILIPPINES

PULMONARY REHABILITATION

WARM-UP & COOL DOWN

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

BREATHING EXERCISES

CARDIOPULMONARY EXERCISES

Materials for Virtual Sessions

Digital Platforms Requirements
- -Zoom Account
- -Viber Account

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

CONDITIONS RECOMMENDED FOR THE PROGRAM

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

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Original Article

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

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ABSTRACT

Background and Objective. COVID-19 was an emerging infection that has reached pandemic levels with a reported case fatality rate of 3-4%.[1] This study aimed to determine risk factors at baseline that predict in-hospital death from COVID-19 for patients admitted at the Lung Center of the Philippines (LCP). The goal was not only to identify preventable causes of death of COVID-19 cases, but also prognosticate those with severe disease.

Methodology. This research was a retrospective cohort, observational, and analytical study using chart review for data collection. The study subjects included COVID-19 cases confirmed by a positive result via reverse transcriptase polymerase chain reaction (RT-PCR) testing or SARS-CoV-2 GeneXpert admitted and/or discharged/expired at the LCP from March 7 to August 31, 2020.

Results. Out of 531 admitted patients, 258 were included in this study. There were 84 non-survivors, and 174 survivors. Non-survivors were older and have more than one co-morbid illness (specifically chronic kidney disease) compared to survivors. Fever, cough, and dyspnea were the most common symptoms on disease onset. Among the inflammatory markers: AST, C-reactive protein (CRP), lactate dehydrogenase (LDH), procalcitonin and troponin I were significantly elevated among non-survivors. After multivariate analysis, oxygen saturation (OR 0.952 CI 0.92-0.99 p 0.015), 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) were found to correlate 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, mortality, risk factors, Lung Center of the Philippines

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INTRODUCTION

The end of 2019 saw the emergence of a new coronavirus. What was known now as SARS-CoV-2 started out as nCoV-2019 or novel coronavirus 2019 – first reported in Wuhan City, in the province of Hubei, China. From a cluster of cases of pneumonia mostly involving vendors and dealers in a seafood market in Wuhan City, the disease now known as COVID-19 has reached pandemic proportions – affecting 58 million people in 218 countries and killing more than 1,392,000 to date. The Philippines was not exempt from this global pandemic with over 400,000 cases by November 2020 reported with over 8,000 deaths due to the disease. With the ease of lock downs both locally and internationally, the number of COVID-19 cases continues to rise.

SARS-CoV-2 hails from a family of *Coronaviridae* known to infect both humans and animals. This originally zoonotic infection has since adapted to humans. Most people infected develop 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 develop serious illness. Although transmission of the virus was still incompletely understood, person-to-person transmission through respiratory droplets and infected surfaces has been the mode most documented. Incubation period of the virus was thought to be within 2-14 days of exposure with one person infected having the capacity to infect six to fourteen other people. To mitigate the spread of the virus and infection, countries adopted several measures to limit human interactions. This has forced several industries as well as local and international travel to shut down.

Several foreign studies have already been done to study mortality risk factors[3-11] where different demographic, clinical, laboratory, and radiographic findings were found to influence mortality. Self-reported dyspnea,[4,5] tachypnea,[5,8] elevated inflammatory markers[5,7,8,10,17] conferred greater risk of mortality. Baseline chest x-ray and chest CT scan findings were not found to be associated with greater mortality risk.[8]

As the knowledge about COVID-19 was still evolving, local data tackling disease characteristics and outcomes have yet to be published. Local studies on outcomes of COVID-19 in-patients and predictors of mortality were still lacking. In addition, the Lung Center of the Philippines (LCP) has been designated as a COVID referral hospital hence majority of the patients admitted were classified as severe to critical, with co-morbidities, and with risk for mortality. This study aims to determine modifiable and non-modifiable risk factors that predict in-hospital death. This will not only help identify preventable causes of death of COVID-19 cases, but also prognosticate those with severe disease.

METHODOLOGY

Study Subjects and Design

This research was a retrospective cohort, observational, and analytical study using chart review for data collection. The study subjects included COVID-19 cases confirmed by a positive result via reverse transcriptase polymerase chain reaction (RT-PCR) testing or SARS-CoV-2 GeneXpert admitted and discharged or expired at the LCP from March 7 to August 31, 2020. Patients less than 18 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.

Data Collection and Processing

A pooled patient master list from the Hospital Epidemiologic Surveillance Unit (HESU), admitting and records section of LCP was obtained to identify subjects. Demographic, clinical characteristics, baseline radiologic and laboratory parameters of the identified patients were extracted through chart review using a standard data collection tool (see Appendix A and B). 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 was required. Out of the total number of cases recorded for the study period, a simple random sampling was done using a random number generator to retrieve the charts. Descriptive statistics was used to summarize the demographic and clinical characteristics of the patients. Frequency and proportion were 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 was computed to determine significant predictors for mortality. Stepwise method was utilized to determine the final multivariate model. All statistical tests were two tailed tests. 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

This study was approved by the Institutional Ethics Review Board (IERB).

RESULTS

Out of the 531 identified subjects, 270 charts were retrieved for data extraction and analysis. Twelve subjects were excluded due to age less than 18 years old (n=6) and presence of advanced directives (n=6). From the charts analyzed, 174 subjects survived and 84 did not, putting the crude mortality rate at 33% (Figure 1). Table 1 summarizes the demographic, clinical, baseline physical, laboratory and radiographic findings of admitted patients. The mean age of patients admitted was 57 years old (56.83 ± 14.4, p<0.001) with majority having no known exposure to a COVID-19 case (n=118, 47.01%, p 0.273). The mean age of non-survivors was significantly higher compared to survivors (61.82 ± 12.6 vs 54.43 ± 14.66, p<0.001). Most patients admitted were male

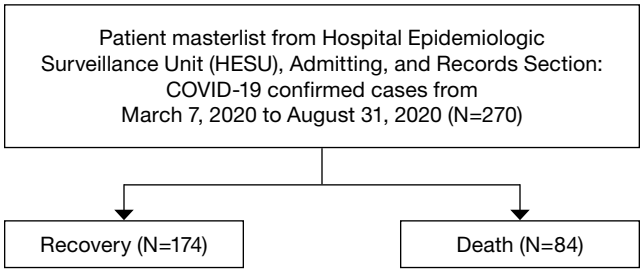

Figure 1. Flow diagram of data collected on admitted COVID-19 cases at the Lung Center of the Philippines from March 7, 2020 to August 31, 2020.

but differences in sex distribution and time of illness onset to hospital admission for the two cohorts were non-significant. Among the symptoms reported on admission, the most common were fever, cough, and dyspnea – however, more survivors reported dyspnea and sore throat as their presenting symptoms. Hypertension and diabetes mellitus type 2 were the most common co-morbid illness among COVID-19 inpatients. Non-survivors reported having 2 or more co-morbidities (chronic kidney disease being more prevalent) compared to survivors (p<0.015). Smoking status and pack year history did not significantly differ between the two groups.

In terms of disease severity on admission, 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). Majority of the patients who belonged to the moderate severity on admission survived (n=132, 77.65% p<0.001), while those classified as critical did not (n=37, 44.05% p<0.001). Among patients admitted under severe disease, there were significantly more survivors compared to non-survivors (n=24 vs 20, p<0.001).

On admitting physical examination, the patients in the non-survivor cohort were noted to be more tachycardic, tachypneic, and desaturated at room air – requiring a significantly higher oxygen support on admission compared to survivors. Baseline arterial blood gases also showed a more decreased mean pH and metabolic acidosis in non-survivors. PO_2/FiO_2 (PF) ratio was lower in non-survivors (n=162.2, range 91-265.7 p<0.001). Complete blood count (CBC) done on admission also revealed increased white blood cell count (WBC) and neutrophil fraction for non-survivors. Among the inflammatory markers examined: C-reactive protein (CRP), lactate dehydrogenase (LDH), procalcitonin and troponin I were found to be significantly elevated among non-survivors. Conversely, higher estimated glomerular filtration rate (eGFR), and a lower baseline creatinine was observed in survivors. ALT levels were higher among the non-survivor group. 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. Demographic, clinical, baseline laboratory and radiographic findings of admitted COVID-19 patients

	Total (n=258)	Non-Survivors (n=84, 33%)	Survivors (n=174, 67%)	P-value
	Frequency (%); Mean ± SD; Median (IQR)			
Age	56.83 ± 14.42	61.82 ± 12.6	54.43 ± 14.66	**<0.001**
Sex				0.491
Male	163 (63.18)	56 (66.67)	107 (61.49)	
Female	95 (36.82)	28 (33.33)	67 (38.51)	
Time from illness onset to hospital admission (in days)	7 (5 to 9)	7 (5 to 8)	7 (5 to 9)	0.497
History of exposure				0.273
Close contact	59 (23.51)	14 (17.07)	45 (26.63)	
History of travel	8 (3.19)	2 (2.44)	6 (3.55)	
Unknown	66 (26.29)	21 (25.61)	45 (26.63)	
None	118 (47.01)	45 (54.88)	73 (43.2)	
Clinical signs and symptoms (admission)				
Cough				
Non-productive	175 (67.83)	56 (66.67)	119 (68.39)	0.743
Productive	34 (13.18)	13 (15.48)	21 (12.07)	
Fever	192 (74.42)	61 (72.62)	131 (75.29)	0.651
Dyspnea	190 (73.64)	70 (83.33)	120 (68.97)	**0.016**
Fatigue	7 (2.71)	2 (2.38)	5 (2.87)	1.000
Colds	14 (5.43)	3 (3.57)	11 (6.32)	0.559
Diarrhea	16 (6.2)	3 (3.57)	13 (7.47)	0.280
Myalgia	14 (5.43)	4 (4.76)	10 (5.75)	1.000
Anosmia	9 (3.49)	3 (3.57)	6 (3.45)	1.000
Sore throat	24 (9.30)	3 (3.57)	21 (12.07)	**0.037**
Body weakness	27 (10.47)	11 (13.1)	16 (9.2)	0.387
Co-morbidities				
Diabetes mellitus	91 (35.27)	31 (36.9)	60 (34.48)	0.781
Hypertension	142 (55.04)	55 (65.48)	87 (50)	**0.023**
Cardiovascular disease/CAD	21 (8.14)	9 (10.71)	12 (6.9)	0.334
Cerebrovascular disease	9 (3.49)	5 (5.95)	4 (2.3)	0.156
CHF	4 (1.55)	2 (2.38)	2 (1.15)	0.598
COPD	5 (1.94)	1 (1.19)	4 (2.3)	1.000
PTB				
Active	8 (3.10)	3 (3.57)	5 (2.87)	0.293
Previous	19 (7.36)	9 (10.71)	10 (5.75)	
BA	20 (7.75)	5 (5.95)	15 (8.62)	0.620
Malignancy	7 (2.71)	3 (3.57)	4 (2.3)	0.686
Chronic Kidney Disease	17 (6.59)	10 (11.9)	7 (4.02)	**0.029**
Other co-morbidities	29 (11.24)	11 (13.1)	18 (10.34)	0.532
Number of Co-morbidity	1 (1 to 2)	2 (1 to 3)	1 (1 to 2)	**0.015**
Smoking Status				0.881
Smoker (current or previous smoker)	70 (27.89)	24 (28.92)	46 (27.38)	
Non-Smoker	181 (72.11)	59 (71.08)	122 (72.62)	
Pack Years (n=50)	15 (10 to 30)	25 (10 to 38)	15 (7 to 30)	0.405
Disease severity (admitting diagnosis)				**<0.001**
Mild	8 (3.15)	2 (2.38)	6 (3.53)	
Moderate	157 (61.81)	25 (29.76)	132 (77.65)	
Severe	44 (17.32)	20 (23.81)	24 (14.12)	
Critical	45 (17.72)	37 (44.05)	8 (4.71)	
SBP	130 (120-140)	130 (120-150)	130 (119-140)	0.096
DBP	80 (70-89)	77.5 (70-90)	80 (70-88)	0.139
Pulse rate	99 (87-110)	105.5 (89-115)	97.5 (86-109)	**0.010**
Respiratory rate	24 (22-26)	25 (23-30)	24 (21-25)	**<0.001**
Temperature	36.5 (36.2-37)	36.7 (36.3-37)	36.5 (36.2-37)	0.181
O_2 saturation	94 (88-96)	87.5 (76-94)	95 (91-97)	**<0.001**
GCS Scoring	15 (3-15)	15 (3-15)	15 (11-15)	**<0.001**
Height (cm) (n=24)	162 (157-166)	160 (155-170)	162 (160-165)	0.788
Weight (kg) (n=27)	60 (53-65)	55 (52-67)	60 (55.5-62.5)	0.520
O_2 support	28 (21-45)	41 (28-80)	24 (21-36)	**<0.001**
pH	7.46 (7.43-7.5)	7.45 (7.41-7.49)	7.47 (7.44-7.5)	**0.005**

Table 1. Demographic, clinical, baseline laboratory and radiographic findings of admitted COVID-19 patients *(continued)*

	Total (n=258)	Non-Survivors (n=84, 33%)	Survivors (n=174, 67%)	P-value
	Frequency (%); Mean ± SD; Median (IQR)			
pCO_2	33.8 (30.1-39)	32.7 (28.4-37.7)	34.4 (30.6-39)	0.135
HCO_3	24 (21.7-27)	22.7 (19.4-25.8)	24.5 (22.6-27.3)	**<0.001**
pO_2	70.8 (60-89)	67.55 (55-90.9)	72 (62.9-87.8)	0.059
PF ratio	259 (152-326)	162.2 (91-265.7)	286 (203-346)	**<0.001**
Laboratory Results				
Hemoglobin	134 (123-144)	131 (116-142)	135 (126-144)	0.092
Hematocrit	0.4 (0.37-0.43)	0.39 (0.35-0.43)	0.4 (0.38-0.43)	0.210
WBC	8.1 (5.9-11.3)	10.5 (7.1-14.6)	7.6 (5.5-9.6)	**<0.001**
Neutrophils	0.8 (0.71-0.87)	0.85 (0.79-0.9)	0.77 (0.65-0.85)	**<0.001**
Lymphocytes	0.17 (0.1-0.26)	0.13 (0.07-0.19)	0.20 (0.12-0.31)	**<0.001**
Platelet Count	268 (192-342)	250 (179-318)	274 (196-344)	0.312
Creatinine	89 (70-120)	115 (83-184)	82 (68-101)	**<0.001**
eGFR (by EPI)	72.5 (50-91.5)	52 (29-74)	79 (63.3-98)	**<0.001**
Serum sodium				0.177
Normal	82 (32.93)	22 (27.16)	60 (35.71)	
Hyper Na	5 (2.01)	3 (3.7)	2 (1.19)	
Hypo Na	162 (65.06)	56 (69.14)	106 (63.1)	
Serum potassium				0.326
Normal	174 (69.88)	60 (74.07)	114 (67.86)	
Hyper K	15 (6.02)	6 (7.41)	9 (5.36)	
Hypo K	60 (24.1)	15 (18.52)	45 (26.79)	
Serum magnesium				0.451
Normal	117 (77.63)	63 (81.82)	114 (75.5)	
Hyper Mg	11 (4.82)	4 (5.19)	7 (4.64)	
Hypo Mg	40 (17.54)	10 (12.99)	30 (19.87)	
Serum calcium				0.427
Normal	153 (68.92)	49 (65.33)	104 (70.75)	
Hyper Ca	2 (0.90)	0	2 (1.36)	
Hypo Ca	67 (30.18)	26 (34.67)	41 (27.89)	
ALT	53 (35-83)	51 (30-98)	53 (35-80)	0.912
AST	50 (34-80)	66.5 (43.5-109)	44 (31-67)	**<0.001**
CRP (n=118)	101 (47-160)	141.5 (73.4-160)	80.5 (35-128)	**0.004**
D-dimer (n=118)	200 (200-200)	200 (200-400)	200 (200-200)	0.301
Ferritin (n=162)	1200 (627-1200)	1200 (920-1200)	1200 (598-1200)	0.121
LDH (n=212)	397 (276-589)	590 (445-778)	315 (247-462)	**<0.001**
Procalcitonin (ng/mL) (n=171)	0.14 (0.05-0.52)	0.54 (0.1-2.35)	0.09 (0.05-0.27)	**<0.001**
Troponin I (n=184)	0.01 (0.01-0.06)	0.05 (0.01-0.14)	0.01 (0.01-0.02)	**<0.001**
Presence of organism on sputum/ETA culture				1.000
With growth	111 (97.37)	42 (97.67)	69 (97.18)	
No growth	3 (2.63)	1 (2.33)	2 (2.82)	
Presence of organism on blood culture				**0.011**
With growth	9 (9.38)	7 (20)	2 (3.28)	
No growth	87 (90.63)	28 (80)	59 (96.72)	
Chest x-ray result				
Normal	24 (9.3)	5 (5.95)	19 (10.92)	0.255
Hazy infiltrates/patchy density	200 (77.52)	63 (75)	137 (78.74)	0.526
Consolidation	35 (13.57)	21 (25)	14 (8.05)	**<0.001**
Pleural effusion	7 (2.71)	2 (2.38)	5 (2.87)	1.000
Other CXR	13 (5.04)	6 (7.14)	7 (4.02)	0.363
CT scan result				
Normal CT	9 (3.49)	3 (3.57)	6 (3.45)	1.000
Peripheral GGO	210 (81.4)	65 (77.38)	145 (83.33)	0.306
Reticulonodular opacity	44 (17.05)	11 (13.1)	33 (18.97)	0.291
Consolidation CT	52 (20.16)	22 (26.19)	30 (17.24)	0.100
Not done	17 (6.59)	11 (13.1)	6 (3.45)	**0.006**
Others CT	21 (8.14)	6 (7.14)	15 (8.62)	0.810

Table 2. Treatment initiated on admission

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

Table 2 summarizes treatment initiated on patients upon admission. Most patients received non-invasive forms of ventilation, with majority belonging to the survivor cohort. Invasive ventilation on admission was seen more in patients who did not survive (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 (26 vs 21 p 0.006) and hemodialysis (21 vs 6 p<0.001) initiated on admission were also seen more in non-survivors.

Table 3 shows the significant risk factors for mortality 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 confer 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 3. Multivariate Odds Ratio of the significant risk factors for mortality of COVID-19 patients

Parameters	Adjusted Odds Ratio	95% CI	P-value
O_2 saturation	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 were the first done among all the designated referral centers in the country. Overall, mortality rate was 33% and was consistent with other studies, ranging between 20 and 44%.[20-23] We found through multivariate logistic regression that lower baseline oxygen saturation (76-94%), eGFR (29-74 mL/min) and Glasgow Coma Scale (GCS) Score (3-5), 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 low oxygen saturation on admission was previously found in another retrospective cohort by Wang et al. where it was largely attributed to disease severity and impending acute lung injury through cytokine storm.[7] This was also found on a recent study by Bahl et al. which showed that low oxygen saturation on admission was a risk factor for in-hospital death.[20] Another published report by Xie et al[24] stated that it was the most powerful predictor of death among the multiple variables measured and that severe hypoxia was associated with elevation of inflammatory markers, which was also consistent with our study.

A low GCS score in association with increased mortality was seen on a study of COVID patients in Italy[25] and on COVID patients with pre-existing stroke.[26] It was regarded as part of the Sequential Organ Failure Assessment (SOFA) score in the retrospective cohort

done by Zhou et al.[8] – where an increased SOFA score conferred a 5x higher risk of mortality. A low GCS score can therefore be seen as part of advanced end-organ damage associated with sepsis syndrome. GCS score was 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.[27]

A study by Lin et al. showed that the mechanism of kidney injury in COVID-19 involves direct attack of the virus to the intrinsic renal cells and that high Angiotensin Converting Enzyme 2 (ACE2) found on the proximal tubular epithelial cells were targets of SARS-CoV-2 and induces decreased eGFR.[28] In an international registry in Europe and America, there was 30% prevalence of kidney disease on admission, and this was associated with greater in-hospital mortality.[29] Chronic kidney disease, which can also yield a decreased eGFR at baseline, has also been found in our univariate analysis as a co-morbidity with significant effect on mortality. In addition, the study by Uribarri et al[29] stated that when CKD patients were excluded from the analysis, results still showed that patients with low eGFR conferred greater risk of mortality. Decreased eGFR at baseline can likewise be a manifestation of end organ damage due to sepsis which was usually present in COVID patients admitted in our institution.

Increased neutrophilic ratio was found in this study to confer increased mortality. This finding has likewise been found in other cohorts and descriptive studies[7,19,20] which 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. The pathophysiology of increase in 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 in China also found that neutrophilia was significantly associated with greater risk of developing ARDS and it can lead to severe pneumonia and death.[30]

LDH was another proinflammatory marker found in this study as well as others[8,17] that increases the odds for mortality. LDH was a housekeeping enzyme present in various tissue types including the cardiomyocytes, pneumocytes, kidneys, liver and striated muscle. As such, the release/increased levels of LDH in the circulation often heralds cytokine-mediated tissue damage and/or injury. As for COVID-19, increased LDH levels often correlate with acute lung injury from severe interstitial pneumonia often culminating in Acute Respiratory Distress Syndrome (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[5,7,8] which may be due to the limited availability of these laboratory exams during the initial months of the pandemic. The utility of these inflammatory markers can therefore be realized by doing a prospective cohort study in the future.

The Coronavirus Clinical Characterizations Consortium (4C) mortality score developed by the International and Severe Acute Respiratory and Emerging Infections Consortium (ISARIC) of the WHO developed a risk stratification score that predicts in-hospital mortality for admitted COVID-19 patients.[31] Included in this scoring was the oxygen saturation, GCS, kidney function, and inflammatory markers which was consistent with our study. Thus, the combination of physical examination findings and laboratory values deemed to be significant predictors of mortality elicited in this retrospective cohort can be used as a guide to patients who have poorer prognosis at baseline, therefore warranting a more aggressive management. Although no treatment regimen has yet been identified to significantly alter mortality, risk factors for mortality can help clinicians delineate patients who need more close monitoring and allocate care accordingly.

Limitations and Study Recommendations

The study having a retrospective design has several limitations, namely the incompleteness of some of the data gathered (such as body mass index and other inflammatory markers). There was likewise non-uniformity of some laboratory examinations due to their initial unavailability in-house. The lack of specific data in some of the subjects analyzed may underestimate their role in COVID-19 mortality. The interpretation of the findings in this study was 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.

CONCLUSION

Oxygen desaturation, low GCS score, decreased eGFR, increased LDH and neutrophilia were found in this study to increase 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. Knowing which parameters (clinical and laboratory findings) confer increased risk for mortality may guide the healthcare team in pursuing more aggressive management for COVID-19 patients.

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APPENDICES

Appendix A. Data collection procedures

Exclusion criteria:
- Age <18yrs old
- Missing data or information
- Death at ER or within 24hours of admission
- Advanced directives (DNR/DNI)
- DAMA or transfer to another hospital

Patient masterlist from Hospital Epidemiologic Surveillance Unit (HESU), Admitting, and Records Section: COVID-19 confirmed cases from March 7, 2020 to August 31, 2020

Recovery

Death

Risk factors measured:
Age, sex, healthcare worker, history of exposure, co-morbidities, clinical signs and symptoms on admission, time from illness onset to hospital admission, smoking status, disease severity on admission, vital signs on admission, laboratory data on admission (CBC, electrolytes, inflammatory markers, kidney function tests, liver function tests, troponin I), radiologic and CT scan findings on admission

Appendix B. Data collection tool

Patient Name: _____ Patient Code: _____ Age: _____ Gender: _____

Address: _____

Time from illness onset to admission (days): _____ Total no. of days admitted: _____ Outcome: ☐ Expired ☐ Recovered

☐ Clinical signs and symptoms
- o Fever
- o Cough (Productive or Non-productive)
- o Dyspnea
- o Fatigue
- o Colds
- o Diarrhea
- o Myalgia
- o Anosmia
- o Sore throat
- o Body weakness
- o Others _____

☐ Disease severity
- o Mild
- o Moderate
- o Severe
- o Critical

☐ Smoking status
- o Current/Previous smoker
- o Non-smoker

☐ History of Exposure
- o History of overseas travel in 3 months
- o Close contact w/ confirmed COVID-19 case
- o Unknown
- o None

☐ Co-morbidities:
- o Hypertension
- o Diabetes Mellitus
- o Chronic kidney disease
- o COPD
- o Asthma
- o Tuberculosis
  - o Active
  - o Previous
- o Cardiovascular disease
- o Malignancy
- o Cerebrovascular disease
- o CHF
- o Peripheral vascular disease
- o Connective Tissue Disease/Rheumatologic disease
- o Chronic Liver Disease
- o HIV/AIDS
- o Pregnancy
- o Other _____

☐ Vital signs on admission
- o Systolic BP
- o Diastolic BP
- o Pulse rate
- o Respiratory rate
- o Temperature
- o Oxygen saturation
- o GCS scoring
- o Height _____
- o Weight _____
- o O_2 support (in %FiO_2)

☐ ABG on admission
- o pH _____
- o pCO_2 _____
- o HCO_3 _____
- o pO_2 _____
- o PF ratio _____

☐ Laboratory data on admission
- o Hemoglobin _____
- o Hematocrit _____
- o WBC _____
- o Platelet _____
- o Creatinine _____
- o eGFR (by EPI) _____
- o Serum Na _____
- o Serum K _____
- o Serum Mg _____
- o Serum Ca _____
- o AST
- o ALT
- o Presence of other organisms on ETA/sputum culture
- o Presence of organisms on blood culture

Inflammatory markers on admission
- o CRP
- o D-dimer
- o Ferritin
- o LDH
- o Procalcitonin
- o Troponin I

Radiologic and CT scan findings on admission

☐ Chest x-ray
- o Normal
- o Hazy infiltrates
- o Consolidation
- o Pleural effusion

☐ CT-scan
- o Normal
- o Peripheral ground glass opacities
- o Reticulonodular opacities
- o Consolidation

Intervention given upon admission

☐ Oxygen support
- o None
- o Nasal cannula
- o Nonrebreather mask
- o High flow nasal cannula
- o Mechanical Ventilation
- o Use of hemoperfusion
- o Use of hemodialysis

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

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ABSTRACT

Background. Identifying clinical factors that may be of utility to clinicians to predict COVID-19 outcomes will help clinicians immediately recognize disease severity of COVID-19 and provide timely personalized management to prevent fatal consequences and save resources.

Objective. This study aims to determine the association of clinical characteristics with disease severity in COVID-19 confirmed cases admitted at Lung Center of the Philippines (LCP). Specifically, we aim to compare socio-demographic and clinical profile according to disease severity of COVID-19 confirmed cases admitted in LCP and to determine which clinical characteristics can be associated with COVID-19 disease severity.

Methodology. This is a cross-sectional study design which involved a retrospective chart review of 366 confirmed COVID-19 patients admitted at the LCP from March 7 to August 31, 2020.

Results. Majority of the patients were males (n=233, 63.44%) and the median age was 58.5 years (IQR 54-70). Multivariable regression analysis showed increasing odds of having severe or critical COVID-19 associated with age 40 to 59 years (OR=7.79, 95% CI=1.28 to 47.2, p=0.026) and ≥60 years (OR=8.17, 95% CI=1.4 to 47.6, p=0.020). Result also showed that patient who presented with dyspnea (OR=4.16, 95% CI=1.60 to 10.8, p=0.003), tachypnea (OR=1.17, 95% CI=1.08 to 1.28, p≤0.001) and increase O_2 support (OR=1.03, 95% CI=1.01 to 1.05, p=0.010) increased the odds of having severe to critical COVID-19. There was decreased odds of having severe or critical COVID-19 with increasing PF ratio (OR=0.9938, 95% CI=0.98 to 0.998, p=0.001) and increasing O_2 saturations (OR=0.9361, 95% CI=0.90 to 0.97, p=0.001).

Conclusion. Advanced age, patients presenting with dyspnea, tachypnea, and increase in O_2 support requirement were significantly associated with disease severity of COVID-19. Higher O_2 saturations and higher PF ratios were significantly associated with decreased odds of having severe or critical COVID-19. Hence, clinicians should always be mindful of these contributing factors to recognize the disease severity of COVID-19 early and to identify those who need urgent measures to prevent poor outcomes.

Keywords: COVID-19, disease severity, demographic characteristics, clinical characteristics

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INTRODUCTION

On the latter part of December 2019, an outbreak of a mysterious pneumonia happened in Huanan Seafood Wholesale Market, in Wuhan City, Hubei province of China.[1] The coronavirus which was causing the outbreak of unknown pneumonia was named as COVID-19 last February 11, 2020. It was subsequently declared as a pandemic by the World Health Organization (WHO) on March 11, 2020 due to the considerable countries affected by the disease.[2] In the Philippines, since the first reported case of COVID-19 on January 30, 2020 and the detection of sustained community transmission on March 7, 2020, the numbers of confirmed COVID-19 cases worldwide have grown to 58,057,411 cases and counting as of November 19, 2020.[3] The estimated mortality rate was 6.26% and most of the cases were seen in Metro Manila.[3] COVID-19 affected both the health system and economic aspect of the country, and the government imposed strict lockdown on the affected areas as early as March 2020.

In a study conducted in China, nearly half of the patients with COVID-19 had co-morbidities like hypertension, diabetes and coronary artery disease.[4] Most of the patients with COVID-19 reported in the literature were males.[4-8] Previous studies revealed that male gender and older patients infected with COVID-19 had increased risk of death.[4,8,9] The presence of coexisting illnesses were also noted to develop severe COVID-19 than those without co-morbid condition.[10,11] Since this novel virus is an emerging disease and due to the continuous threat to the health system and lack of available local data in our country, local studies should be conducted to identify the clinical characteristics of the patients that can be associated with the disease severity of COVID-19. This information is vital to help clinicians readily recognize severe and critical patients to be able to immediately provide the appropriate management. The Lung Center of the Philippines (LCP), a specialty center for lung diseases, was designated as one of the COVID-19 referral centers to accommodate mild to critical cases of COVID-19 and a fertile ground for studies regarding this disease. As to our knowledge, there were no studies done locally that describe the demographic and clinical characteristics of the patients with COVID-19 and associate it with the disease severity. Thus, this study aims to present clinical data of COVID-19 cases here in the Philippines in order to understand the novel disease and to associate the demographic and clinical characteristics on presentation and disease severity of COVID-19 during admission.

OBJECTIVES

This study aims to determine the association of demographic and clinical characteristics with disease severity among COVID-19 confirmed cases admitted at the LCP. Specifically, we aim to compare socio-demographic and clinical profile according to disease severity of COVID-19 confirmed cases admitted in LCP in terms of age, sex, occupation, smoking status, and clinical characteristics such as co-morbidities, symptoms, time from illness onset to hospital admission, and findings on admission; and to determine which of these characteristics can be associated with COVID-19 disease severity.

METHODOLOGY

Study Design and Site

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

Study Population

Three hundred and sixty-six (366) adult patients who were confirmed with COVID-19 according to WHO interim guidelines and who were admitted in the LCP between March 7, 2020 to August 31, 2020, were included in this study. Missing or incomplete data in the chart was excluded in our study.

Sample Size and Sampling Design

A minimum of 221 confirmed COVID-19 patients satisfying the inclusion/exclusion criteria was required to have a 90% chance of determining, as significant at the 5% level, the relationship of clinical characteristics with disease severity based on anticipated medium effect size of 0.3 of duration of symptoms versus disease severity.

Study Procedure

Medical charts of patients diagnosed with confirmed COVID-19 and admitted at the LCP from March 7, 2020 to August 31, 2020 were retrieved for review. Demographic profile including age, sex, co-morbidities, exposure history, smoking status, occupation, symptoms, duration of symptoms and time from illness onset to hospital ward admission were recorded. The co-morbidities included hypertension, diabetes mellitus (DM), cardiovascular disease, chronic obstructive pulmonary disease (COPD), pulmonary tuberculosis (PTB), bronchial asthma (BA), malignancy, and chronic kidney disease (CKD). Other diseases not specified were described under the other category. Co-morbidities were further classified based on the number of co-morbid conditions present if there was none, one, or more than one. The symptoms experienced prior to admission by the patient and its duration prior to admission were described in this study. Symptoms included were cough, dyspnea, diarrhea, fever and myalgia. Additional symptoms not were recorded under the other option. The initial physical examination included the following: vital signs (systolic blood pressure, diastolic blood pressure, pulse rate, respiratory rate), and partial pressure of oxygen/fraction of inspired oxygen ratio (pO_2/FiO_2). The disease severity classification of each case was based on the admitting diagnosis, either as mild, moderate, severe, and critical according to the classification and definition of the WHO Clinical Management of COVID-19 Interim Guidelines as of May 2020. To ensure that all important information were gathered, the researchers used a pre-specified Microsoft Excel file data collection form to record the said data. All the necessary data were encoded in the Excel sheet.

Statistical Analysis

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

Ethical Considerations

The study protocol was approved by the LCP Institutional Ethics Review Board.

RESULTS

A total of 526 cases were identified. One hundred and sixty (160) cases were excluded, among which, six cases were aged 18 and below, 11 cases had incomplete data, and 143 charts were unavailable during data collection. A total of 366 cases were finally randomly retrieved from the medical records based on availability of the charts and were included in the final data analysis.

Table 1 shows the demographic and clinical characteristics of the patients according to the disease severity of COVID-19. Most of the patients admitted were classified as moderate COVID-19 that comprised 211 (58%) of cases. The rest were classified under mild, severe and critical, which comprised 18 (5%), 60 (16%) and 77 (21%) of the population respectively.

Forty eight percent (48%) of the study subjects were aged 60 years old and older, while 39% (142) of the population belonged to the age group 40 to 59 years old. The median age of patients with severe and critical COVID-19 were older [60 (IQR:53-67) and 64 (IQR:54-70) years old respectively] in comparison with mild and moderate cases (37 and 57 respectively). For each disease severity, there was a predominating age group population. More than half (61.11%) of mild cases wherein the younger age group of 19 to 39 years old. Moderate cases of COVID-19 were mostly in the age group 40 to 59 (41.7%) and more than 60 years old (43.13%). On the other hand, more than half of the severe and critical cases were 60 years and older. Majority of the patients were males, although there was almost similar distribution of gender among the four diseases severity classification.

Table 1. Demographic and clinical characteristics of COVID-19 subjects according to disease severity

	Total (n=366)	Disease severity				p-value (<0.05)
		Mild (n=18, 5%)	Moderate (n=211, 58%)	Severe (n=60, 16%)	Critical (n=77, 21%)	
Age [Median (Interquartile Range)]	58.5 (48 to 67)	37 (28 to 59)	57 (46 to 67)	60 (53 to 67)	64 (54 to 70)	**<0.001**
19 to 39 years old n (%)	50 (13.66)	11 (61.11)	32 (15.17)	2 (3.33)	5 (6.49)	**<0.001**
40 to 59 years old n (%)	142 (38.8)	3 (16.67)	88 (41.71)	25 (41.67)	26 (33.77)	
≥60 years old n (%)	174 (47.54)	4 (22.22)	91 (43.13)	33 (55)	46 (59.74)	
Sex n (%)						0.503
Male	233 (63.66)	11 (61.11)	129 (61.14)	43 (71.67)	50 (64.94)	
Smoking Status n (%)						**0.028**
Smoker (current/previous)	100 (27.32)	3 (16.67)	48 (22.75)	24 (40)	25 (32.47)	
Occupation n (%)						**<0.001**
Healthcare worker	27 (7.38)	6 (33.33)	19 (9)	1 (1.67)	1 (1.3)	
Non healthcare worker	339 (92.62)	12 (66.67)	192 (91)	59 (98.33)	76 (98.7)	
Number of co-morbidity n (%)						**0.003**
Two co-morbidities	154 (42.08)	5 (27.78)	95 (45.02)	23 (38.33)	31 (40.26)	
One co-morbidity	138 (37.7)	5 (27.78)	67 (31.75)	32 (53.33)	34 (44.16)	
No co-morbidity	74 (20.22)	8 (44.44)	49 (23.22)	5 (8.33)	12 (15.58)	
Co-morbidities n (%)						
Hypertension	197 (53.83)	5 (27.78)	102 (48.34)	42 (70)	48 (62.34)	**0.001**
Diabetes mellitus	129 (35.25)	3 (16.67)	85 (40.28)	15 (25)	26 (33.77)	**0.048**
Bronchial Asthma	34 (9.29)	3 (16.67)	21 (9.95)	5 (8.33)	5 (6.49)	0.562
Cardiovascular	26 (7.1)	0	17 (8.06)	2 (3.33)	7 (9.09)	0.311
Chronic Kidney Disease	23 (6.28)	1 (5.56)	12 (5.69)	5 (8.33)	5 (6.49)	0.902
Cerebrovascular disease	12 (3.28)	1 (5.56)	4 (1.9)	2 (3.33)	5 (6.49)	0.253
Malignancy	14 (3.83)	1 (5.56)	9 (4.27)	3 (5)	1 (1.3)	0.611
COPD	7 (1.91)	0	4 (1.9)	1 (1.67)	2 (2.6)	0.905
PTB						
Active	13 (3.55)	0	11 (5.21)	0	2 (2.6)	**0.005**
Previous	25 (6.83)	1 (5.56)	6 (2.84)	7 (11.67)	11 (14.29)	
Time from Illness Onset to Hospital Admission [In Days (IQR)]	7 (5 to 9)	2 (0 to 4)	7 (5 to 9)	7 (4 to 8)	7 (5 to 7)	**<0.001**
Clinical Signs and Symptoms (on admission) n (%)						
Cough	235 (64.21)	3 (16.67)	139 (65.88)	43 (71.67)	50 (64.94)	**<0.001**
Non productive	59 (16.12)	1 (5.56)	29 (13.74)	10 (16.67)	19 (24.68)	
Productive	266 (72.68)	4 (22.22)	135 (63.98)	57 (95)	70 (90.91)	**<0.001**
Dyspnea	246 (67.21)	4 (22.22)	153 (72.51)	39 (65)	50 (64.94)	**<0.001**
Fever	43 (11.75)	0	25 (11.85)	8 (13.33)	10 (12.99)	0.447
Body Weakness	31 (8.47)	2 (11.11)	24 (11.37)	3 (5)	2 (2.6)	0.078
Sore throat	19 (5.19)	1 (5.56)	16 (7.58)	2 (3.33)	0	0.069
Diarrhea	19 (5.19)	1 (5.56)	12 (5.69)	3 (5)	3 (3.9)	0.945
Myalgia	18 (4.92)	4 (22.22)	10 (4.74)	1 (1.67)	3 (3.9)	**0.004**
Colds	15 (4.1)	0	7 (3.32)	6 (10)	2 (2.6)	0.077
Anosmia	9 (2.46)	0	6 (2.84)	0	3 (3.90)	0.430
Fatigue	10 (2.73)	7 (38.89)	3 (1.42)	0	0	**<0.001**

In general, most patients with confirmed COVID-19 cases were non-cigarette smokers. It was noted that mild cases of COVID-19 were mostly non-smokers (83.33%). In contrast, most of the severe and critical patients were previous and active smokers. Only seven percent (n=27) of the included population were health care workers wherein six was classified as mild and 19 was classified as moderate cases. Only two health care worker patients were classified under severe and critical COVID-19 cases.

Co-morbid conditions were also present in 37.7% (n=138) of the over-all 366 COVID-19 confirmed cases were noted to have one co-morbid condition while 42.08% (n=154) cases had more than one co-morbid condition. Most of the severe and critical cases have at least 1 co-morbid condition while the majority of moderate cases have two or more co-morbid conditions. Conversely, most mild cases have no co-morbid condition. In this study, hypertension (53.83%), DM (35.25%) and BA (9.29%) were the top 3 self-reported co-morbid conditions with hypertension predominating in all severity classification.

Table 2. Physical examination findings of COVID-19 patients according to disease severity

	Total (n=366)	Disease severity				p-value (<0.05)
		Mild (n=18, 5%)	Moderate (n=211, 58%)	Severe (n=60, 16%)	Critical (n=77, 21%)	
	Median (IQR)					
SBP	130 (120 to 140)	121 (120 to 137)	130 (120 to 140)	129 (120 to 137)	140 (120 to 158)	**0.007**
DBP	80 (70 to 88)	80 (78 to 85)	80 (70 to 88)	78 (68.5 to 84.5)	80 (70 to 90)	0.447
Pulse rate	98 (87 to 110)	95 (84 to 110)	95 (86 to 105)	99 (84.5 to 110)	109 (98 to 119)	**<0.001**
Respiratory rate	24 (21 to 28)	20 (20 to 22)	22 (21 to 25)	25 (23 to 28)	30 (26 to 35)	**<0.001**
Temperature	36.5 (36.1 to 37)	36.3 (36 to 37)	36.5 (36.3 to 37)	36.5 (36 to 36.7)	36.7 (36 to 37)	0.099
O_2 Saturation	94 (87 to 97)	98 (97 to 99)	95 (92 to 97)	89 (83 to 94)	80 (60 to 89)	**<0.001**
ABG on admission						
O_2 support	29 (21 to 53)	21 (21 to 21)	21 (21 to 32)	47 (32 to 72)	100 (52 to 100)	**<0.001**
pH	7.46 (7.4 to 7.49)	7.44 (7.42 to 7.5)	7.46 (7.44 to 7.5)	7.46 (7.43 to 7.5)	7.4 (7.3 to 7.46)	**<0.001**
pCO_2	34.7 (31 to 39.6)	37.6 (32 to 43.6)	34.3 (31 to 38.8)	32 (28.5 to 37.7)	35.9 (31.7 to 46)	**0.008**
HCO_3	23.9 (22 to 26.3)	23.85 (23 to 29)	24.5 (22.5 to 27)	23.6 (20.3 to 26)	22.3 (18.6 to 25)	**<0.001**
pO_2	74.3 (62.4 to 92)	94.85 (86 to 98)	73.2 (64 to 88.9)	67 (56 to 83.6)	75 (56.3 to 102)	**<0.001**
PF ratio	251 (140 to 336)	452 (408 to 465)	303 (244 to 363)	165 (88 to 216)	107 (88 to 160)	**<0.001**

Remarkably, there was a significant increase in the number of hypertensive patients among severe (70%) and critical cases (62.34%). Diabetes, the second leading co-morbid condition, was reported in 40.28% of moderate, 25% of severe and 33.77% critical cases. Interestingly, 80 (21.86%) cases had respiratory conditions which includes PTB, BA, COPD and bronchiectasis. Of the 38 patients who self-reported PTB, 13 were active and 25 cases had previous PTB.

The median time from symptom onset to hospital admission for mild cases of COVID-19 was shorter [2 days (IQR 0-4 days)] in comparison to moderate, severe and critical cases with mean length of 7 days. The most prominent symptoms reported were non-productive cough (64%), dyspnea (72%) and fever (67%). These three symptoms were prevalent among patients with moderate to critical cases ($p \leq 0.001$) while it was less likely reported among patients with mild COVID-19. Notably, dyspnea was present in more than 90% of patients who were classified under severe and critical cases. In contrary, mild COVID-19 patients were mostly asymptomatic. Other symptoms reported which included body weakness, sore throat, diarrhea and myalgia, anosmia, anorexia, dysgeusia and headache.

Table 2 shows the initial physical examination findings of COVID-19 patients admitted in the LCP. The median SBP measurement was significantly different among the–severity classification with p value of 0.007. The median SBP in critical COVID-19 patients was elevated at 140mmHg as compared to mild, moderate, severe cases with median SBP values of 129mmHg, 130mmhHg, 121mmHg respectively.

The median pulse rate was also significantly higher in critical patients, with a median value of 109 as compared to mild, moderate, severe cases with pulse rate median values of less than 100 per minute.

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

Lowest oxygen saturation was seen in critical patients with a median value of 80% as compared to mild with 98%, moderate with 95%, and severe with 89% oxygen saturation respectively. Higher oxygen supports were given to critical and severe cases with median values of 100% and 47% as compared to moderate and mild cases wherein most of them were stable at room air (FiO_2 21%).

All of the patients enrolled in the study with the exception of the mild cases had a respiratory alkalosis with mild to moderate hypoxemia on ABG, with median values of pH 7.4 for critical and 7.46 for both severe and moderate cases. Noted decreased in the pCO_2 (<36) median values for critical, severe, and moderate cases. The PF ratio was also seen significantly lowest among critical and severe patients with median value of 107 and 165.

Table 3. Association with disease severity in COVID-19 patients admitted at LCP

Parameters	Univariate			Multivariate		
	Crude OR	95% CI	p-value	Adjusted OR	95% CI	p-value
Age	1.0364	1.02 to 1.05	**<0.001**	-	-	-
19 to 39 years old	(reference)	-	-	(reference)	-	-
40 to 59 years old	3.4427	1.44 to 8.21	**0.005**	7.7895	1.28 to 47.2	**0.026**
≥60 years old	5.1083	2.18 to 12	**<0.001**	8.1663	1.4 to 47.6	**0.020**
Healthcare worker	0.1209	0.03 to 0.52	**0.004**			
Smoking Status						
Smoker (current/previous)	1.9434	1.2172 to 3.1030	**0.005**	-	-	-
Non smoker	(reference)		-	-	-	-
Number of co-morbidity						
Two	1.8105	0.96 to 3.42	0.067	-	-	-
One	3.0735	1.63 to 5.81	0.001	-	-	-
None	(reference)	-	-	-	-	-
Hypertensive	2.1833	1.41 to 3.38	**<0.001**	-	-	-
Pulmonary tuberculosis						
None	(reference)	-	-	-	-	-
Active	0.3279	0.07 to 1.150	0.151	-	-	-
Previous	4.6374	1.88 to 11.4	**0.001**	-	-	-
Clinical Signs and Symptoms (on admission)						
Cough						
No cough	(reference)	-	-	-	-	-
Non productive	2.4888	1.33 to 4.65	**0.004**	-	-	-
Productive	3.6733	1.71 to 7.89	**0.001**	-	-	-
Dyspnea	8.2230	4.10 to 16.5	**<0.001**	4.1606	1.60 to 10.8	**0.003**
Sore throat	0.2957	0.11 to 0.79	**0.015**	-	-	-
Diarrhea	0.1847	0.04 to 0.81	**0.025**	-	-	-
Physical exam during admission						
SBP ≥131	1.2536	0.82 to 1.92	**0.301**	-	-	-
Pulse rate ≥101 bpm	2.7241	1.76 to 4.21	**<0.001**	-	-	-
Respiratory rate ≥25 cpm	7.1558	4.46 to 11.5	**<0.001**	1.1747	1.08 to 1.28	**<0.001**
O_2 Saturation ≤93%	6.7347	4.17 to 10.9	**<0.001**	0.9361	0.90 to 0.97	**0.001**
ABG on admission						
O_2 support ≥37%	23.246	13.3 to 40.6	**<0.001**	1.0285	1.01 to 1.05	**0.010**
pH ≤7.453	2.0283	1.32 to 3.12	**0.001**	-	-	-
HCO_3 ≤23.8	1.9683	1.28 to 3.03	**0.002**	-	-	-
PF ratio ≤215.3	24.305	13.8 to 42.7	**<0.001**	0.9938	0.98 to 0.998	**0.010**

The proponents of this study obtained the highest sensitivity and specificity possible for each significant variable including pulse rate, respiratory rate, O_2 saturations, pH, bicarbonate and PF ratio and used it as the significant cut off value to associate with the disease severity of COVID-19.

Using the univariate analysis, results showed that among the socio-demographic variables of the patients with COVID-19, older age, healthcare workers and smokers were significantly associated with the disease severity of COVID-19. It was noted in Table 3 that for every year increase in age, the odds of having severe or critical COVID-19 disease also increased by 3.64%. The patients under 40 to 59 years old have 3-fold risk of having severe or critical COVID-19 disease compared to 19 to 39 years old patients. Sixty years and older patients were five times more likely to have severe or critical COVID-19 disease compared to 19 to 39 years old patients. Smokers were 94.34% more likely to have severe or critical COVID-19 disease compared to non-smoker patients.

Univariate analysis noted that only hypertension and previous history of PTB were noted to have increased risk of having severe or critical COVID-19. Hypertensive patients were twice more likely to have severe or critical COVID-19 disease. While the patients with previous PTB were four times more likely to have severe or critical COVID-19 disease compared to patients without PTB. Compared to patients without co-morbidity, patients with a single co-morbidity were three times more likely to have severe or critical COVID-19 disease.

Among the symptoms self-reported by the patients, cough and dyspnea were noted to be significantly associated with severe to critical COVID-19. Specifically, the patients with non-productive cough were twice more likely to have severe or critical COVID-19 disease compared to patients without cough. Those with productive cough were three to four times more likely to have severe or critical COVID-19 disease compared to patients without cough. Dyspneic patients were 8 times more likely to have severe or critical disease. In contrast, those with sore throat and diarrhea were 70.43% and 81.53% respectively less likely to have severe or critical COVID-19 disease.

Physical examination findings that were identified as high risk for developing severe to critical COVID-19 were increases in systolic blood pressure, pulse rate and respiratory rate. The patients with SBP of greater than or equal to 131mmHg had 25.36% increased risk of having severe or critical COVID-19. The odds of having severe or critical COVID-19 were also increased by 2 to 3 folds for pulse rate greater than or equal to 101bpm. The patients with respiratory rate more than or equal to 25cpm, had higher odds of having severe or critical COVID-19 disease by 7 folds. It was also noted that there was a six times increased risk of having severe or critical COVID-19 for O_2 saturations below or equal to 93%. Oxygen saturations of less than or equal to 93% also showed 6 times risk of having severe or critical disease.

Notably, the patients with O_2 support of ≥37% were 23 times more likely to have severe to critical COVID-19 disease. It was noted in the ABG that having a pH of ≤7.453 were 2 times more likely to have severe to critical COVID-19 disease while a HCO_3 of less than or equal to 23.8 were 96.83% more likely to have severe to critical COVID-19 disease. A PF ratio of less than or equal to 215.3 was also significantly associated with disease severity with 24 times more likely to have severe to critical COVID-19 disease.

Although multivariate analysis showed that only older age, those presenting with dyspnea, tachypnea with lower O_2 saturations, higher O_2 support and lower PF ratio were significantly associated with severe to critical COVID-19. Those aged 40 to 59 years old were 7 to 8 times more likely to have severe or critical COVID-19 disease compared to those aged 19 to 39 years old after adjusting for dyspnea, respiratory rate, O_2 saturation, O_2 support and PF ratio. The patients ≥60 years old had an 8-fold increased risk of having severe or critical COVID-19 disease compared to those 19 to 39 years old after adjusting for dyspnea, respiratory rate, O_2 saturation, O_2 support and PF ratio.

Dyspneic patients had fourfold likelihood of having severe or critical COVID-19 disease after adjusting for age, respiratory rate, O_2 saturation, O_2 support and PF ratio. For every 1cpm increase in respiratory rate above 25cpm, the odds of having severe or critical COVID-19 disease also increased by 17.47% after adjusting for dyspnea, age, O_2 saturation, O_2 support and PF ratio. For every percent increase in O_2 saturation more than 93%, the odds of having severe or critical COVID-19 disease decreased by 6.39% after adjusting for dyspnea, respiratory rate, age, O_2 support and PF ratio. There was also an increased risk by 2.85% for every percent increase in O_2 support more than 37% FiO_2 after adjusting for dyspnea, respiratory rate, O_2 saturation, age, and PF ratio. Lastly, for every unit increase in PF ratio more than 215.3, the odds of having severe or critical COVID-19 disease decreased by 0.62% after adjusting for dyspnea, respiratory rate, O_2 saturation, O_2 support and age.

DISCUSSION

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

Majority of the patients were males (n=233, 63.44%) and the median age was 58.5 years (IQR=54-70) which was similar in the profile of patients in the previous literatures.[4,5,8,9,11] The US Centers for Disease Control (US CDC) identified that advanced age was shown to be associated with disease severity of COVID-19.[38] In many studies, advanced age was a

major independent predictor of severity and mortality for COVID-19.[4,5,8,9,10,39] Similarly, the result of our study using the multivariate analysis showed that advanced age was significantly associated with severe and critical COVID-19 with 7-fold increase (CI=1.28-47.2, p=0.026) for age 40 to 59 years old and 8 fold increase (CI=1.4 to 47.6, p=0.020) for 60 years old and older of having severe to critical COVID-19. This may be due to increasing medical conditions associated with advanced age, and factors like the differences in the immune system, glycation, epigenome, inflammasome activity, and biological age. The ability to control viral load was one of the best prognostic factor of whether a patient developed mild or severe COVID-19 symptoms. For the immune system to effectively suppress then eliminate SARS-CoV-2, it must perform four main tasks like to recognize, be alert, destroy and clear the pathogen. Each of these mechanisms were known to be dysfunctional and increasingly heterogeneous in older people. During aging, there was a gradual decline in immune function called immunosenescence, which hampers pathogen recognition, alert signaling and clearance. Other immune system change during aging was chronic increased in systemic inflammation termed inflammaging, which arose from an overactive, yet ineffective alert system.[40]

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

Only seven percent (n=27) of the included population were health care. Among the healthcare workers, only 2 were classified as severe and critical COVID cases. Univariate analysis noted that smoking has 87% less likely to have severe or critical COVID-19. This low percentage of healthcare workers infected with COVID-19 may be due to the better knowledge of healthcare workers in responding to the threat of COVID-19 disease as demonstrated by the study of Limbu D et al. on knowledge, attitude and practices of healthcare workers in which 81.5% answered correctly the knowledge questionnaire.[41]

The patients who were reported with one co-morbid condition in this study was shown to have increased chance of having severe or critical COVID-19, while patients who were reported with more than one co-morbid condition did not show significant additional risk for disease severity. Similarly in a nationwide analysis on the impact of co-morbid condition in the outcome of COVID-19 patients done in China involving 1,590 subjects, their result showed that those who presented with one co-morbid condition had increased risk for ICU admission, invasive ventilation, and death. However, their findings also reported an increase in risk for poor clinical outcome among patients who have 2 or more co-morbid conditions which was not reflected in our study.[18] This may be explained by the increased number of patients who self-reported with only one co-morbid condition during admission among those with severe and critical cases.

The presence of co-morbid conditions had been identified as one of the predictors of poor outcome, severity, and mortality for COVID-19. Similar in other reports, hypertension and DM were also identified in this study as the most common co-morbid conditions among patients with COVID-19.[4,5,8,10,18,39] The strength of association between the different co-morbidities and disease severity, however, was less consistent when compared with the literature reports. For instance, co-morbid conditions including DM and COPD that were identified as strong predictors for severity in other studies.[4,5,10,18,38,39] These, however, were not reflected in this study. Only hypertension and previous history of PTB were shown to have increased odds of having severe or critical COVID-19. Hypertensive patients were two times ($p \leq 0.001$) more likely to have severe or critical disease. This was congruent with other studies showing hypertension as the most common co-morbidity seen in COVID-19.[4,5,10,17,18] However multivariate analysis revealed that it was not an independent predictor for disease severity. This was because the majority of the population

in each disease severity had hypertension as the predominating co-morbid condition.

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

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

The most common symptoms self-reported by the patients with confirmed COVID-19 were non-productive cough, dyspnea and fever. These three symptoms were commonly presented by patients with moderate to critical cases as compared to mild cases which was congruent with the reports in other literatures.[4,9,10,17,42] Among these three prominent symptoms, dyspnea was reported by more than 90% of patients classified under the severe and critical category. Those reporting dyspnea as an initial symptom were significantly associated with a higher odds (OR=4, CI=1.6-10.8, p=0.003) of having severe and critical cases as compared to those who did not. This was similarly reported by Jiang Xie et al. and Lang Wang et al. in their study in which dyspnea was identified as an independent predictor for mortality in patients with COVID-19.[9,42] Extensive inflammation of the bilateral and respiratory bronchioles in patients with COVID-19 due to excessive activation of proinflammatory cytokines and chemotactic aggregation of T-lymphocytes at the site of inflammation were possible mechanisms which underlay chest distress and dyspnea in patients with COVID-19. Continuous and unresolved dyspnea often indicates the progression of lung lesions.[43]

On adjusted logistic regression analysis, the physical examination that had higher odds of having a severe or critical COVID-19 were increased SBP, pulse rate, respiratory rate, O_2 support requirement and decreased O_2 saturations. In one study done in London, among the physical examination findings, body temperature of more than 38°C has the strongest association with increased mortality among COVID-19 patients while pulse rate, respiratory rate and BP did not show association with disease severity.[44] As reported in other studies, fever was one of the common presentations of COVID-19.[4,5,8,9,10,44] However, most of the patients in our study were afebrile during admission and our results did not show the association with disease severity as compared to what were seen from other studies.

All moderate to critical patients enrolled in the study had respiratory alkalosis with mild to moderate hypoxemia on ABG however it did not show significant association. Oxygen saturations of ≥94% among COVID-19 patients notably decreased the odds of having severe or critical COVID-19 after adjusting for dyspnea, respiratory rate, age, O_2 support and PF ratio. The result of our study was somehow similar with the study by Xie Jiang et al. which demonstrated that higher SpO_2 levels after O_2 supplementation were associated with reduced mortality independently of

age and sex (hazard ratio per 1 unit SpO_2, 0.93; 95% CI, 0.91 to 0.95; p≤0.001).[42] Hence it was prudent to maintain higher oxygenation saturations or more than 93% among COVID-19 patients. It was also noted that an increased PF ratio had decreased the odds of having severe or critical COVID-19 disease while a decreased PF ratio of less than 215 was associated with increased risk of severe to critical COVID-19. This was supported by other study which showed a low PaO_2/FiO_2 ratio ≤200 mm Hg as one of the independent risk factors for mortality (HR 3.57; 95% CI 2.20 to 5.77, p<0.0001) and the in-hospital mortality proportionally increased with increasing impairment of gas exchange (p<0.001).[42]

Microvascular thrombosis was well documented to occur in COVID-19 due to hypercoagulable state resulting from the underlying inflammatory process. The implication of this process in the context of the lung represents dead space with reduced or absent pulmonary capillary flow without affecting ventilation leading to a high V/Q ratio. The overt inflammatory process occurring in COVID-19 may be presumed to cause capillary hyperperfusion due to inducible nitric oxide synthase production, released of nitric oxide, and local vasodilation.

In early stages, inflammation was expected to occur in a nonuniform manner in the lungs, leading to uneven distribution of capillary perfusion. This process led to some alveolocapillary units with low V/Q ratios referred to as type A units, and other units in which this pathology was not occurring in the early stages was referred to as type B units. Hyperperfusion of the type A units led to a circulatory steal of flow from type B units, which reduced their perfusion, while ventilation remains unchanged which increased the V/Q. This differing V/Q ratios in the same lung led to mismatched and hypoxemia. Other mechanism was precapillary shunts, and this caused hypoxemia by leading to a decreased or absent capillary perfusion, without compromising ventilation and having a high V/Q ratio. Blood flow through this anastomosis was also inversely proportional to the FiO_2 which leads to further requirement of higher FiO_2 to improve O_2 saturation. These mechanisms may lead to hypoxemia, low PF ratios, and a high A-a gradient as seen in COVID-19. Hypoxemia led to increased respiratory drive through the stimulation of peripheral and central chemoreceptors thus increased the respiratory rate. Increased respiratory rate was a sign of hypoxemia. Therefore, it is important to maintain a higher PF ratio among COVID-19 patients, while a decreasing PF ratio should alert clinicians to be aggressive with the management to avoid fatal outcomes.[45]

CONCLUSION

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

Limitations

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

Recommendations

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

Authorship

All authors have certified fulfillment of Scientific Proceedings authorship criteria.

Disclosure of Conflicts of Interest

All authors have no conflict of interest to disclose.

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Association of Hematologic and Biochemical Markers with Disease Severity, Progression, and Recovery in COVID-19 Cases at Lung Center of the Philippines

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ABSTRACT

Background. SARS-CoV-2 infections have led to significant morbidity and mortality worldwide. Certain laboratory parameters were taken from these patients and were found to be useful for baseline assessment and disease monitoring during the hospital stay.

Objective. This study aimed to determine the association of hematologic and biochemical markers with disease severity, progression and mortality.

Methodology. This is a retrospective cohort study using chart review of COVID-confirmed patients admitted to the Lung Center of the Philippines (LCP) from March to June 2020. Demographics and severity of disease were recorded at the emergency room. The hematologic markers analyzed include the baseline and values during progression. For the biochemical markers, only the baseline values were analyzed.

Results. Among 185 patients, the highest mortality (72%) was seen among the critically-ill. Increasing levels of baseline white blood cell count, neutrophils, and neutrophil-lymphocyte ratio showed a moderate positive correlation with increased level of disease severity on admission. A strong positive relationship with disease severity was calculated for baseline LDH and procalcitonin. While a moderate positive correlation with disease severity was noted for baseline ferritin, alanine transaminase (ALT), and C-Reactive Protein (CRP). Elevated CRP, Leukocyte dehydrogenase (LDH), ferritin, and procalcitonin were associated with higher odds of disease progression. The odds of in-hospital mortality were higher for patients with elevated LDH, CRP and elevated procalcitonin of more than 10 ng/ml.

Conclusions. Hematologic (elevated leukocyte, neutrophil and NLR with lymphopenia) and biochemical (elevated CRP, LDH, ferritin and procalcitonin) findings are correlated with COVID-19 severity and disease progression. These laboratory markers, when taken together with other associated factors of COVID-19 severity and prognosis, may be used to establish a reproducible COVID-19 severity scoring.

Keywords: COVID-19, SARS-CoV-2, hematologic tests, biochemical markers, mortality

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INTRODUCTION

The 2019 novel coronavirus disease (COVID-19), an outbreak that originated in Wuhan, China last December 2019,[1] was declared a pandemic by the World Health Organization (WHO) last March 28, 2020.[2] COVID-19 is identified as a novel single-stranded ribonucleic acid (RNA) beta coronavirus with 70% similarity in genetic sequence to SARS-CoV, thus it was also named as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[3,4] The rapid progression of the disease has led to complications including critical pneumonia, acute respiratory distress syndrome (ARDS), multiple organ failure, arrhythmia, septic shock, acute cardiac injury, acute kidney injury, and even death.[1,3,5,6] According to the WHO,[7] confirmed cases around the world have already reached 5,103,006, among which 333,401 have died from the disease as of May 24, 2020. In the Philippines, a total of 13,597 confirmed cases have been recorded with 857 confirmed deaths.[8] These numbers are still increasing rapidly, thus it is imperative to detect and monitor COVID-19 severity to minimize such complications. The use of real-time reverse transcription-polymerase chain reaction (rRT-PCR) assay is the test currently used to confirm COVID-19 infection and detect the virus. Nasal or pharyngeal samples, sputum, broncho-alveolar lavage fluid, and other bodily fluids, including feces and blood may be extracted from patients to detect SARS-CoV-2.[9] Diagnostic laboratory tests are taken at various frequencies to help monitor and guide management of COVID-19 patients.

Multiple infection and inflammatory markers have been reported to be associated COVID-19 progression, severity, and outcome, with the aim of using such markers as a prognosis tool.[3] For instance, C-reactive protein (CRP)[10,11] and serum ferritin were shown to increase as severity of the disease increases[12] (Weighted mean difference [WMD] = -41.78 mg/l, 95% CI = [-52.43, 31.13]) and (WMD = -398.80 mg/l, 95% CI = [625.89, -171.71], respectively.[3] In another study, laboratory abnormalities on hematologic and biochemical markers among COVID-19 patients were analyzed to determine if such abnormalities can be used as severity markers for the disease. Although higher white blood cell (WBC) count (1.5-fold), higher neutrophil count (1.7-fold), lower lymphocyte count (0.9-fold) were recorded for COVID-19 patients in intensive care units (ICU).[13] Procalcitonin (PCT), WBC, and platelet count (PLT) were found to have no significant change based on the severity of the disease.[12] Creatinine was also observed to be elevated for patients as COVID-19 becomes more severe.[13-15] Similarly, liver function tests recorded higher values of Lactate dehydrogenase (LDH) (2.1-fold), alanine aminotransferase (ALT) (1.5-fold), aspartate aminotransferase (AST) (1.8-fold), total bilirubin (1.2-fold), and cardiac troponin I (2.2-fold) which may be due to liver cell infection.[13,16] Electrolytes recorded comparing different severity of COVID-19 shows that readings were significantly lower in patients with severe COVID-19 for sodium (WMD: –0.91mmol/L [95% CI: –1.33 to –0.50mmol/L]), potassium (WMD: –0.12mmol/L [95% CI: –0.18 to –0.07mmol/L]), and calcium (WMD: –0.20mmol/L [95% CI: –0.25 to –0.20mmol/L]), while chloride shows no statistical differences (WMD: 0.30mmol/L [95% CI: –0.41 to 1.01mmol/L]).[17] Initial laboratory findings therefore can be used by physicians for prognosticating patients on admission.

The aim of this study is to identify the laboratory abnormalities that are associated with disease severity and higher mortality rates among patients with COVID-19. Furthermore, early stratification of these patients at higher risk for deterioration based on the inflammatory markers will aid in identifying which patients will need closer monitoring or early admission to critical care units. The results of the study will also help in tailoring and improving clinical management of the said cases.

METHODOLOGY

Study design and site

This is a retrospective cohort study, done at the Lung Center of the Philippines (LCP), a 210-bed capacity specialty center for lung diseases. It was designated as one of the COVID-19 referral centers by the Department of Health and has allotted 81 beds to accommodate mild to critical cases. It is located in Quezon City, Metro Manila, which is currently the Philippines' epicenter of the COVID-19 pandemic.

Study Subjects

The study subjects included COVID-19 cases confirmed by either RT-PCR or SARS-CoV-2 GeneXpert and admitted at LCP from March 7 to June 30, 2020.

This included adult patients ages 18 years old and above, who have either recovered or died. Patients with missing data or information were excluded from the study.

Sampling Design

Convenience sampling of all closed cases within the study period (March 7 to May 31, 2020) was done.

Study Procedure

A retrospective patient chart review and electronic data extraction (via BizBox records) of included subjects was done. On admission, the demographic data including age, gender, co-morbidities, and laboratory findings were collected. The patient's condition upon their arrival at the emergency room was classified based on the COVID-19 disease severity set by the WHO.

The specified hematologic markers were recorded twice only, upon admission and upon disease progression. For the biochemical markers, only the markers taken on admission was recorded.

Hematologic markers taken at the emergency room were recorded and served as the baseline. In case of disease progression during the course of admission, the repeat hematologic markers taken at the time of progression was recorded. In case of mortalities, the last hematologic markers taken prior to death was used.

We obtained a master list of all laboratory-confirmed COVID-19 cases from the Hospital Epidemiologic Surveillance Unit (HESU). The list was submitted to the medical records section for chart retrieval of the admitted patients. The demographic, clinical, and laboratory data were extracted from paper and electronic medical records using a standardized data collection form. The laboratory tests recorded include the hematologic markers (WBC, differential count, neutrophil: lymphocyte ratio) and the biochemical markers (ALT, D-dimer, ferritin, CRP, LDH, procalcitonin). In order to describe the dynamic changes of the laboratory tests, the hematologic markers taken upon admission and upon disease progression were analyzed. For the biochemical markers, only the values taken upon admission was submitted for analysis.

Data Analysis

Descriptive statistics of counts and percentages was used for categorical variables (i.e., sex, disease severity, and recovery status), while the interquartile range and standard deviation were used for continuous data in showing the characteristics of patients with COVID-19 and its severity. One-way analysis of variance (ANOVA) was used for normally distributed continuous data while the Pearson's chi-square test and Fisher's exact test were used to compare proportions for categorical variables.

The correlation between hematological markers on baseline and during in-hospital disease progression were analyzed using the Spearman correlation analysis. Odds ratio and corresponding 95% confidence intervals from binary logistic regression was used in analyzing data for the biochemical markers and its correlation with disease progression, death or recovery. Statistical significance was based on 5% level. Data processing and statistical analysis was performed using SPSS v22.

Ethical Considerations

This study was approved by the LCP Technical Review Board and Institutional Ethics Review Board. Compliance with the ethical considerations on retrospective medical records review with the National Ethical Guidelines for Health and Health Related Research 2017 and Data Privacy Act 2012 was ensured.

RESULTS

A total of 205 COVID-19 patients were admitted from March – June 2020. Twenty-five (25) subjects were not included for final analysis due to incomplete demographic profiles and missing laboratory results.

Table 1 summarizes the demographic characteristics and recovery status of the admitted COVID-19 patients. Majority of the cases that were admitted were moderate cases (n=134, 74%). Most of the admissions were male (n=110, 61.1%) and were more than 60 years old (n=79, 43.9%). Fifty-one patients (28.3%) died while 129 of them recovered and were discharged. Among the severe and the critical COVID-19 cases, majority of them died (58.3% and 72.7% vs 41.7% and 27.3%, $p<0.001$). The proportion of mortality was highest among the critical cases (72.7%).

Table 1. Demographic characteristics and recovery status of admitted COVID-19 patients

	Total N=180	Mild n=12 (7%)	Moderate n=134 (74%)	Severe n=12 (7%)	Critical n=22 (12%)	P value
Age						
18-45 years old	39 (21.7%)	9 (75%)	27 (20.1%)	1 (8.3%)	2 (9.1%)	<0.001
46-60 years old	62 (34.4%)	2 (16.7%)	47 (35.1%)	6 (50%)	7 (31.8%)	
>60 years old	79 (43.9%)	1 (8.3%)	60 (44.8%)	5 (41.7%)	13 (59.1%)	
Sex						0.694
Male	110 (61.1%)	8 (66.7%)	79 (59%)	9 (75%)	14 (63.6%)	
Female	70 (38.9%)	4 (33.3%)	55 (41%)	3 (25%)	8 (36.4%)	
Smoking History						
Smoker	46 (25.6%)	3 (25%)	33 (24.6%)	4 (33.3%)	6 (27.3%)	0.803
Non-smoker	134 (74.4%)	9 (75%)	101 (75.4%)	8 (66.7%)	16 (72.7%)	
Day of Illness	7.77 (±5.56)	1.33 (±2.23)	8.28 (±5.61)	7.92 (±3.99)	8.09 (±5.32)	<0.001
Disposition						
Expired	51 (28.3%)	1 (8.3%)	27 (20.1%)	7 (58.3%)	16 (72.7%)	<0.001
Recovered	129 (71.7%)	11 (91.7%)	107 (79.9%)	5 (41.7%)	6 (27.3%)	

Table 2. Hematologic markers on admission according to disease severity

	Overall Mean (SD) N=180	Mild n=12	Moderate n=134	Severe n=12	Critical n=22	r**	P value
WBC Mean (SD)	8.49 (4.26)	7.93 (2.07)	7.62 (3.54)	9.94 (4.68)	13.35 (5.55)	0.300	<0.001
Absolute Neutrophil Count (ANC)	6662.3 (4081.8)	5155.0 (2033.0)	5810.0 (3279)	8626.1 (4213.3)	11700.1 (5359.3)	0.471	<0.001
Absolute Lymphocyte Count (ALC)	1457.1 (786.9)	1866.4 (1082.4)	1487.9 (772.4)	1046.2 (452.4)	1265.9 (723.4)	-0.206	0.005
Neutrophil-to-lymphocyte ratio (NLR)	7.26 (9.93)	7.19 (14.87)	6.09 (8.78)	8.74 (5.25)	13.6 (13.0)	0.360	<0.001
Platelets	278.7 (108.8)	272.1 (129.4)	271.6 (104.7)	262.9 (77.3)	333.7 (126.1)	0.154	0.039

*Units of measurement used: WBC (g/L), ANC and ALC (cells/mm^3), Platelets (10^9/L)
**Spearman rho interpretation: ≥0.7 (very strong relationship), 0.4-0.69 (strong relationship), 0.3-0.39 (moderate relationship), 0.2-0.29 (weak relationship), 0.01-0.19 (no or negligible relationship).
Adapted from: Dancey C, Reidy J. 2004. Statistics without maths for psychology: using SPSS for windows. London, England: Prentice-Hall

The mean duration from symptom onset to admission was 7.77 + 5.5 days. Those with shorter time from symptom onset presented as mild cases (1.33 + 2.23 days), whereas those who came in with more than 7 days of symptoms presented as moderate cases to critically ill (8.28 + 5.61, 7.92 + 3.9, 8.09 + 5.3, respectively).

Increasing levels of baseline WBC (r=0.300, p<0.001), Absolute Neutrophil Count (ANC) (r=0.309, p<0.001), and Neutrophils-Lymphocytes ratio (r=0.360, p<0.001) showed moderate positive correlation with increased level of disease severity on admission (Table 2). The Absolute Lymphocyte Count (ALC) (r=-0.206, p=0.005) however showed a weak negative correlation, with a decreasing mean lymphocyte count trend as COVID-19 severity increases.

The mean values of WBC, ANC, ALC, platelets and NLR showed a mean positive increase of 50.06%, 62.3%, 2.09%, 1.22% and 56.47%, respectively. The mean baseline and progression values of all hematologic markers show a significant strong positive relationship (r>6.0, p<0.001) (Table 3). The strongest correlations were noted for NLR (r=0.745), followed by ANC (r=0.714).

Most baseline biochemical markers showed a significant positive correlation with disease severity on admission, except for D-dimer (Table 4). A strong positive relationship was calculated for LDH (r=0.410, p<0.001) and procalcitonin (r=0.448, p<0.001). While a moderate positive correlation with disease severity was noted for ferritin (r=0.316, p=0.001), ALT (r=0.225, p=0.002), and CRP (r=0.277, p=0.009).

The odds of in-hospital mortality were higher for patients with elevated LDH (OR: 2.9, p=0.04) with the highest noted for those with levels more than twice the normal (OR: 5.8, 95%CI:1.7-18.8) (Table 5). Other biochemical markers associated with higher mortality are elevated CRP (OR:16.7, p=0.05) as well

Table 3. Hematologic markers during disease progression

	Baseline Mean (SD)	Progression Mean (SD)	% Change	r**	P value
WBC	8.49 (4.26)	12.74 (13.52)	50.06%	0.672	<0.001
ANC	6,662.3 (4081.8)	10,810.7 (12350.6)	62.3%	0.714	<0.001
ALC	1,457.1 (786.9)	1,487.5 (1070.2)	2.09%	0.485	<0.001
Platelets	278.7 (108.8)	282.10 (114.49)	1.22%	0.662	<0.001
NLR	7.26 (9.93)	11.36 (14.69)	56.47%	0.745	<0.001

*Units of measurement used: WBC (g/L), ANC and ALC (cells/mm^3), Platelets (10^9/L)
**Spearman rho interpretation: ≥0.7 (very strong relationship), 0.4-0.69 (strong relationship), 0.3-0.39 (moderate relationship), 0.2-0.29 (weak relationship), 0.01-0.19 (no or negligible relationship).
Adapted from: Dancey C, Reidy J. 2004. Statistics without maths for psychology: using SPSS for windows. London, England: Prentice-Hall

Table 4. Biochemical markers on admission according to disease severity

	Overall Mean	Mild	Moderate	Severe	Critical	r	P value
ALT	62.82 (49.21)	49.83 (27.27)	55.95 (43.28)	103.08 (55.28)	89.45 (68.57)	0.225*	0.002
CRP	75.12 (67.59)	38.4 (43.86)	66.66 (68.39)	93.25 (59.78)	127.15 (49.25)	0.277*	0.009
D-DIMER	356.9 (440.83)	199.2 (0.45)	290.6 (164.41)	649.75 (640.55)	563.18 (898.28)	0.241	0.064
Ferritin	837 (590.51)	336.92 (161.71)	794.07 (466.85)	1897.74 (1334.8)	901.18 (342.92)	0.316*	0.001
LDH	343.54 (167.36)	209.5 (45.65)	323.68 (164.44)	463.1 (160.78)	449.1 (141.31)	0.410*	<0.001
Procalcitonin	3.74 (17.99)	0.08 (0.06)	2.78 (15.23)	0.65 (0.64)	12.83 (34.27)	0.479*	<0.001

Table 5. Baseline biochemical markers according to recovery status

	Total (N)	Recovery status		Odds Ratio (95% CI)	P value
		Expired	Recovered		
LDH (Total)	139	40	99		
Normal	34	5	29	1 (ref)	
Elevated (Total)	105	35	70	2.9 (1.033 – 8.141)	0.043
Less than 1.5x	51	9	42	1.243 (0.377 – 4.090)	0.721
1.5-2x	22	10	12	4.833 (1.361 – 17.158)	0.015
More than 2x	32	16	16	5.8 (1.791 – 18.784)	0.003
CRP (Total)	88	27	61		
Normal	14	0	14	1 (ref)	
Elevated (Total)	74	27	47	16.789 (0.963 – 292.61)	0.053
Less than 1.5x	4	2	2	29 (1.048 – 802.031)	0.047
1.5-2x	4	0	4	3.222 (0.056 – 186.839)	0.572
More than 2x	66	25	41	17.819 (1.018 – 311.792)	0.049
Ferritin (Total)	104	26	78		
Normal	23	4	19	1 (ref)	
Elevated (Total)	81	22	59	1.771 (0.542 – 5.788)	0.344
Less than 1.5x	11	1	10	0.475 (0.046 – 4.839)	0.529
1.5-2x	13	4	9	2.111 (0.427 – 10.423)	0.359
More than 2x	57	17	40	2.018 (0.597 – 6.827)	0.258
ALT (Total)	179	51	128		
Normal	135	37	98	1 (ref)	
Elevated (Total)	44	14	30	1.236 (0.591 – 2.587)	0.574
Less than 1.5x	25	3	22	0.361 (0.102 – 1.279)	0.114
1.5-2x	8	4	4	2.649 (0.629 – 11.141)	0.184
More than 2x	11	7	4	4.635 (1.281 – 16.761)	0.019
Procalcitonin (Total)	112	29	83		
Normal	64	9	55	1 (ref)	
Elevated (Total)	48	20	28	4.365 (1.759 – 10.832)	0.001
0.5 – 0.2 ng/ml	6	2	4	3.056 (0.486 – 19.199)	0.234
0.2 – 10 ng/ml	9	1	8	0.764 (0.085 – 6.860)	0.810
>10 ng/ml	33	17	16	6.493 (2.434 – 17.321)	0.0002
D-DIMER (Total)	60	18	42		
Normal	36	10	26	1 (ref)	
Elevated (Total)	24	8	16	1.30 (0.425 – 3.980)	0.646
Less than 1.5x	6	0	6	0.194 (0.01 – 3.761)	0.278
1.5-2x	9	5	4	3.25 (0.722 – 14.617)	0.124
More than 2x	9	3	6	1.3 (0.271 – 6.224)	0.740

as an elevated procalcitonin of more than 10 ng/ml (OR: 6.4, p=0.002).

Univariate analysis shows that the odds of in-hospital disease progression was higher among patients with more than twice the normal elevation of CRP (OR: 3.843, p=0.027), LDH (OR: 7.0, p=0.002), and ferritin (OR: 2.44, p=0.046). An elevated procalcitonin is also associated with higher odds of disease progression (OR: 2.16, p=0.073) (Table 6). Among the hematologic markers, univariate analysis shows that the odds of COVID-19 in-hospital progression was higher among those with elevated WBC (OR: 3.385, p=0.019), Neutrophil (OR: 4.712, p=0.001) and the NLR (OR: 3.0, p=0.001) when compared to normal. A lower odds of disease progression was noted among those with elevated lymphocyte count (OR: 0.05, p=0.005) when compared to normal.

DISCUSSION

In this retrospective observational study, the clinical characteristics, hematologic and biochemical markers of a cohort of 185 COVID-confirmed admitted patients were analyzed. Majority of the admissions recovered (71.7%), while 28.3% of them eventually died. The proportion of mortality was highest among the severe and critically ill (58.3% and 72.7% respectively). The occurrence of ARDS with COVID-19 has already been associated with significant mortality in a previous study reporting a 50% 28-day survival among those with severe disease.[18]

Hematologic Markers

In our study, the increasing levels of leukocytes, ANC, ALC and NLR has been noted to have a positive correlation with increasing severity of COVID-19

Table 6. Baseline biochemical markers according to disease progression

	Total (N)	Disease progression		Odds Ratio (95% CI)	P value
		With	Without		
LDH (Total)	139	94	45		
Normal	34	17	17	1 (ref)	
Elevated (Total)	105	77	28	2.75 (1.24 – 6.11)	0.013
Less than 1.5x	51	32	19	1.684 (0.699 – 4.06)	0.246
1.5-2x	22	17	5	3.4 (1.021 – 11.318)	0.046
More than 2x	32	28	4	7.0 (2.026 – 24.306)	0.002
CRP (Total)	88	59	29		
Normal	14	6	8	1 (ref)	
Elevated (Total)	74	53	21	3.36 (1.04 – 10.87)	0.043
Less than 1.5x	4	3	1	4.0 (0.329 – 48.6579)	0.277
1.5-2x	4	1	3	0.444 (0.036 – 5.406)	0.525
More than 2x	66	49	17	3.843 (1.164 – 12.679)	0.0271
Ferritin (Total)	104	71	33		
Normal	23	13	10	1 (ref)	
Elevated (Total)	81	58	23	1.94 (0.75 – 5.04)	0.174
Less than 1.5x	11	4	7	0.439 (0.1001 – 1.930)	0.2762
1.5-2x	13	9	4	1.731 (0.411 – 7.288)	0.454
More than 2x	57	45	12	2.885 (1.178 – 8.175)	0.046
ALT (Total)	179	124	55		
Normal	135	92	43	1 (ref)	
Elevated (Total)	44	32	12	1.25 (0.59 – 2.65)	0.568
Less than 1.5x	25	17	8	0.993 (0.398 – 2.48)	0.988
1.5-2x	8	5	3	0.779 (0.178 – 3.410)	0.740
More than 2x	11	10	1	4.674 (0.579 – 37.687)	0.148
Procalcitonin (Total)	112	76	36		
Normal	64	39	25	1 (ref)	
Elevated (Total)	48	37	11	2.16 (0.93 – 4.99)	0.073
0.5 – 0.2 ng/ml	6	6	0	8.392 (0.453 – 155.492)	0.153
0.2 – 10 ng/ml	9	6	3	1.282 (0.293 – 5.598)	0.741
>10 ng/ml	33	25	8	2.003 (0.781 – 5.135)	0.148
D-DIMER (Total)	60	45	15		
Normal	36	25	11	1 (ref)	
Elevated (Total)	24	20	4	2.20 (0.61 – 7.97)	0.229
Less than 1.5x	6	3	3	0.440 (0.076 – 2.533)	0.358
1.5-2x	9	9	0	8.567 (0.458 – 160.125)	0.150
More than 2x	9	8	1	3.52 (0.914 – 31.658)	0.261

upon presentation at the emergency room. The levels of these same markers were also associated with increased odds of in-hospital progression when compared to normal. This trend has also been noted in a study which pooled the data of 1,099 COVID-19 patients and 552 hospitals in China.[19] This association between increased WBC and neutrophil count with disease severity highlights its role in the hyperinflammatory response associated with severe forms of COVID-19.

In pneumonia, when the alveolar macrophages are overwhelmed by an invading pathogen, cytokines and chemokines are released in order to draw neutrophils to the affected area.[20] This release of neutrophil-chemoattractive elements and its resulting attraction of neutrophils are a global host response to viral infection[21] and are involved in early antiviral defense.[22] However, through degranulation and lysis they can be cytotoxic in severe pneumonia.[23] This innate immune response however, appears dysregulated and excessive in severe forms of COVID-19 similar to previous findings seen in severe SARS-CoV and MERS-CoV infections.[24]

Lymphopenia has been observed to be associated with severe COVID-19.[25] Those who have died of COVID-19 were observed to have lower lymphocyte counts than survivors.[26] The decrease in lymphocyte count has been linked with elevated IL-6, increased NKG2A expression, increased cell surface expression of programmed cell death protein 1 (PD-1) and T cell immunoglobulin and mucin domain 3 (TIM-3). This has been found to cause functional exhaustion of NK, CD4+ and CD8+ T cells, which have important roles in antiviral immunity.[27,28] Moreover, those recovering from COVID-19 were noted to have decreased NKG2A expression and subsequent increase in NK and CD8+ T cells.[28]

The elevated neutrophils and decreased lymphocyte count, both independently associated with increased disease severity and progression, equates to an elevated neutrophil-to-lymphocyte ratio (NLR). And thus, higher levels of NLR have been found to be associated with increased COVID-19 severity.[30,31] A systematic review and meta-analysis of 13 studies involving 1,579 patients showed that NLR has a good predictive value in COVID-19 disease severity, mortality and early identification of severe cases and progressors.[31] However, there has been no consensus yet regarding threshold in order to categorize disease severity and predict prognosis.

Biochemical Markers

In this study, the results showed that increased baseline levels of ALT, CRP, ferritin and LDH were associated with increased COVID-19 severity on admission. Those with twice the normal elevations of LDH, CRP and procalcitonin showed higher odds of disease progression and mortality when compared to normal.

Patients with severe forms of COVID-19 appear to have increased frequency of liver dysfunction than those with milder disease. This has been observed in studies involving severe COVID-19 and ICU patients.[19,32] Many possible mechanisms exist to explain liver injury in COVID-19, either singly or concurrently. These include direct viral infection of liver cells, drug hepatotoxicity, immune-mediated inflammation, and pneumonia-associated hypoxia.[32]

CRP and LDH are reliable markers of inflammation. Although non-specific, levels of CRP and LDH has been found to be higher in severe COVID-19 infections than the non-severe group.[33] In a study by Poggiali et al., they found a strong inverse correlation between CRP and LDH with PaO_2/FiO_2 ratio, suggesting that the levels of CRP and LDH are related to lung damage and might reflect the respiratory distress associated with hyperinflammatory state.[34] In a small cohort study by Chaochao et al. correlating CRP with chest CT scan findings in COVID-19, observed that patients who later progressed to a more severe disease already had significantly elevated CRP levels even before CT scan changes became apparent.[35] Their study suggested that early elevated CRP might have a role in identifying patients at higher risk of disease progression.

Ferritin, which is normally an iron-storing protein, has been found to increase with COVID-19. Levels of ferritin has been observed in some studies to be directly correlated with COVID-19 disease severity.[36,37] A meta-analysis by Cheng et al. showed that higher levels of ferritin are linked to severe COVID-19 and ARDS.[38] This elevation in ferritin has been associated with cytokine storm. The rapid release of cytokines stimu-

lates the hepatocytes, Kupfer cells, and macrophages to secrete ferritin.[39] Ultimately, the dysregulated and uninhibited immune response, macrophage activation and hyperferritinemia leads to multiple organ damage.

Procalcitonin, normally secreted by the thyroid parafollicular C-cells, gets synthesized by extra-thyroid tissue in response to a bacterial infection. This increase in procalcitonin is mediated by higher levels of tumor necrosis factor-alpha (TNF-α) and interleukin 6 (IL-6).[40] Both TNF-α and IL-6 are among the cytokines released during the cytokine storm of COVID-19. Earlier studies have already reported a positive correlation between elevated procalcitonin and COVID-19 severity.[19,25] A meta-analysis by Lippi et al. showed that elevated procalcitonin is associated with up to 5-fold higher risk of severe COVID-19.[41] However, they suggested that serial measurements of procalcitonin, rather than a single elevated value, appears to be better in predicting COVID-19 progression.

In our study, the D-dimer did not appear to be significantly associated with disease severity or disease progression based on the available data. This non-uniformity in D-dimer data among the admitted patients during the study period has been limited by the unavailability of D-dimer testing at the start of the pandemic. However, a study in China has demonstrated that elevated D-dimer is associated with increased severity and mortality in COVID-19 with no confirmed DVT or pulmonary embolism.[42]

CONCLUSIONS

In the months since the pandemic began, it has become imperative to identify which among the patients are at higher risk for severe or fatal forms of COVID-19, as well as who among them are at higher risk for disease progression. This has highlighted the role of laboratory tests, both hematologic and biochemical, in identifying such patients in whom more aggressive treatment and close monitoring are needed.

Based on our study, we observed that hematologic (elevated leukocyte, neutrophil and NLR with lymphopenia) and biochemical (elevated CRP, LDH, ferritin and procalcitonin) are associated with COVID-19 severity and disease progression. Although limited by available data, our findings are consisted with available published data. There is therefore a role for these laboratory markers, when taken together with other associated factors of COVID-19 severity and prognosis, in being used to establish a reproducible COVID-19 severity scoring.

Authorship

All authors have certified fulfillment of Scientific Proceedings authorship criteria.

Disclosure of Conflicts of Interest

All authors have no conflict of interest to disclose.

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LUNG CENTER OF THE PHILIPPINES
Scientific Proceedings

Chest CT Findings on Admission of COVID-19 Pneumonia and its Association with Disease Severity and Duration of Illness: A Retrospective Study

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ABSTRACT

Background. Coronavirus Disease 2019 (COVID-19) was diagnosed by reverse transcription polymerase chain reaction (RT-PCR) test. Diagnostic imaging such as chest computed tomography (CT) scans shows typical changes of COVID-19 but there was limited data comparing CT scan findings with clinical severity and illness duration.

Objective. The study aimed to determine the common chest CT findings of COVID-19 pneumonia in association with clinical severity and duration of symptoms.

Methodology. This was a cross-sectional study including all adult patients with COVID-19 pneumonia, admitted from March 2020 to August 2020, with baseline RT-PCR and chest CT scan. Demographic data and CT scan findings were analyzed using STATA 13.1.

Results. Out of 304 patients, majority were above 60 years old (49%), male (62%), non-smokers (72.6%) with associated hypertension (56%) and diabetes mellitus (34%). Most common symptoms were cough (82%), dyspnea (76%) and fever (69%). Predominant chest CT patterns of COVID-19 pneumonia were ground glass opacity (GGO) (65%), crazy paving (55.92%) and consolidation (39%), in bilateral, peripheral, and lower lobe distribution. Moderate group had higher GGO (72%, P=0.047), unilateral (10%, P=0.001) and peripheral distribution (68%, P=0.001). Severe to critical groups had greater consolidation, opacity, and number of lobes (>4 lobes), with more diffuse involvement of the lower, middle to upper lobes. Subjects with more than 4 days of symptoms, had CT findings that were bilateral, multilobar (≥4 lobes), and involving the middle and upper lobes.

Conclusion. Chest CT patterns typical of COVID-19 pneumonia and their extent of involvement were associated with clinical severity and illness duration. A simple chest CT scan would help support physicians' decision making and prognostication.

Keywords: COVID-19, SARS-CoV-2, diagnostic imaging, computed tomography, pneumonia

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a new emerging infectious disease caused by a novel strain of beta coronavirus named as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) which initially started in Wuhan, China in December 2019 and spread very rapidly leading to a pandemic in March 2020.[1] As of this writing, there were 46 million COVID-19 cases and 1.2 million deaths globally.[2] According to the latest World Health Organization interim guideline, COVID-19 can present as mild, moderate, severe or critical disease.[3] It can be self-limiting or it can progress rapidly to respiratory failure, acute respiratory distress syndrome (ARDS), and eventually deaths.[4]

Timely and rapid diagnosis of this rapidly spreading, and even fatal pneumonia is critical to improve patient outcome, facilitate isolation, and reduce the spread of infection. To date, the reference test in the diagnosis of COVID-19 infection is a reverse transcription-polymerase chain reaction test (RT-PCR).[5,6] Few drawbacks of RT-PCR included limited availability, long processing time, and low sensitivity of 71-78.2% with reported false-negative results.[7,8] Chest imaging of great significance in this pandemic disease was a plain chest computed tomography (CT) scan which can be helpful in the initial diagnosis, understanding the disease stage, treatment management, and prognosis of COVID-19. Common chest CT findings typical of COVID-19 pneumonia include bilateral, peripheral, lower lobe ground-glass opacities (GGO) and consolidation.[9-12] Few studies showed that the sensitivity of chest CT scan in the diagnosis of COVID was as high as 97-98%.[7,13] Previous studies showed that the frequency of consolidation, crazy-paving pattern, and lobar involvement were higher in the severe to critical group compared with the non-severe group.[14,15] GGO was found to be more predominant within the first week of illness, progressing to consolidation in the second week, and reticular or crazy-paving pattern in the later phase.[12,16]

The objective description of CT findings in COVID-19 may help physicians improve screening efforts, stratify individuals according to their risk, predict progression, severity and prognosis, and optimize early treatment. However, previous studies comparing the CT findings of COVID-19 pneumonia with different levels of clinical severity and illness duration were still few and were rather limited by their small population. The general objective of this study was to determine the chest CT scan findings on admission of COVID-19 pneumonia and its association with disease severity and duration of illness. The specific objectives were to determine the demographic and clinical profile of confirmed COVID-19 cases, the association between chest CT scan findings in COVID-19 confirmed pneumonia cases with disease severity, and the common chest CT scan findings in COVID-19 pneumonia in relation to duration of symptoms.

METHODOLOGY

Study Design

This was a cross-sectional study which retrospectively reviewed the hospital records of all adult patients 19 years old and above, with COVID-19 pneumonia confirmed by at least 1 positive RT-PCR with a baseline chest CT scan, and admitted at Lung Center of the Philippines (LCP) from March 2020 to August 2020. Those with incomplete scan, imaging artifacts, algorithm failure, or those with destroyed lung and massive pleural effusion on chest CT scan were excluded from the study.

Statistical Analysis

Descriptive statistics was used to summarize the demographic and clinical characteristics of the patients. In between group comparisons was done using Mann-Whitney U test and Fisher's exact test. Shapiro-Wilk was used to test the normality of the continuous variables. STATA 13.1 was used for data analysis.

Ethical Considerations

This study complied with the National Ethical Guidelines for Health and Health Related Research 2017 for health research. It was approved by the Lung Center of the Philippines-Institutional Ethics Review Board (LCP-IERB). The informed consent process was waived and approved by the LCP-IERB. All the information from each and all the patients involved in this study were managed with strict confidentiality.

SARS-CoV-2 RT-PCR

The molecular tests used in this study to detect the presence of SARS-CoV-2 in nasopharyngeal or

oropharyngeal swab were nucleic acid-based tests which utilized plate-based Real Time RT-PCR and cartridge-based GeneXpert Xpress system. The tests were conducted by the LCP, a COVID-19 molecular laboratory licensed by the Department of Health.

Chest CT Scan Imaging and Analysis

Plain Chest CT scan utilized in this study was based on standard scan protocol with a 1mm slice thickness. Chest CT scan of patients included in this study were processed using an Automated Quantification system by Siemens (AI). Automatic percentage involvement by the different lobes of the lungs were provided. All CT scans were anonymized in compliance with the data privacy act. Image analysis and interpretation was done by two certified radiologists with at least 3 years of clinical practice. Two radiologists reviewed the predominant pattern of the CT scan (GGO, consolidation, mixed GGO and consolidation, or crazy paving). Presence of intercurrent findings like PTB, pulmonary mass and pleural effusion were recorded by the radiologists. Digital images and results were stored in an online electronic imaging system.

RESULTS

A total of 321 patients were diagnosed with COVID-19 pneumonia and admitted from March to August 2020. After exclusion of 17 patients due to presence of destroyed lung, massive pleural effusion and algorithm failure, a total of 304 patients were included in this study. Out of 304 patients, 149 were categorized as moderate, 84 were severe, and 71 were critical based on their clinical disease severity (Figure 1).

Table 1 shows that most of the patients belong to the age group of 40 to 60 and more than 60 years (41% and 49%, respectively p=0.040). There was predominance of male patients (62%). Only about 27% were smokers. Only 6% of the total patients were healthcare workers. Around 81% of them had no known history of exposure while 17% had a close contact with a confirmed COVID-19 patient. Among the associated co-morbidities, the most prevalent were hypertension (56%) followed by diabetes mellitus (34%) and BA (8.5%). Lone cases of HIV, hypothyroidism, hyperthyroidism and dyslipidemia were noted. The most common clinical signs and symptoms on admission were cough (82%), dyspnea

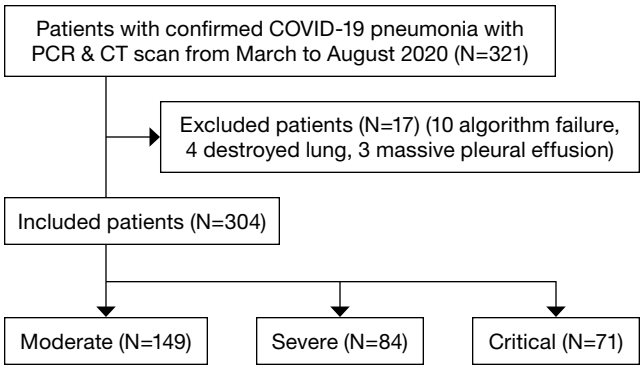

Figure 1. Flow of the study.

(76%) and fever (69%). Other symptoms were headache, anorexia, anosmia, and ageusia. The average time from onset of symptoms to hospital admission was 7 days. With regards to WBC count, majority of patients with COVID-19 pneumonia had a normal WBC count (5 to 10 x10^9/L).

Table 2 shows that the most predominant chest CT patterns of COVID-19 pneumonia were GGO (65%), crazy paving (55.92%), and consolidation (39.14%), in peripheral (53.29%), bilateral (94.72%), and lower lobe distribution (99.67%). Common chest CT findings were shown in Figure 2. Majority of patients had involvement of at least 4 lobes (87.83%), but the lower lobe opacity was predominantly more than 50% compared with middle and upper lobes.

Moderate group had predominance of GGO (72%) followed by crazy paving (56%). The severe group had predominance of crazy paving (64.29%) and GGO (60.71%). While consolidation (74.65%) dominates the CT pattern of the critical group, followed by GGO (56%).

Significant difference was observed between groups of disease severity across chest CT pattern, distribution, number and site of lobar involvement, lobar opacity, and total percent opacity.

There was a higher frequency of GGO in the moderate group and severe group compared to critical group (71.81% and 60.71% vs 56.34% respectively, p=0.047). The frequency of consolidation significantly increased with increasing severity, as consolidation was observed in only 21.48% in the moderate group, but 40.48% in the severe group, and 74.65% in the

Table 1. Demographic and clinical profile of patients with confirmed COVID-19 pneumonia

Characteristic	Total (n=304)	Disease severity			P-value
		Moderate (n=149, 49%)	Severe (n=84, 28%)	Critical (n=71, 23%)	
	Frequency (%); Median (IQR)				
Age (in years)					
<40	29 (9.54)	21 (14.09)	5 (5.95)	3 (4.23)	**0.040**
40 to 60	126 (41.45)	61 (40.94)	40 (47.62)	25 (35.21)	
>60	149 (49.01)	67 (44.97)	39 (46.43)	43 (60.56)	
Sex					
Male	187 (61.51)	86 (57.72)	56 (66.67)	45 (63.38)	0.381
Female	117 (38.49)	63 (42.28)	28 (33.33)	26 (36.62)	
Smoking Status					
Smoker	83 (27.39)	39 (26.17)	22 (26.51)	22 (30.99)	0.745
Non smoker	220 (72.61)	110 (73.83)	61 (73.49)	49 (69.01)	
Occupation					
Healthcare worker	18 (5.96)	13 (8.78)	3 (3.57)	2 (2.86)	0.173
Non healthcare worker	284 (94.04)	135 (91.22)	81 (96.43)	68 (97.14)	
History of Exposure					
Close Contact	51 (16.94)	31 (21.09)	16 (19.05)	4 (5.71)	**0.010**
History of Travel	7 (2.33)	5 (3.4)	0	2 (2.86)	
None	243 (80.73)	111 (75.51)	68 (80.95)	64 (91.43)	
Co-morbidities					
Diabetes mellitus	102 (33.55)	60 (40.27)	20 (23.81)	22 (30.99)	**0.034**
Hypertension	169 (55.59)	69 (46.31)	53 (63.1)	47 (66.2)	**0.006**
Cardiovascular disease	21 (6.91)	12 (8.05)	6 (7.14)	3 (4.23)	0.639
Cerebrovascular disease	12 (3.95)	4 (2.68)	4 (4.76)	4 (5.63)	0.472
COPD	5 (1.64)	3 (2.01)	0	2 (2.82)	0.370
Bronchial asthma	26 (8.55)	15 (10.07)	8 (9.52)	3 (4.23)	0.328
Malignancy	10 (3.29)	6 (4.03)	3 (3.57)	1 (1.41)	0.644
CKD	18 (5.92)	8 (5.37)	3 (3.57)	7 (9.86)	0.270
PTB					0.591
Active	11 (3.62)	5 (3.36)	3 (3.57)	3 (4.23)	
Previous	21 (6.91)	7 (4.7)	8 (9.52)	6 (8.45)	
Others	9 (2.96)	4 (2.68)	3 (3.57)	2 (2.82)	0.909
Duration of Illness (Days) (From symptom onset to admission)	7 (5 to 8)	7 (5 to 8)	7 (5 to 10)	7 (4 to 8)	0.864
Clinical Signs and Symptoms (on admission)					
Fever	209 (68.75)	99 (66.44)	56 (66.67)	54 (76.06)	0.318
Cough	250 (82.24)	117 (78.52)	73 (86.9)	60 (84.51)	0.267
Dyspnea	230 (75.66)	90 (60.4)	71 (84.52)	69 (97.18)	**<0.001**
Fatigue	5 (1.64)	1 (0.67)	1 (1.19)	3 (4.23)	0.146
Colds	12 (3.95)	8 (5.37)	1 (1.19)	3 (4.23)	0.294
Diarrhea	16 (5.26)	11 (7.38)	5 (5.95)	0	**0.044**
Myalgia	11 (3.62)	2 (1.34)	4 (4.76)	5 (7.04)	0.081
Anosmia	14 (4.61)	4 (2.68)	8 (9.52)	2 (2.82)	0.059
Sore throat	18 (5.92)	13 (8.72)	4 (4.76)	1 (1.41)	0.083
Body Weakness	41 (13.49)	20 (13.42)	10 (11.9)	11 (15.49)	0.800
Others	38 (12.5)	17 (11.41)	12 (14.29)	9 (12.68)	0.788
Asymptomatic	1 (0.33)	1 (0.67)	0	0	1.000
WBC (count in 10^9/L) on admission					
<5	45 (14.85)	35 (23.49)	7 (8.33)	3 (4.29)	**<0.001**
5 to 10	148 (48.84)	92 (61.74)	39 (46.43)	17 (24.29)	
>10	110 (36.3)	22 (14.77)	38 (45.24)	50 (71.43)	

COVID-19: coronavirus disease 2019, COPD: Chronic Obstructive Pulmonary Disease, CKD: Chronic Kidney Disease, PTB: Pulmonary Tuberculosis, WBC: White Blood Cell.
Data presented as median (interquartile range) or count (percent).

Table 2. Chest CT scan findings of patients with confirmed COVID-19 pneumonia according to clinical disease severity

Parameter	All Patients (n=304)	Disease severity			P-value [a]	P-value [b]	P-value [c]
		Moderate (n=149, 49%)	Severe (n=84, 28%)	Critical (n=71, 23%)			
	Frequency (%); Median (IQR)						
Predominant pattern							
GGO	198 (65.13)	107 (71.81)	51 (60.71)	40 (56.34)	0.108	**0.032**	**0.047**
Consolidation	119 (39.14)	32 (21.48)	34 (40.48)	53 (74.65)	**0.002**	**<0.001**	**<0.001**
Mixed GGO & consolidation	48 (15.79)	12 (8.05)	11 (13.1)	25 (35.21)	0.215	**<0.001**	**<0.001**
Crazy paving	170 (55.92)	84 (56.38)	54 (64.29)	32 (45.07)	0.268	0.148	0.055
Distribution					**0.007**	**0.002**	**0.001**
Unilateral	17 (5.59)	16 (10.74)	1 (1.19)	0			
Bilateral	287 (94.72)	133 (89.86)	83 (98.81)	71 (100)			
Peripheral	162 (53.29)	102 (68.46)	43 (51.19)	17 (23.94)	**0.011**	**<0.001**	**<0.001**
Predominantly central	53 (17.43)	27 (18.12)	18 (21.43)	8 (11.27)	0.605	0.239	0.231
Diffuse	77 (25.33)	11 (7.38)	21 (25)	45 (63.38)	**<0.001**	**<0.001**	**<0.001**
Numbers of lobes involved					**<0.001**	**<0.001**	**<0.001**
1	10 (3.29)	10 (6.71)	0	0			
2 to 3	27 (8.88)	24 (16.11)	3 (3.57)	0			
4 to 5	267 (87.83)	115 (77.18)	81 (96.43)	71 (100)			
Site of lobar involvement							
Upper lobe	286 (94.08)	131 (87.92)	84 (100)	71 (100)	**<0.001**	**0.001**	**<0.001**
Middle lobe	254 (83.55)	105 (70.47)	79 (94.05)	70 (98.59)	**<0.001**	**<0.001**	**<0.001**
Lower lobe	303 (99.67)	148 (99.33)	84 (100)	71 (100)	1.000	1.000	1.000
Left upper lobe					**<0.001**	**<0.001**	**<0.001**
Less than 50% opacity	177 (65.56)	108 (92.31)	49 (59.76)	20 (28.17)			
More than 50% opacity	93 (34.44)	9 (7.69)	33 (40.24)	51 (71.83)			
Left lower lobe					**<0.001**	**<0.001**	**<0.001**
Less than 50% opacity	110 (38.33)	88 (65.67)	16 (19.28)	6 (8.57)			
More than 50% opacity	177 (61.67)	46 (34.33)	67 (80.72)	64 (91.43)			
Right upper lobe					**<0.001**	**<0.001**	**<0.001**
Less than 50% opacity	169 (62.83)	108 (93.1)	44 (53.66)	17 (23.94)			
More than 50% opacity	100 (37.17)	8 (6.9)	38 (46.34)	54 (76.06)			
Right middle lobe					**<0.001**	**<0.001**	**<0.001**
Less than 50% opacity	165 (64.96)	89 (84.76)	50 (63.29)	26 (37.14)			
More than 50% opacity	89 (35.04)	16 (15.24)	29 (36.71)	44 (62.86)			
Right lower lobe					**<0.001**	**<0.001**	**<0.001**
Less than 50% opacity	98 (33.11)	81 (57.04)	13 (15.66)	4 (5.63)			
More than 50% opacity	198 (66.89)	61 (42.96)	70 (84.34)	67 (94.37)			
Total percent opacity	41.23 (20.3 to 64.8)	20.91 (7.01 to 36.21)	53.47 (36.37 to 64.8)	71.38 (63.69 to 77.39)	**<0.001**	**<0.001**	**<0.001**
Other findings							
PTB	30 (9.87)	18 (12.08)	8 (9.52)	4 (5.63)	0.667	0.157	0.352
Mass/soft tissue density	17 (5.59)	8 (5.37)	5 (5.95)	4 (5.63)	1.000	1.000	1.000
Pleural effusion	22 (7.24)	6 (4.03)	10 (11.9)	6 (8.45)	**0.030**	0.208	0.073
Emphysema	13 (4.28)	5 (3.36)	6 (7.14)	2 (2.82)	0.210	1.000	0.326

CT: computed tomography, COVID-19: coronavirus disease 2019, GGO: ground glass opacity, PTB: Pulmonary Tuberculosis
p-value [a] – Moderate vs. Severe; p-value [b] – Severe vs. Critical; p-value [c] – Moderate vs. Severe vs. Critical

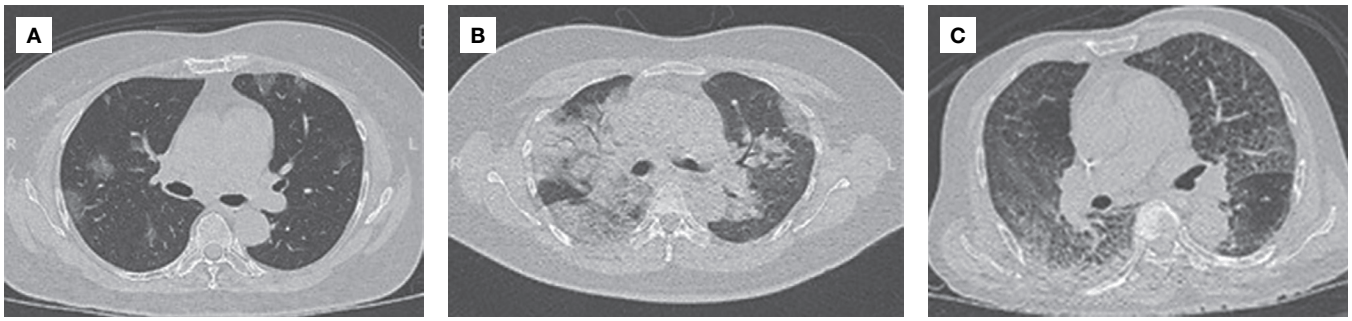

Figure 2. **(A)** Plain chest CT showing bilateral peripheral lower lobe ground glass opacities. **(B)** Plain chest CT showing bilateral diffuse ground glass opacities and consolidation. **(C)** Plain chest CT showing bilateral patchy consolidation and crazy paving pattern.

critical group (p<0.001). On the contrary, crazy paving pattern did not differ significantly with disease severity.

Unilateral lung involvement was seen in only 5.59% of the total subjects (17/304) and was almost exclusively observed in the moderate group (16/17), while bilateral involvement was associated with increasing disease severity (moderate=89.86%, severe=98.81%, critical=100%, p=0.001). Frequency of peripheral involvement decreased with increasing severity (moderate=68%, severe=51%, critical=24%, p<0.001), while diffuse lung involvement increased with increasing disease severity (moderate=7%, severe=25%, critical=63%, p<0.001).

The number of lobar involvement increased with severity. There were only 10 cases of unilobar involvement, which was observed exclusively in the moderate group (10/10). The frequency of those with higher number of lobes involved (≥4 lobes) increased with increasing severity (moderate=77.18%, severe=96.43%, critical=100%, p<0.001).

According to site of lobar involvement, lower lobe involvement was seen mostly in 99.67% (303/304) of COVID-19 cases, and did not differ with disease severity. However, the frequency of middle lobe involvement was increased with increasing severity of disease (moderate=70%, severe=94%, critical=99%, p<0.001), while upper lobe was involved in 100% of severe and critical cases (p<0.001).

With regards to lobar opacity, majority of the moderate group had less than 50% opacity in every lobe (lower, middle and upper lobes). Compared with the moderate group, the severe group showed more than 50% percent opacity in the lower lobes. Among the critical group, more than 50% opacity was observed not only in the lower lobes, but also in the middle and upper lobes.

Specifically, more than 50% opacity of the lower lobes was associated with more severe disease (severe and critical group) while more than 50% opacity of all lobes (lower, middle and upper lobes) were associated with critical disease severity.

In general, a higher total percent opacity is significantly associated with higher severity, as those with moderate severity had a median of 20.91, severe had 53.47, and critical had 71 percent opacity.

Other CT findings noted by the radiologists were the presence of PTB, pleural effusion, and pulmonary mass or soft tissue density.

Table 3 shows the predominant CT patterns of COVID-19 pneumonia with different duration of illness (from onset of symptoms to admission). In the earliest phase of illness (duration: ≤4 days), the predominant CT patterns were GGO followed by consolidation (64.71%, 51.47% respectively). During the second phase (duration: 5-8 days), GGO was still predominant but now followed by crazy paving pattern (66.26%, 61.96% respectively). Similarly, the third phase of illness (duration: 9-13 days) had predominance of GGO and crazy paving patterns (82.76%, 51.72% respectively). The fourth phase of illness (duration: ≥14 days) was marked by the predominance of crazy paving followed only by GGO (56.82%, 50% respectively). Among all these CT patterns, only GGO was significantly associated with duration of illness. GGO increased from 64.71% of the 1st phase, 66.26% of the second phase, up to 83% of the third phase (p=0.037). But frequency of GGO declined on the fourth phase or after 14 days, when crazy paving pattern dominated the picture.

Aside from the GGO pattern, significant difference was observed with different duration of illness across laterality, number, and site of lobar involvement.

In terms of laterality, unilateral distribution was highest in the group which presented early with less than 4 days of symptoms (11.76%) as compared to those with longer duration of illness (p=0.029). Bilateral distribution was observed among all phases of illness, but significantly greater among those who presented with more than 4 days of symptoms (p=0.029).

Patients who presented the earliest (≤4 days) had the highest frequency of unilobar involvement (7.35%, p=0.049). Patients with longer duration of illness (>4 days) had higher number of lobes involved (>4 lobes), which was significantly higher than those with ≤4 days of symptoms (p=0.049).

Table 3. Appearance of chest CT scan findings of patients with confirmed COVID-19 pneumonia according to duration of illness

Appearance	Duration of Illness/symptoms (in days)				P-value
	≤4 (n=68, 22%)	5 to 8 (n=163, 54%)	9 to 13 (n=29, 10%)	≥14 (n=44, 14%)	
	Frequency (%); Median (IQR)				
Predominant pattern					
GGO	44 (64.71)	108 (66.26)	24 (82.76)	22 (50)	**0.037**
Consolidation	35 (51.47)	57 (34.97)	10 (34.48)	17 (38.64)	0.127
Mixed GGO and Consolidation	16(23.53)	21(12.88)	7(24.14)	4(9.09)	0.068
Crazy paving	29 (42.65)	101 (61.96)	15 (51.72)	25 (56.82)	0.058
Distribution					
Unilateral	8 (11.76)	5 (3.07)	1 (3.45)	3 (6.82)	**0.029**
Bilateral	60 (88.24)	158 (96.93)	28 (96.55)	41 (93.18)	**0.029**
Peripheral	32 (47.06)	90 (55.21)	14 (48.28)	26 (59.09)	0.536
Predominantly central	6 (8.82)	36 (22.09)	3 (10.34)	8 (18.18)	0.072
Diffuse	23 (33.82)	35 (21.47)	11 (37.93)	8 (18.18)	0.060
Numbers of lobes involved					
1	5 (7.35)	2 (1.23)	1 (3.45)	2 (4.55)	**0.049**
2 to 3	10 (14.71)	10 (6.13)	3 (10.34)	4 (9.09)	
4 to 5	53 (77.94)	151 (92.64)	25 (86.21)	38 (86.36)	
Site of lobar involvement					
Upper lobe	60 (88.24)	159 (97.55)	26 (89.66)	41 (93.18)	**0.016**
Middle lobe	49 (72.06)	143 (87.73)	25 (86.21)	37 (84.09)	**0.042**
Lower lobe	67 (98.53)	163 (100)	29 (100)	44 (100)	0.464
Left upper lobe					0.153
Less than 50% opacity	30 (55.56)	101 (67.79)	15 (57.69)	31 (75.61)	
More than 50% opacity	24 (44.44)	48 (32.21)	11 (42.31)	10 (24.39)	
Left lower lobe					0.298
Less than 50% opacity	26 (42.62)	63 (39.87)	11 (39.29)	10 (25)	
More than 50% opacity	35 (57.38)	85 (60.13)	17 (60.71)	30 (75)	
Right upper lobe					0.103
Less than 50% opacity	31 (53.45)	94 (63.95)	14 (56)	30 (76.92)	
More than 50% opacity	27 (46.55)	53 (36.05)	11 (44)	9 (23.08)	
Right middle lobe					0.605
Less than 50% opacity	28 (57.14)	94 (65.73)	17 (68)	26 (70.27)	
More than 50% opacity	21 (42.86)	49 (34.27)	8 (32)	11 (29.73)	
Right lower lobe					0.968
Less than 50% opacity	22 (34.92)	52 (32.1)	9 (32.14)	15 (34.88)	
More than 50% opacity	41 (65.08)	110 (67.9)	19 (67.86)	28 (65.12)	
Total percent opacity	43.78 (11.62 to 72.3)	44.37 (20.65 to 64.38)	52.28 (26.65 to 68.59)	36.57 (21.86 to 55.43)	0.660
Other findings					
PTB	12 (17.65)	8 (4.91)	2 (6.9)	8 (18.18)	**0.004**
Mass/soft tissue density	7 (10.29)	5 (3.07)	2 (6.9)	3 (6.82)	0.113
Pleural effusion	8 (11.76)	7 (4.29)	2 (6.9)	5 (11.36)	0.112
Emphysema	5 (7.35)	5 (3.07)	1 (3.45)	2 (4.55)	0.487

CT: computed tomography, GGO: ground glass opacity, PTB: Pulmonary Tuberculosis,
Duration of illness: from onset of symptoms to time of initial CT scan. Data presented as count (percent).

COVID-19 pneumonia predominantly involved the lower lobes and it did not differ with duration of illness. Middle lobe and upper lobe involvement were significantly higher among the group with longer duration of illness (>4 days), which was higher than those with ≤4 days of symptoms.

Percent opacity of each lobe and total percent opacity did not differ significantly with duration of illness.

Lastly, presence of PTB was significant. Patients who presented with less than 4 days (18%) and more than 14 days (18%) of symptoms prior to admission had higher percentage of PTB as compared to other groups (p=0.004).

DISCUSSION

Out of 304 patients with COVID-19 pneumonia, majority of the patients were in the age group of 40-60 and >60 years old (41% and 49%, respectively), males, and nonsmokers which were similar in the previous studies.[4,17] Only 6% of the total patients were healthcare workers. Only 17% had history of close contact exposure with a COVID-19 patient which can be due to limited contact tracing practices. Similar with other studies, the most prevalent associated co-morbidities were hypertension (56%) followed by diabetes mellitus (34%).[9,18] The three most common presenting signs and symptoms on admission were cough (82%), dyspnea (76%) and fever (69%), hence presence of cough even in the absence of fever should prompt suspicion of a possible COVID-19 and practice isolation and quarantine. Almost half (49%) of the patients with COVID-19 pneumonia had a normal WBC count (5-10 x10^9/L) on admission, which was comparable with other studies.[10,19]

With regards to the chest CT scan findings among patients with COVID-19 pneumonia, the most predominant pattern was GGO in bilateral, peripheral and lower lobe distribution which was comparable with other studies.[9-12] We were able to demonstrate a significant association between CT findings and disease severity, particularly in terms of CT patterns (GGO, consolidation), lung distribution (unilateral, bilateral, peripheral, diffuse), number and site of lobar involvement, and percent opacity. In addition, CT findings such as GGO, laterality of distribution (unilateral or bilateral), number and site of lobar involvement were also shown to be associated with duration of illness.

With regards to disease severity, GGO was significantly higher in the moderate group (72%) and severe group (61%) compared with the critical group (56%). On the contrary, consolidation was significantly increased with increasing disease severity. Hence, GGO characterized with partial filling of airspaces and interstitium can indicate a less severe disease, while consolidation marked with greater degree of involvement of alveolar spaces replacing the alveolar air affecting ventilation can denote a more severe COVID-19 pneumonia.[20] Consolidation, in addition to increased inflammatory changes, may be connected with the findings of dyspnea and increased WBC count that were predominant among the critical group, respectively.

As to lung distribution, peripheral lung involvement was predominant among the less severe group while diffuse involvement was predominant among the critical group. Bilateral lung involvement was significantly increased with increasing disease severity, while unilateral lung involvement was rarely seen in COVID-19, but once found, it denotes a less severe disease.

COVID-19 pneumonia mostly involved at least 4 lobes or more in increasing percentage as the disease severity progressed, while involvement of a fewer lobes (3 or less) was almost exclusive among moderate cases. There was significant association with disease severity and the number of lobes involved, as the higher the number of lobes involved, the higher the degree of disease severity.

COVID-19 pneumonia mainly involved the lower lobes but it did not significantly affect the disease severity as almost all patients have this result (99.7%). However, middle and upper lobe involvement increased with increasing severity of disease. COVID-19 pneumonia involving up to the middle lobe denotes an increasing severity of disease. While involvement from the base to the upper lobes indicates severe to critical disease severity as 100% of the severe and critical groups had upper lobe involvement.

Taking into account the percent opacity seen per lobe, CT findings with less than 50% opacity in all lobes indicates a less severe disease, while a higher percent opacity (>50%) in any lobe is associated with higher disease severity. Specifically, lower lobe opacity of more than 50% is linked to a severe to critical disease, while more than 50% opacity of the lower, middle and upper lobe denotes a critical disease. Similarly, a higher total percent opacity is a significant factor that will likely result to a severe or critical disease, and it was comparable with another study where CT lung opacity score was higher in severe cases.[21]

In comparing the chest CT patterns of COVID-19 pneumonia with respect to the duration of symptoms, GGO followed by consolidation were the predominant

patterns during the earlier phase of illness (≤4 days of symptoms), while GGO followed by crazy paving were predominant during the second phase (5-8 days of symptoms). This CT patterns during the first two phases of illness were comparable to the study of Pan et al.[22] GGO pattern can be seen as the earliest presentation on chest CT scan, however other CT patterns such as consolidation, and crazy paving cannot reliably relate to duration of illness as many factors can possibly contribute to the rate of lung consolidation and crazy paving process such as host immune response, co-morbidity, or older age.

CT findings were mostly bilateral in any phase of illness, while unilateral lung involvement was significantly higher in the first phase of illness (duration: ≤4 days). Hence, a unilateral lung involvement points to an early and less severe disease. Patients who presented with longer duration of symptoms (>4 days) had a significantly higher number of lung involvement (≥4 lobes) on chest CT scan compared with those who presented earlier (less than 4 days). Lower lobe involvement was predominant in COVID-19 pneumonia but it did not differ with duration of illness, however middle lobe and upper lobe involvement by the COVID-19 pneumonia was significantly higher among patients who presented with longer duration of symptoms (>4 days), compared with those who presented earlier.

This study has a few limitations. First, it is a single-center study involving only one institution. Second, as a retrospective study, a follow up CT scan was not routinely done during the duration of admission. A series of chest CT scan results would be of use in the comparison of CT changes with the disease progression. A prospective, multicenter study is recommended.

CONCLUSION

As the COVID-19 pandemic continues worldwide, diagnostic tests were evolving but with limitations. In conditions where RT-PCR is not readily available or with delayed results, one diagnostic imaging that is readily available and can give faster results is the plain chest CT scan.

The most predominant chest CT pattern among patients with COVID-19 pneumonia was GGO in bilateral, peripheral and lower lobe distribution. Chest CT scan patterns typical of COVID-19 pneumonia and their extent of involvement were associated with severity of disease and duration of illness.

COVID-19 pneumonia is likely to be of higher clinical severity when the chest CT scan showed the presence of consolidation, bilateral, more diffuse and more opacified lung involvement, involving at least 4 lobes, particularly extending to the middle or upper lobes. Less severe disease is likely when the CT scan showed predominance of GGO, unilateral or unilobar, peripheral, basal and less opacified lung involvement. In addition, CT findings in the presence of GGO, unilateral or unilobar distribution likely denotes an earlier disease.

Chest CT scan is a useful imaging tool for initial diagnosis of COVID-19 pneumonia in determining the severity of disease and in distinguishing an early vs. later phase of illness. These CT findings when correlated with patient's clinical presentation would help support physician's decision making, prognostication, and timely interventions.

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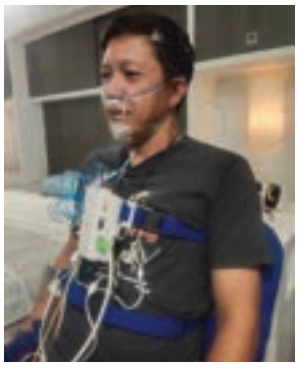

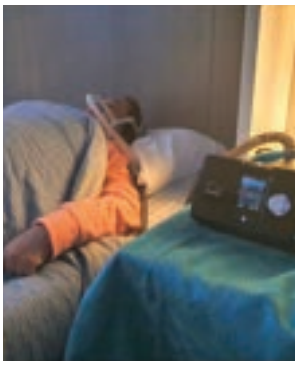

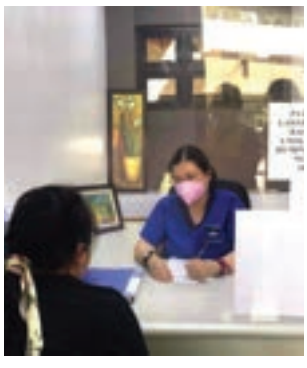

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Scientific Proceedings

Outcomes of COVID-19 Confirmed Cases treated with Investigational Products and Interventions in Lung Center of the Philippines

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ABSTRACT

Objective. The World Health Organization emphasized that currently there is no identified cure for COVID-19 hence all treatment modalities are still investigational. The aim of this study is to determine the outcomes of COVID-19 confirmed cases treated with COVID-19 investigational products and interventions in Lung Center of the Philippines in terms of mortality, morbidity and length of hospital stay. Specifically, morbidity was described in terms of use of mechanical ventilation, higher forms of non-invasive oxygenation and occurrence of an adverse drug event or adverse drug reaction.

Methodology. This is a retrospective, cohort study that included all adults more than 18 years old admitted from March 7, 2020 to August 31, 2020 with a diagnosis of COVID-19 confirmed disease via RT-PCR or GeneXpert, classified as moderate, severe or critical with at least one investigational product or intervention.

Results. Out of 376 patients, 154 (41.0%) expired, most of them were given convalescent plasma, hemoperfusion and combination of steroid + hemoperfusion. Fifty-eight patients initially on room air and prescribed with non-invasive ventilation eventually required invasive ventilation (15.4%), most of them were given convalescent plasma and combinations of hydroxychloroquine/chloroquine ± azithromycin + tocilizumab and steroid + hemoperfusion + tocilizumab. Patients who were less frequently shifted to invasive ventilation received favipiravir and steroid. A higher form of non-invasive oxygen support was needed in 39 patients (10.4%) who were given tocilizumab, interferon, and combination steroid + hemoperfusion + tocilizumab. Average length of hospital stay was 14.11 days. The shortest mean length of hospital stay among discharged patients were among those who received favipiravir (11.55 days) and steroid (14.2 days). Twenty-nine cases with adverse drug events (7.7%) were noted, most common were transaminitis, arrhythmia, bleeding and acute kidney injury.

Conclusion. Patients with critical severity had a high mortality regardless of what kind of investigational product or intervention was given. Favipiravir and steroid may reduce the need for invasive ventilation and length of hospitalization. Determination of adverse drug events among COVID-19 patients using investigational products/intervention was difficult due to its multi-organ affectation.

Keywords: COVID-19, investigational products, hemoperfusion, convalescent plasma

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INTRODUCTION

COVID-19, a disease caused by the novel coronavirus, SARS-CoV-2, was first isolated in Wuhan City, Hubei province, in China last December 2019. Since then, it has caused a global pandemic with staggering speed. In the beginning of the pandemic, the Department of Health (DOH) appointed the Lung Center of the Philippines (LCP) to be a COVID-19 referral hospital that would cater to patients with moderate to critical severity. During this time, there was no established institutional standard of care that can be applied to patients. As of December 31, 2020 there were 83 million COVID-19 confirmed cases and 1.8 million deaths globally. In the Philippines, there were 569 thousand confirmed cases and 12,201 deaths.

The World Health Organization (WHO) stated that there was currently no evidence for any specific COVID-19 treatment.[1] Ongoing clinical trials in different countries were yet to be completed and released their results during the time of the writing of this paper. Furthermore, global impact of the outbreak led to a race to develop vaccines; however, it was still not yet readily available. In the meantime, investigational therapies were explored which targeted viral inhibition, suppression of the secondary effects of cytokine storm and/or modulation of the host immune system to mount its defense.[2]

OBJECTIVES

The aim of this study was to determine the outcomes of COVID-19 confirmed cases treated with COVID-19 investigational products and interventions in terms of mortality, morbidity (in terms of use of invasive ventilation or higher form of non-invasive oxygen support and/or occurrence of adverse drug event or adverse drug reaction), and length of hospital stay. The results of this study would guide clinicians in the choice of investigational products and interventions for our COVID-19 confirmed cases and may contribute to the preliminary global data on the real-world treatment outcomes of COVID-19 investigational product/intervention.

METHODOLOGY

Study Design

This was a retrospective, cohort study conducted at the LCP, a 210-bed capacity specialty center for lung diseases. It was designated as one of the COVID-19 referral centers by the DOH to accommodate moderate to critical cases. It is located in Quezon City, Metro Manila, where most cases of COVID-19 were found during this pandemic.

Study Population

The study included all adults (at least 18 years old) with a final diagnosis of COVID-19 confirmed disease diagnosed by RT-PCR or GeneXpert performed by a DOH-licensed testing laboratory, classified as moderate, severe or critical based on WHO guideline, admitted at the LCP from March 7, 2020 to August 31, 2020, and who have received at least one investigational product or intervention. Confirmed COVID-19 patients who died within 24 hours of admission were excluded.

Sample Size and Sampling Design

Consecutive sampling of all cases within the six months study period was done. A minimum of 239 confirmed COVID-19 patients satisfying the inclusion/exclusion criteria was required to have an 80% chance of determining, as significant at 5% level of error, the outcomes of COVID-19 confirmed cases given with COVID-19 investigational product or intervention. Sample size was derived based on observed 19.2% mortality among patients treated with lopinavir/ritonavir (Cao et al., 2020).[3]

Study Procedure

We did a retrospective patient chart review and laboratory data extraction through an electronic hospital record software (called BizBox) of included patients. We obtained a list of all patients admitted due to COVID-19 from March 7, 2020 to August 31, 2020 from the central medical records. We then screened and reviewed the charts using a data collection tool to extract necessary data of those patients who met the inclusion criteria. The assignment of investigational product/intervention was physician initiated or would depend on randomization under Solidarity trial if the patient was enrolled under it.

Outcome Measurements

- In-hospital mortality – refers to deaths related to COVID-19 caused by SARS-CoV-2 and its associated complications while a patient was admitted in the ward. Patients with home orders and pending discharge (inability to do home quarantine, those unable to settle accounts, still processing documents) who expired were not included
- Morbidity – refers to a state of being symptomatic or unhealthy from a disease or in this study, to conditions arising as consequences or complications (other than death) due to COVID-19 disease in terms of use of invasive ventilation or higher form of non-invasive oxygenation, and occurrence of adverse drug event or adverse drug reaction.
- Length of hospital stay – duration of hospital stays (counted as days) beginning on day of admission to day of discharge. Day of discharge was based on the day when the patient was alive and medically ready for discharge as determined by the investigator based on WHO criteria for clinical recovery as evidenced by resolution of symptoms (absence of fever, improvement of respiratory symptoms, and no longer requiring oxygen). This included those hospitalized or re-hospitalized patients who no longer required ongoing medical care but remained hospitalized due to delay in identifying living accommodation outside the hospital. This may have been different from the actual discharge date affected by the evolving criteria for discharge at the time of the study.
- Use of invasive ventilation – refers to the institution of endotracheal intubation to provide mechanical ventilation to a patient who was initially admitted without use of invasive ventilatory support. Patients initially on non-invasive ventilation who eventually required invasive ventilation were categorized under invasive ventilation.
- Use of higher form of non-invasive oxygenation – refers to the provision of any form of non-invasive ventilatory support or shifting of a present oxygen delivery device to a higher form of non-invasive oxygen support such as high-flow nasal cannula, continuous positive airway pressure (CPAP), or bilevel positive airway pressure (BIPAP).
- Occurrence of adverse drug event or adverse drug reaction
- Adverse drug event - refers to any untoward response during treatment which may or may not have a causal relationship with the different investigational product/intervention used
- Adverse drug reaction - refers to any response to the different investigational product/intervention which is noxious and unintended and which occurs at doses normally used for treatment.

Statistical Analysis

Data processing and analysis was done using STATA v14. Summary statistics were presented in tables or graphs and reported as mean standard deviation for continuous data with normal distribution or as median (interquartile range) for quantitative variables with skewed distribution, and as count (percent) for qualitative measures. Minimum and maximum values of continuous data were also reported. Pairwise comparison of proportions was based on adjusted p-values. Statistical significance was based on p-value ≤ 0.05.

Ethical Considerations

The study was approved by the LCP Ethics Review Board.

RESULTS

We retrieved and screened a total of 499 charts with a diagnosis of COVID-19 admitted between the period of March 7, 2020 to August 31, 2020. There were 110 patients who were not given investigational products or interventions and 13 patients were classified as mild disease.

Table 1 shows the baseline characteristics of the patients analyzed in this study. We included a total of 376 COVID-19 confirmed cases with an average age of around 58 years old (±13.77). Majority of the patients were male (64.9%) and 84.6% of them had at least one co-morbidity. Majority had hypertension (59.3%) followed by diabetes mellitus (37.5%), and cardiovascular disease (CVD) (10.1%). Among co-morbid conditions relating to the respiratory system, pulmonary tuberculosis (9.6%) was the most common followed by bronchial asthma (7.7%) and chronic obstructive pulmonary disease (2.9%). Furthermore, we also noted that 26.1% of the total patients were either current or previous smokers. Around 44% of the

Table 1. Demographic profile of COVID-19 confirmed cases

Demographic Profile	Values
Age, mean ± SD	58.21 ±13.77
Gender, n (%)	
Male	244 (64.9)
Female	132 (35.1)
Co-morbidities, n (%)	
With Co-morbidities	318 (84.6)
Hypertension	223 (59.3)
Diabetes Mellitus	141 (37.5)
Cardiovascular disease	38 (10.1)
Cerebrovascular disease	14 (3.7)
Chronic obstructive pulmonary disease	11 (2.9)
Pulmonary tuberculosis	36 (9.6)
Active infection	11 (2.9)
Previous infection	25 (6.6)
Bronchial asthma	29 (7.7)
Malignancy	11 (2.9)
Chronic kidney disease	28 (7.4)
Pregnancy	1 (0.3)
Hyperthyroidism	3 (0.8)
Hypothyroidism	3 (0.8)
Dyslipidemia	6 (1.6)
Benign prostatic hypertrophy	5 (1.3)
Connective tissue disease	2 (0.5)
Without Co-morbidity	58 (15.4)
Smoking Status, n (%)	
Smoker	98 (26.1)
Non-smoker	278 (73.9)
Disease Severity, n (%)	
Moderate	167 (44.4)
Severe	44 (11.7)
Critical	165 (43.9)

patients were classified as moderate, 11.7% were considered severe and 43.9% were under critical severity.

Table 2 shows the initial ventilatory support upon admission of COVID-19 confirmed cases. Only 11.7% of the total patients had no ventilatory support upon admission while 24.5% needed invasive mechanical ventilation upon admission. The rest of the patients were prescribed with non-invasive oxygen support (63.8%) wherein the most common was nasal cannula (78.8%), followed by high-flow nasal cannula (12.9%) and face mask (5.83%).

Table 3 reflects the outcomes of COVID-19 confirmed cases after using investigational products and interventions. The overall in- hospital mortality among COVID-19 confirmed patients whose severity is at least moderate is 41%, with resulting average length of stay of 14 days (±10.15). We also noted that 15.4% of patients were eventually shifted to an invasive mechanical ventilation, while 10.4% of patients were shifted to a higher form non-invasive oxygenation.

Table 2. Ventilatory support upon admission of COVID-19 confirmed cases

Ventilatory Support upon Admission	Values
None (Room Air)	44 (11.7%)
Invasive mechanical ventilation	92 (24.5%)
Non-invasive Oxygen Support	240 (63.8%)
High-flow Nasal Cannula	31 (12.9%)
Bilevel Positive Airway Pressure (BIPAP)	2 (0.8%)
Continuous Positive Airway Pressure (CPAP)	2 (0.8%)
Nasal cannula	189 (78.8%)
Face mask	14 (5.83%)
Non-rebreather mask	2 (0.8%)

Table 3. Outcomes of COVID-19 confirmed cases using investigational products and interventions

Outcomes	Values
1. In-hospital mortality	154 (41.0)
2. Morbidity	
a. Length of hospital stay	14.11 ± 10.15
b. Shift to invasive mechanical ventilation	58 (15.4)
c. Shift to higher form of non-invasive oxygenation	39 (10.4)
• Nasal cannula	8 (2.1)
• Face mask	2 (0.1)
• Non-rebreather mask	0 (0.0)
• High-flow nasal cannula	27 (7.2)
• BIPAP	2 (0.5)
• CPAP	0 (0.0)
3. Adverse drug event / Adverse drug reaction	
a. None	347 (92.3)
b. Present	29 (7.7)
• Arrhythmia	5 (1.3)
• Transaminitis	6 (1.6)
• Bleeding	5 (1.3)
• Acute kidney injury (AKI)	4 (1.1)
• Prolonged QTc interval	2 (0.5)
• Seizure	1 (0.3)
• Arrhythmia and transaminitis	3 (0.8)
• Transaminitis and AKI	1 (0.3)
• Ischemia and Prolonged QTc interval	1 (0.3)
• Allergy	1 (0.3)

Among the 39 patients who were shifted to the latter, 27 of them used high-flow nasal cannula (7.2%) while 8 started with nasal cannula (2.1%). Adverse drug events were observed to be at 7.7% and the most common reactions were transaminitis (1.6%), arrhythmia (1.3%) and bleeding (1.3%). One adverse drug reaction in the form of an allergic reaction to remdesivir was observed.

Table 4 shows a significant difference in mortality and discharge rates among patients who received the different investigational products and interventions except for those given lopinavir/ritonavir (p=0.1134) and convalescent plasma (p=0.1912). This study

Table 4. Mortality and discharge rate of COVID-19 confirmed cases using investigational products and interventions

	Death	Discharged	P-values
HCQ/Chloroquine (Chl) ± Azithromycin (A) (n=82)			
Moderate	3 (9.7)	45 (88.2)	0.0001
Severe	5 (16.1)	3 (5.9)	
Critical	23 (74.2)	3 (5.9)	
Lopinavir/Ritonavir (L/R) (n=23)			
Moderate	0 (0.0)	6 (50)	0.1134
Severe	0 (0.0)	2 (16.7)	
Critical	11 (100)	4 (33.3)	
Remdesivir (R) (n=78)			
Moderate	2 (6.7)	28 (58.3)	0.0001
Severe	1 (3.3)	12 (25.0)	
Critical	27 (90.0)	8 (16.7)	
Tocilizumab (T) (n=83)			
Moderate	1 (2.6)	18 (40.0)	0.0001
Severe	1 (2.6)	14 (13.1)	
Critical	36 (94.7)	13 (28.9)	
Steroid (S) (n=252)			
Moderate	4 (3.6)	90 (63.8)	0.0001
Severe	2 (1.8)	33 (23.4)	
Critical	105 (94.6)	18 (12.8)	
Favipiravir (F) (n=24)			
Moderate	0 (0.0)	21 (95.5)	0.0109
Severe	0 (0.0)	0 (0.0)	
Critical	2 (100)	1 (4.5)	
Interferon (IFN) (n=16)			
Moderate	0 (0.0)	1 (16.7)	0.0082
Severe	0 (0.0)	3 (50.0)	
Critical	10 (100)	2 (33.3)	
Hemoperfusion (HP) (n=105)			
Moderate	1 (1.5)	10 (26.3)	0.0001
Severe	1 (1.5)	12 (31.6)	
Critical	65 (97.0)	16 (42.1)	
Convalescent Plasma (CP) (n=17)			
Moderate	0 (0.0)	1 (20.0)	0.1912
Severe	1 (8.3)	1 (20.0)	
Critical	11 (91.7)	3 (60.0)	
Steroid + HP (n=94)			
Moderate	1 (1.6)	8 (26.7)	0.0001
Severe	1 (1.6)	11 (36.7)	
Critical	62 (96.9)	11 (36.7)	
Steroid + HP +Tocilizumab (n=31)			
Moderate	0 (0)	2 (16.7)	0.0001
Severe	0 (0)	6 (50)	
Critical	19 (100)	4 (33.3)	
Steroid + HP + Remdesivir (n=39)			
Moderate	0 (0)	5 (29.4)	0.0001
Severe	1 (4.5)	6 (35.3)	
Critical	21 (95.5)	6 (35.3)	
HCQ/Chl ± A + Tocilizumab (n=11)			
Moderate	0 (0)	2 (33.3)	-
Severe	1 (20)	1 (16.7)	
Critical	4 (80)	3 (50)	

found that most deaths occurred among patients with critical disease regardless of the kind of investigational product or intervention used.

Among investigational products or interventions used alone, the most commonly prescribed were steroid, followed by hemoperfusion and tocilizumab (Table 4). Majority of the patients who died, regardless of the kind of single investigational product or intervention used, had critical disease classification (74.2% - 100%). Furthermore, all the deaths that were recorded among those who were given lopinavir/ritonavir, favipiravir and interferon were classified under critical severity. On the other hand, the majority of the discharged patients who were classified to have critical severity received steroids (n=18), hemoperfusion (n=16) and tocilizumab (n=13). Moreover, highest rates of discharge among those classified under moderate risk received favipiravir (95.5%), hydroxychloroquine/chloroquine ± azithromycin (88%) and steroid (63.8%).

Among combination therapies, steroid + hemoperfusion was prescribed more often followed by steroid + hemoperfusion + remdesivir. Regardless of the combinations that were given, majority of the patients who died were classified under critical severity (80% - 100%). Most of the discharged patients under combination therapy with severe (n=11) to critical (n=11) severity received hemoperfusion + steroid. Furthermore, among discharged patients who were prescribed with hemoperfusion, 73.7% belong to the severe and critical classification.

In terms of clinical characteristics, age turned out to be a significant factor for mortality for those who received hydroxychloroquine/chloroquine ± azithromycin (p= 0.0128) where 67.7% of those who died are at least 60 years old and this was significantly higher than 39.2% of those who were discharged. A similar pattern was observed for those who received steroid (p=0.0085), as 58.6% of those who died belong to the older group and this was significantly higher than 41.8% of those who were discharged. In terms of gender differences, a higher discharge rate was seen among males who received remdesivir (p=0.0352) and combination steroid + hemoperfusion + remdesivir (p=0.0490). In terms of co-morbidity, mortality was more frequent among patients with hypertension who received remdesivir (p=0.0469) and patients

with chronic kidney disease given steroid alone (p=0.0401) (Supplementary Table 1).

Our results showed that regardless of the type of investigational product or intervention, mortality was more evident in patients classified under critical severity as seen in Table 5. Specifically, overall mortality was highest among patients given convalescent plasma alone (71%), steroid + hemoperfusion combination (68%) and hemoperfusion alone (64%), however most of these patients were under critical severity.

Among patients classified under critical severity, mortality rate was highest among those given hydroxychloroquine/chloroquine ± azithromycin (88%), steroid (85%), Interferon (83%), and hemoperfusion (80%). If we consider the most common combination therapies, mortality was highest among patients given steroid + hemoperfusion + tocilizumab (83%). Table 6 summarizes the COVID-19 confirmed cases that were shifted to mechanical ventilation and higher form of non-invasive oxygenation. We noted highest rate of intubation among patients given convalescent plasma (50%), hemoperfusion (42%) and Interferon (38%). In terms of combination therapy, hydroxychloroquine/chloroquine ± azithromycin + tocilizumab (55%) and steroid + hemoperfusion + tocilizumab (47%) had the highest rate of need for invasive ventilation. Invasive mechanical ventilation was not seen among those who received favipiravir. Furthermore, only 18% of patients given steroid were eventually shifted to invasive ventilation.

Table 5. Mortality rate among COVID-19 patients on different investigational products and interventions

Investigational Product or Intervention	Among patients of all severity	n	Mortality		n	%
			%	Among critical patients		
HCQ/Chl ± A	82	31	38%	26	23	88%
Lopinavir/Ritonavir	23	11	48%	15	11	73%
Remdesivir	78	30	38%	35	27	77%
Tocilizumab	83	38	46%	49	36	73%
Steroid	252	111	44%	123	105	85%
Favipiravir	24	2	8%	3	2	67%
Interferon	16	10	63%	12	10	83%
Hemoperfusion	105	67	64%	81	65	80%
Convalescent Plasma	17	12	71%	14	11	79%
Steroid + HP	94	64	68%	94	62	66%
Steroid + HP + Tocilizumab	31	19	61%	23	19	83%
Steroid + HP + Remdesivir	39	22	56%	27	21	78%
HCQ/Chl ± A + Tocilizumab	11	5	45%	7	4	57%

Table 6. COVID-19 confirmed cases shifted to mechanical ventilation and higher form of non-invasive oxygenation

Cases shifted to mechanical ventilation				Cases shifted to higher form of non-invasive oxygenation	
Investigational Product or Intervention	All severity	n	%	n	%
HCQ/Chl ± A	76	21	28%	6	7%
Lopinavir/Ritonavir	16	7	44%	3	19%
Remdesivir	63	13	21%	9	14%
Tocilizumab	53	18	34%	14	26%
Steroid	175	31	18%	29	17%
Favipiravir	24	0	0%	3	13%
Interferon	8	3	38%	2	25%
Hemoperfusion	60	25	42%	14	23%
Convalescent Plasma	10	5	50%	2	20%
Steroid + HP	94	23	24%	12	13%
Steroid + HP + Tocilizumab	15	7	47%	6	40%
Steroid + HP + Remdesivir	29	11	38%	5	17%
HCQ/Chl ± A + Tocilizumab	11	6	55%	1	9%

There were more patients who eventually needed higher form of non-invasive oxygenation among patients given tocilizumab (26%), interferon (25%) and hemoperfusion (23%). Among patients using combination regimen, steroid + hemoperfusion + tocilizumab had the highest rate of shift to a higher form of non-invasive oxygenation (40%).

The length of hospital stay among discharged COVID-19 cases is reflected in Table 7. Among discharged patients who received investigational product or intervention, those with the shortest length of hospital stay were given favipiravir (11.55 days) and steroid (14.12 days) while those with the longest hospital stay were given convalescent plasma (30.6 days) and lopinavir/ritonavir (27.83 days). In terms of combination therapies, patients with the shortest length of hospital stay were given steroid + hemoperfusion (18.43 days) while those with the longest length of hospital stay were given hydroxychloroquine/chloroquine ± azithromycin + tocilizumab (26.83 days).

The adverse drug events included transaminitis, arrhythmia, bleeding, acute kidney injury, prolonged QT interval, ischemia, and seizure (Table 8). One adverse drug reaction in the form of allergic reaction to remdesivir was observed. There were 5 patients with co-existing adverse drug events – 3 had arrhythmia and transaminitis, 1 had acute kidney injury and transaminitis, and 1 had prolonged QTc interval and myocardial ischemia. Investigational products or interventions with most adverse drug events were hydroxychloroquine/chloroquine ± azithromycin, interferon, remdesivir, and combination of steroid

Table 7. Length of hospital stay (in days) among discharged COVID-19 patients

Investigational Product or Intervention	Mean	SD	Shortest	Longest
HCQ/Chl +/- A	18.20	9.56	4.00	49.00
Lopinavir/Ritonavir	27.83	14.63	11.00	55.00
Remdesivir	17.42	8.57	5.00	48.00
Tocilizumab	21.33	11.09	11.00	55.00
Steroid	14.12	6.83	3.00	42.00
Favipiravir	11.55	3.42	6.00	19.00
Interferon	15.50	6.02	10.00	23.00
Hemoperfusion	21.74	11.51	9.00	55.00
Convalescent Plasma	30.60	10.31	16.00	41.00
Steroid + HP	18.43	7.77	9.00	42.00
Steroid + HP + Tocilizumab	21.92	9.43	13.00	42.00
Steroid + HP + Remdesivir	18.12	8.08	9.00	42.00
HCQ/Chl ± A + Tocilizumab	26.83	10.26	16.00	41.00

Table 8. Adverse drug event/adverse drug reactions among COVID-19 confirmed cases with investigational products or interventions

Adverse drug event or Adverse drug reaction	HCQ/CQ ± A (n=82)	L / R (n=23)	Favipiravir (n=24)	Remdesivir (n=78)	Steroid (n=252)	Interferon (n=16)	S + HP (n=94)	S + HP + R (n=39)	S + T (n=10)	Total (n=376)
1. Arrhythmia	3 (3.7%)	0	0	0	0	1 (6.3%)	0	1 (2.6%)	0	5 (1.3%)
2. Transaminitis	0	1 (4.3%)	1 (4.2%)	1 (1.2%)	0	3 (18.8%)	0	0	0	6 (1.6%)
3. Bleeding	0	0	0	0	0	1 (6.3%)	2 (2.1%)	2 (5.1%)	0	5 (1.3%)
4. AKI	0	0	0	2 (2.6%)	1 (0.4%)	0	0	0	1 (0.1%)	4 (1.1%)
5. Prolonged QTc interval	2 (2.4%)	0	0	0	0	0	0	0	0	2 (0.5%)
6. Seizure	1 (1.2%)	0	0	0	0	0	0	0	0	1 (0.3%)
7. Ischemia and prolonged QTc interval	1 (1.2%)	0	0	0	0	0	0	0	0	1 (0.3%)
8. Arrhythmia and transaminitis	0	1 (4.3%)	0	0	0	1 (6.3%)	1 (1.1%)	0	0	3 (0.8%)
9. Transaminitis and AKI	0	0	0	0	0	0	0	1 (2.6%)	0	1 (0.3%)
10. Allergy	0	0	0	1 (1.2%)	0	0	0	0	0	0
Total	7	2	1	4	1	6	3	4	1	0

+ hemoperfusion + remdesivir. Favipiravir use has 1 case of transaminitis.

DISCUSSION

The mortality rate among COVID-19 confirmed cases in our study is high (41%) owing to the exclusion of mild cases and that majority (43.9%) of cases were classified under critical severity. Studies show similar high mortality rates in other countries ranging 25-43%.[4,5] Many studies have shown findings of in-hospital mortality being more frequent among the older population likely due to declining immune system and already existing co-morbidities.[6] In our study, mortality was more likely among older age groups (≥60 years old) who received steroid alone (58.6%) and hydroxychloroquine/chloroquine ± azithromycin (67.7%). In terms of gender, it is hypothesized that females have stronger immune system, with one study showing a higher concentration of IgG antibody in early phase and in severe disease than men.[7] However, multifactorial factors could be considered in gender differences as well. Our study showed a higher discharge rate among males who received remdesivir (79.2%) and combination of steroid + hemoperfusion + remdesivir (82.4%). Furthermore, majority of patients in this study have pre-existing co-morbidities like hypertension (59.3%), diabetes mellitus (37.5%), and CVD (10.1%) predisposing them to increased risk of mortality. In this study, mortality was more frequent among patients with hypertension who received remdesivir and those with chronic kidney disease given steroid. The link between hypertension and CVD with COVID-19 disease among studies has been due to the theoretical effect of renin-angiotensin-aldosterone system (RAAS) inhibition of SARS-CoV-2 and interplay of various mechanisms such as inflammation, endothelial dysfunction, and direct viral damage.[8,9]

In terms of oxygen support, we have observed that 92 (24.5%) of patients required immediate invasive ventilation upon admission while 58 (15.4%) eventually required intubation after being admitted in the ward. All in all, a total of 150/376 (39.8%) subsequently needed invasive mechanical ventilation. Data regarding intubation rate from different countries are varying. In a paper published by Meng et al. last April 2020, COVID-19 intubation rate in Wuhan, China was 3.2%.[10] On the other hand, a paper published by Grasselli, et al. on April 2020 in Italy reflected an intubation rate as high as 88%.[11] Data obtained from July 2020 from France showed that 68.6% of the participants required invasive ventilation.[12]

Our study was able to demonstrate that regardless of what kind of investigational product or intervention was given to patients with a critical classification, mortality was high. Mortality was high among convalescent plasma (91.7%), steroid + hemoperfusion combination (96.9%) and hemoperfusion (97%) groups due to the fact that these therapies were given towards those patients belonging to severe and critical classification. Furthermore, it could also be implied that before the widespread availability of tocilizumab and compassionate use of remdesivir, majority of the severe to critically ill patients who were unfortunately not given other investigational products (i.e., patients under Solidarity trial enrolled to standard of care) can be readily prescribed with steroid and hemoperfusion due to its availability.

Multiple studies have already elaborated the benefits of hemoperfusion in COVID-19. In a case report that treated five critically ill patients with hemoperfusion, there was a potential positive result with hemoperfusion which saved 4 out of 5 patients and only 2 out 5 required mechanical ventilation.[13] In our study, among discharged patients who underwent hemoperfusion, 73.7% were under severe and critical classification. This suggests that even patients with severe and critical classification could still have a good chance of survival when treated with hemoperfusion.

Steroids in the form of methylprednisolone given to patients with ARDS secondary to COVID-19 showed reduction in the Alveolar-arterial (A-a) 02 gradient implying improvement in oxygen transfer from the lungs.[14] Furthermore, the RECOVERY collaboration released their preliminary data last July 2020 which also showed that among patients on non-invasive ventilation, death and need for invasive mechanical ventilation was lower in the dexamethasone group versus control.[15] It was also evident in our study that patients using steroid were less frequently shifted to mechanical ventilation (18%) and had shorter mean length of hospital stay (14.55 days).

Patients who were given favipiravir had the shortest length of hospital stay (11.55 days). Among those with moderate severity and were discharged, none needed invasive oxygenation. Ongoing clinical trial regarding favipiravir has shown significant improvement to clinical cure among mild to moderate COVID-19.[16] However further studies are still needed in order to access its overall benefit.

Transaminitis, arrhythmia, acute kidney injury and bleeding were among the most common complications of COVID-19 patients with an estimated rate of 56%, 17%, 25% and 4.8% respectively.[17-19] In our study, the most commonly reported adverse drug event was transaminitis (1.6%), and it was seen in 6 investigational products or interventions. It was observed more among patients who were given interferon-α2b. This finding was also seen in the study done by Zhou et al., wherein mild transaminitis (elevated ALT) was seen early during hospitalization among patients given interferon-α2.[20] In line with the study done by Calvacanti et al., arrhythmia and prolonged QTc interval were also observed more in patients who were given hydroxychloroquine ± azithromycin.[21] Three incidents of acute kidney injury among patients given remdesivir were recorded in our study. Acute kidney injury was also the most frequent adverse event leading to treatment discontinuation of remdesivir given via compassionate use in the study done by Antoniri et al.[22] Our study showed that bleeding events were more common among investigational products or interventions with established bleeding risk (steroid and hemoperfusion). However, the bleeding rate in our study population was only 3% which could be attributed more to the disease pathology of COVID-19 rather than the investigational product or intervention given.

Knowledge on the usual length of hospital stay of admitted patients helps health care facilities prepare allocation of resources such as bed capacity, healthcare staff and facilities. This study showed an average length of hospital stay of 14 days consistent with one systematic review by Rees et al. showing a median hospital length of stay of 14 days (ranging 10-19 days) in China and 5 days (ranging 10-19 days) outside China.[23] In this study, the day of discharge was based on the day when the patient is alive and medically ready for discharge based on criteria by WHO. During the pandemic, evolving criteria for hospitalization and discharge emerged and this made a great impact on the difference in the length of hospital stay through time. For instance, in March to May 2020, a consensus based on WHO exists requiring resolution of symptoms and evidence of two negative SARS-CoV-2 RT-PCR samples at least 24 hours apart before discharge. Following this guideline, some patients in this study were delayed in discharge due to pending repeat SARS-COV2 swab results. By May to August 2020, WHO revised this recommendation by no longer requiring a repeat negative RT-PCR and patients may be discharged if clinically recovered.[24,25]

CONCLUSION

Patients with critical severity had a high mortality regardless of what kind of investigational product or intervention was given. Favipiravir and steroid may reduce the need for invasive ventilation and length of hospitalization. Determination of adverse drug events among COVID-19 patients using investigational products was difficult due to multi-organ affectation.

Limitations and Recommendations

The primary limitation of this study was its retrospective cohort design. All data were only taken from a secondary source. Data obtained from the patients from March to August 2020 was not enough to provide statistical power due to multiple combinations of investigational products or interventions that would require a bigger sample size population. Moreover, we were not able to study the dose and frequency of products or interventions and the timing of instituting invasive mechanical ventilation and higher oxygen support. The authors recommend further research to include more patients in the analysis.

Supplementary Material

Supplementary Table 1 is available upon request from the corresponding author.

Authorship

All authors have certified fulfillment of Scientific Proceedings authorship criteria.

Disclosure of Conflicts of Interest

All authors have no conflict of interest to disclose.

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LUNG CENTER OF THE PHILIPPINES
Scientific Proceedings

Factors Affecting Pulmonary and Cardiovascular Outcomes in Adult COVID-19 Confirmed Cases Admitted at the Lung Center of the Philippines

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ABSTRACT

Background. Numerous systemic complications arise during COVID-19 infection, with most originating from the lung and heart. Certain patient characteristics were found to be associated with complicated COVID-19 course affecting the pulmonary and cardiovascular system.

Objective. This study aims to determine the socio-demographic and clinical factors and their relationship with pulmonary and cardiac complications/outcomes in adult COVID-19 confirmed cases admitted at the Lung Center of the Philippines (LCP).

Methodology. In this retrospective/cohort study, we included all moderate to critical adult inpatients (≥18 years old) with laboratory confirmed COVID-19 tests at the LCP. Demographic, clinical, treatment, and laboratory data, were extracted from patient medical records.

Results. Of the 355 patients included, most were male (n=225, 63.4%). Hypertension was the most common co-morbidity (n=202, 56.9%). The top pulmonary complications were Acute Respiratory Distress Syndrome (ARDS) (n=52, 41.9%), followed by Acute Renal Failure (ARF) (n=39, 31.5%) and HAP/VAP (n=30, 24.2%). Pulmonary complications were twice greater ($p<0.007$) in patients with eGFR levels of 30-59 cc/1.73m^2 and 15-29 cc/1.73m^2 and those with Hyperkalemia ($p=0.013$). The 3 most common cardiac complications were Acute Coronary Syndrome (ACS) (N=14, 53.8%), arrhythmia (N=6, 23%), and VTE (N=2, 7.6%). These patients were older (Mean: 64 y.o. vs. 58 y.o., $p=0.039$), diabetic (66.7% vs. 32.3%, $p=0.027$), and hypermagnesemic ($p=0.05$). Lastly, mechanical ventilation was found to be associated with cardiovascular outcomes (33.3% vs. 15.1%, $p\leq0.003$).

Conclusions. ARDS and ACS were the most common pulmonary and cardiovascular outcomes, respectively. Factors that were significantly increased in patients with adverse pulmonary outcomes were age, male gender, hypertension, hyperkalemia, and lower eGFR levels. Cardiovascular outcomes were noted to be significantly increased in older patients, diabetics, ARB/ACEI, bronchodilator, leukocytosis, hyper magnesia, high neutrophil to lymphocyte count, LVH on ECG, low EF and segmental wall-motion abnormality on echocardiography and mechanical ventilation.

Keywords: COVID-19, SARS-CoV-2, respiratory distress syndrome, acute coronary syndrome, pneumonia

This study won 2nd Place at the Lung Center of the Philippines Annual Research Contest 2021 and was a finalist during the 1st National Hospital Week Research Forum 2021.

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INTRODUCTION

During the last month of 2019, a cluster of patients with pneumonia of then unknown origin were reported in Wuhan, Hubei Province, China.[1] Subsequently, through the use of next-generation sequencing of isolates, complete and partial sequence of the RNA genome of the 2019 novel coronavirus (2019-nCoV) was identified.[2] Since its introduction, the virus has spread to other countries and has been declared by the World Health Organization (WHO) as a public health emergency of international concern last February 6, 2020.[3]

The first announcement of a cluster of patients from Hubei with an unknown type of pneumonia occurred last December 2019. A number of these patients were described to have radiographic ground-glass appearance, normal or lower than average white blood cell and platelets, hypoxemia, and complications from both the liver and kidney.[1] Later that month, the Chinese Center for Disease Control and Prevention (China CDC) sent a team to conduct etiologic and epidemiological investigations. Bronchoalveolar lavage samples were collected from patients which yielded the presence of a yet unknown and novel coronavirus (2019-nCoV).[4] A later study confirmed that the 2019-nCoV was adequately different from SARS-CoV to be considered a new human infecting betacoronavirus with possible ACE2 binding tropism.[2]

Though initially thought to be zoonotic, evidence coming from infected clusters of family members and affected medical workers confirmed that the virus was capable of human-to-human transmission.[1] In fact, efficient person to person transmission was noted to be occurring.[5] Forebodingly, on January 14, 2020, the first officially confirmed case of 2019-nCoV outside of China was identified in Thailand.[6] Last Jan 30, 2020, the first confirmed case of 2019-nCoV infection was reported in the United States from a man who travelled from Wuhan, China.[7] From thereon, the virus has been identified in 188 countries and regions in all the 5 continents.[8]

Based on the WHO classification of territories, the Philippines had the 3rd highest number of total confirmed cases (33,069 cases) in the Western Pacific region as of June 16, 2020, coming after China and Singapore, but ahead of Japan, Korea, Malaysia, and others.[9]

Using local data as of Jun 26, 2020 from the Department of Health (DOH), the country had 34,073 total cases, 23,667 active cases, 1,224 deaths of confirmed cases, and 9,182 recovered patients, with most of the confirmed and active cases in the Philippines for both sexes were in the 30-34 age range and deaths at the 60-64 age range.[10]

Clinical Characteristics and Laboratory Examinations of COVID-19 patients

2019-nCoV had a preference for both respiratory and cardiovascular systems although other systems were also involved in the disease process.[11–20] The most common clinical manifestations of COVID-19 included fever (88.7%), cough (67.8%), fatigue (38.1%), sputum production (33.7%), shortness of breath (18.7%), sore throat (13.9%), and headache (13.6%).[15] The most common complications of infection included sepsis, Acute Respiratory Distress Syndrome (ARDS), anemia, acute cardiac injury, acute kidney injury, secondary infection, shock and arrhythmia.[1,15–20] Although less common, neurological, gastrointestinal, and dermatological disorders have also been identified.[11–14]

Several studies have already been published regarding risk factors of COVID-19 as well as its course and outcome. Patients from Jinyintan Hospital and from Wuhan Pulmonary Hospital showed that 48% of patients had co-morbidities with hypertension as the most common (N=58 [30%]), then diabetes, (N=36 [19%]), and lastly coronary heart disease (CAD) at (N=15 [8%]).[17]

In a cohort of 41 patients with identified 2019-NCoV in Wuhan, 12 (29.2%) required Intensive Care Unit (ICU) care, while 28 (68.2%) of patients did not. Those admitted to ICU patients were noted to have higher plasma levels of IL2, IL7, IL10, GSCF, IP10, MCP1, MIP1A, and TNF-α.[18] A study of the clinical features of fatal cases of COVID-19 showed that the median age of patients was 65.8 years of which 72.9% were male.[19] Hypertension, diabetes, and CAD were the most common co-morbidities, with notably 81.2% of patients having very low levels of eosinophil counts at the time of admission.[19] Older age also showed increasing odds of in-hospital death

per year increase, as well as higher Sequential Organ Failure Assessment (SOFA) score, and D-Dimer levels greater than 1 µg/ml on admission.[17]

Pulmonary Outcomes

ARDS, defined according to the Berlin Definition (A patient who has PF ratio <300, chest radiograph findings of bilateral infiltrates, without LV dysfunction) was frequently the most common pulmonary complication of COVID-19.[15,21] In a study involving 109 COVID-19 patients in China, 48.6% progressed to ARDS. These patients with ARDS were noted to be older (mean age 61 vs. 49 years), more likely to suffer from co-morbidities (20.8% vs. 1.8%), and a significantly higher mortality rate (49.1% vs. 8.9%).[22]

Ventilator-associated pneumonia (VAP) was one of the more commonly reported complication in COVID-19 patients.[16,23] VAP occurs due to the interference of the endotracheal tube with mucociliary clearance allowing the formation of biofilms on the inner and outer surfaces of the tracheal cannula. The most common Gram-negative microorganisms identified in VAP are *Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa,* and *Acinetobacter baumannii and Staphylococcus aureus* was the main reported Gram-positive microorganism.[24]

Cardiovascular Outcomes

Cardiac complications including acute cardiac injury and heart failure were identified in admitted COVID-19 patients in China, present in 17% and 23% of patients respectively.[17] In another study, acute cardiac injury was noted to be the most common cardiac compli-cation (12% of patients).[24] Arrhythmia were also noted to be prevalent in COVID-19 patients transferred to the ICU (44.4%).[25] Cardiac complications were also common among fatal cases of COVID-19 (Arrhythmia=60%, Acute Cardiac Injury=44.7%).[19]

OBJECTIVES

While much of the attention has been on the pulmo nary problems, we should be aware of the cardio-vascular complications, which can contribute significantly to the disease's mortality. This brief study will offer a concentrated summary of COVID-19-related cardio-vascular and pulmonary outcomes.

Our study aims to identify factors and their relationship with pulmonary and cardiac complications/outcomes in adult COVID-19 confirmed cases at the Lung Center of the Philippines (LCP). In particular, the clinical characteristics, laboratory parameters, pulmonary and cardiac complications/outcomes, and their relationships will be investigated.

METHODOLOGY

Study Design and Site

This was a retrospective cohort study conducted at the LCP, a 210-bed capacity specialty center for lung diseases. It was designated as one of three COVID-19 referral centers by the DOH and has allotted 81 beds to accommodate moderate to critical cases of COVID-19.

Study Population

The subjects included COVID-19 confirmed adult inpatients (≥18 years old) admitted at the LCP. All adult patients who were diagnosed with COVID-19 according to the WHO interim guidance were screened, and those who died or were discharged were included in our study. Patients who had mild symptoms and did not fulfill the criteria for hospital admission were excluded.

Sample Size and Sampling Design

A minimum of 349 confirmed COVID-19 patients satisfying the inclusion/exclusion criteria were required to have an 80% chance of determining, as significant at the 5% level, the association of clinical factors to occurrence of pulmonary and cardio-vascular outcomes in patients. The minimum sample size was computed using the power sample computation for goodness of fit test.[26] An associated effect size was estimated at 0.15 based on results of various studies.[22,25]

Study Procedure

Data from the medical records were retrieved to identify COVID-19 confirmed adult patients (aged 18 years old and above) admitted at the LCP (Figure 1). The demographic, clinical, laboratory, and outcomes measures were collected from the patients' hospital charts and from the LCP electronic database, Bizbox (Tables 1 to 6).

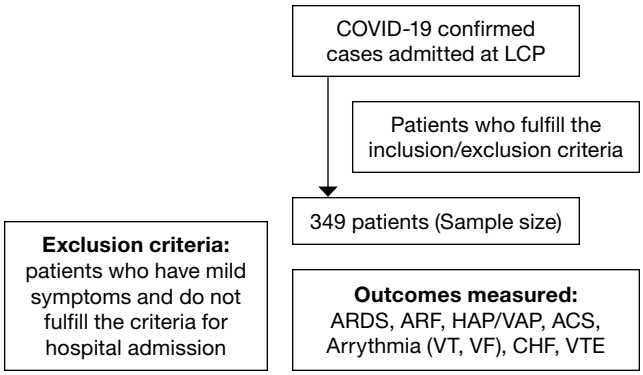

Figure 1. Study flowchart.

Outcome Measures

Both the pulmonary as well as cardiovascular outcomes were measured in this study. Pulmonary outcomes included ARDS, which was defined by the Berlin definition; acute respiratory failure (patient who needed the use of mechanical ventilation and High Flow Nasal Cannula [HFNC], paO_2<55 mmHg, pCO_2>50, pH<7.3 by Arterial Blood Gas (ABG), Hospital Acquired Pneumonia (pneumonia contracted by a patient in a hospital at least 48–72 hours after being admitted, documented by new infiltrates/progression of infiltrates by chest x-ray), and Ventilator Associated Pneumonia (pneumonia contracted by an intubated patient for at least 48 to 72 hrs. after being admitted, documented by new infiltrates/progression of infiltrates by chest x-ray). Cardiovascular outcomes included troponin levels, cardiac physical examination findings, arrhythmia/ECG results and echocardiography findings.

Table 1. Clinical profile of COVID-19 patients admitted at LCP

Factors	Total N=355	Moderate n=218 (61.4%)	Severe n=63 (17.7%)	Critical n=74 (20.8)	P-value
		Frequency (%)			
Age (mean±SD)	58.28	55.93 (15.37)	60.75 (11.32)	63.12 (12.45)	<0.001
18-40 yrs old	45	39 (17.9%)	23 (3.2%)	4 (5.4%)	0.003
41-60 yrs old	144	89 (40.8%)	31 (49.2%)	24 (32.4%)	
61-80 yrs old	148	81 (37.2%)	27 (42.9%)	40 (54.1%)	
>80 yrs old	18	9 (4.1%)	3 (4.8%)	18 (24.3%)	
Gender					
Male	225	128 (58.3%)	48 (76.2%)	50 (67.6%)	0.029
Female	129	90 (41.3%)	15 (23.8%)	24 (32.4%)	
Estimated BMI	23.68	23.56 (4.75)	22.97 (2.89)	24.59 (5.91)	0.796
Underweight <18.5	28	0%	0%	0%	0.454
Normal 18.5-<25	4	17 (89.5%)	5 (71.4%)	6 (31.6%)	
Overweight >25-30	2	1 (5.3%)	2 (28.6%)	1 (11.1%)	
Obese >30		1 (5.3%)	0 (0%)	1 (11.1%)	
Smoking history					
Smoker	95/346	46 (21.5%)	23 (37.7%)	26 (36.6%)	0.409
Non-Smoker	251/346	168 (78.5%)	38 (62.3%)	45 (63.4%)	
Baseline co-morbidities					
Hypertension	202	108 (49.5%)	47 (74.6%)	47 (63.5%)	0.001
Diabetes mellitus type 2	123	80 (36.7%)	20 (31.7%)	23 (31.1%)	0.590
Chronic kidney disease	24	14 (6.4%)	4 (6.3%)	6 (8.1%)	0.874
Chronic Obstructive Pulmonary Disease (COPD)	10	5 (2.3%)	2 (3.2%)	3 (4.1%)	0.718
Asthma	28	21 (9.6%)	3 (4.8%)	4 (5.4%)	0.303
History of Coronary artery disease (CAD)	30	19 (8.7%)	4 (6.3%)	7 (9.5%)	0.788
History of Cerebrovascular disease (CVD)	11	4 (1.8%)	2 (3.2%)	5 (6.8%)	0.108
Chronic Liver Disease	0	0 (0%)	0 (0%)	0 (0%)	-
Malignancy	14	9 (4.1%)	4 (6.3%)	1 (1.4%)	0.317
Connective Tissue disease	1	1 (0.5%)	0 (0%)	0 (0%)	0.730
Pulmonary tuberculosis (PTB) – active or with history of PTB	17	12 (8.3%)	5 (7.9%)	0 (0%)	0.004
HIV/AIDS	1	1 (0.5%)	0 (0%)	0 (0%)	0.730
Initial vital signs					
Systolic Pressure	129.27	126.96 (17.69)	129.08 (19.11)	136.23 (22.38)	0.002
Diastolic Pressure	78.49	78.11 (10.96	78.40 (13.68)	79.69(13.94)	0.627
Mean Arterial Pressure (MAP)	95.42	94.40 (11.46)	95.29 (13.23)	98.54 (15.16)	0.052
Heart Rate	99.11	96.01 (15.19)	98.14 (18.21)	109.07 (16.42)	<0.001
Temperature	36.57	36.72 (0.71)	36.44 (0.49)	36.27 (4.36)	0.236
SpO_2	89.41	94.01 (5.89)	86.49 (12.30)	78.32 (16.27)	<0.001

Statistical Analysis

Descriptive analysis of the demographics, clinical, laboratory, outcomes of the COVID-19 adult patients in LCP was done. Continuous variables were described using mean, standard deviation and range. Categorical variables were described using frequency and percentage. Relationship of the factors with outcomes were determined using Chi-square test for categorical variables (such as the gender, clinical characteristics, baseline co-morbidities) and independent t-test for continuous variables (age, actual laboratory results, ABG). A p-value of less than 0.05 was considered statistically significant. Tables or graphs were utilized to represent data collected during the study.

Table 2. Baseline ancillary parameters of COVID-19 patients admitted at LCP

Factors	Frequency (%) N=355
Complete Blood Count	
Leukocytosis (WBC >10.0)	121 (34.1%)
Leukopenia (WBC <4.5)	37 (10.4%)
Neutrophil to Lymphocyte Ratio (mean±SD)	8.25 (10.12)
Anemia (Hgb <10.0)	34 (9.6%)
Thrombocytopenia (Plt <150,000)	25 (7.1%)
eGFR (mean±SD)	67.28 (32.71)
eGFR >90/1.73m^2	87 (27.2%)
eGFR 60-89cc/1.73m^2	116 (36.6%)
eGFR 30-59cc/1.73m^2	70 (21.9%)
eGFR 15-29cc/1.73m^2	20 (6.3%)
eGFR <15cc/1.73m^2	27 (8.4%)
Troponin I	1.95 (26.47)
Serum Electrolytes	
Sodium	
Normal	119 (33.7%)
Elevated	5 (1.4%)
Decreased	228 (64.6%)
Potassium	
Normal	251 (71.7%)
Elevated	27 (7.6%)
Decreased	75 (21.2%)
Calcium	
Normal	209 (63.9%)
Elevated	5 (1.5%)
Decreased	113 (34.6%)
Magnesium	
Normal	247 (74.4%)
Elevated	21 (6.3%)
Decreased	64 (19.3%)
12-Lead Electrocardiogram (ECG)	
Ischemic changes	88 (24.8%)
Left ventricular hypertrophy (LVH)	18 (5.1%)
Prolonged QT interval on admission	11 (3.1%)
Corrected QT interval on admission	13 (3.7%)
2D-Echocardiogram	155 (43.7%)
Ejection fraction (by M Mode) (mean±SD)	61.83 (12.06)
Dilated chamber	43 (28.1%)
Significant Valvular Heart disease	9 (5.9%)
Segmental wall motion abnormality	22 (14.3%)
Right ventricular (RV) dilatation	14 (9.2%)
Right atrial (RA) dilatation	17 (11.1%)

Ethical Considerations

This study was approved by the LCP Technical Review Board and Institutional Ethics and Review Board. Compliance with the retrospective chart review ethical considerations of the National Ethical Guidelines for Health and Health Related Research 2017 was also ensured.

RESULTS

A total of 355 patients were included in the study. Table 1 shows the baseline characteristics of the patients. The median age was 58.28 (IQR 46・0–67・0), ranging from 18 years to 95 years. Patients who were classified under moderate and severe were mostly in the 41-60 years old (78% and 92.1% respectively) age bracket, while critical patients were mostly in the 61 to 80 age range (54.1%). Most patients were classified as moderate risk (N=218, 60.4%), followed by critical (N=74, 20.4%), and lastly severe (N=63, 17.7%). Patients older than 80 y.o. were found to be significantly higher in number in critical severity as compared to moderate and severe cases (24.3% vs 4.1% and 4.8%; P=0.003). The mean age of patients was also found to increase as the severity of COVID-19 infection increased (Mean Age: moderate=55.93, severe=60.75, critical=63.12). More than half of all patients regardless of disease severity were male (N=225, 63.4%). The proportion of male patients in severe cases (76.2%) was significantly higher compared to moderate and critical cases (58.3% and 67.6%, p=0.029). Regardless of disease severity, majority of patients were non-smokers. Hypertension was the most common baseline co-morbidity, with significantly higher proportions noted for severe and critical cases compared to moderate cases (74.6% and 63.5% vs. 49.5%, p=0.001). History of active PTB was noted to be higher in patients classified as moderate. More severe patients had significantly higher mean systolic pressure (critical 136.23, severe 129.08, and moderate 126.96; p=0.002). The same trend was observed for heart rate (96.01, 98.14, and 109.07; p=<0.001). The opposite trend however was seen for SpO_2 (94.01%, 86.49%, and 78.32%; p≤0.001).

Table 3. Distribution of parameters across pulmonary outcomes

Factors	N=355 No./Mean	ARF (n=39)	ARDS (n=52)	HAP/VAP (n=30)	Others (n=3)
		Frequency (%)			
Age (mean±SD)	63.25	61.77 (13.55)	65.06 (12.60)	62.80 (14.79)	52.33 (5.13)
18-40 yrs old	7	3 (7.7%)	2 (3.8%)	2 (6.7%)	0 (0%)
41-60 yrs old	44	16 (41.0%)	15 (28.8%)	10 (33.3%)	3 (100%)
61-80 yrs old	63	18 (46.2%)	30 (57.7%)	15 (50%)	0 (0%)
>80 yrs old	10	2 (5.11%)	5 (9.6%)	3 (10%)	0 (0%)
Gender					
Male	81	25 (64.1%)	36 (69.2%)	19 (63.3%)	1 (33.3%)
Female	43	14 (35.9%)	16 (30.8%)	11 (36.7%	2 (66.67%)
Estimated BMI	22.48	22.83 (1.55)	22.59 (2.22)	22.04 (1.54)	-
Underweight <18.5		-	-	-	-
Normal 18.5-<25	16	4 (100%)	7 (87.5%)	5 (100%)	-
Overweight >25-30	1	0 (0%)	1 (12.5)	0 (0%)	-
Obese >30	0	0 (0%)	0 (0%)	0 (0%)	-
Co-morbidities					
Hypertension	83	25 (64.1%)	38 (73.1%)	20 (66.67%)	0 (0%)
DM type 2	47	12 (30.8%)	23 (44.2%)	10 (33.3%)	2 (66.7%)
Chronic kidney disease	11	4 (10.3%)	3 (5.8%)	4 (13.3%)	0 (0%)
COPD	2	0 (0%)	2 (3.8%)	0 (0%)	0 (0%)
Asthma	10	4 (10.3%)	3 (5.8%)	3 (100%)	0 (0%)
History of CAD	13	2 (5.1%)	6 (11.5%)	5 (16.7%)	0 (0%)
History of CVD	4	1 (2.6%)	1 (1.9%)	2 (6.7%)	0 (0%)
Chronic Liver Disease		-	-	-	-
Malignancy	7	3 (7.7%)	2 (3.8%)	2 (6.7%)	0 (0%)
Connective Tissue disease	0	0 (0%)	0 (0%)	0 (0%)	0 (0%)
PTB (history of PTB or if active)	11	8 (20.6%)	1 (1.9%)	1 (3.3%)	1 (33.3%)
HIV/AIDS	0	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Pack Years	24.54	30.75 (12.01)	26.64 (18.19)	19.00 (14.47)	11.00 (12.73)
Smoking history					
Smoker	7	11.8 (28.9%)	16.0 (30.8%)	9.9 (31.0%)	1 (33.3%)
Non-smoker	17	27.8 (71.1%)	34.0 (68.0%)	20.9 (69.0%)	2 (67.7%)
Initial vital signs					
Systolic Pressure	136.39	136.41 (18.67)	137.02 (20.44)	136.17 (21.71)	127.33 (25.33)
Diastolic Pressure	78.76	79.69 (10.81)	79.69 (13.02)	76.23 (13.33)	76.00 (5.29)
MAP	97.97	98.60 (11.88)	98.80 (13.44)	96.21 (15.07)	93.11 (11.93)
Heart Rate	105.67	104.33 (16.23)	106.42 (18.08)	106.10 (20.05)	105.67 (6.66)
Temperature	36.61	36.62 (0.80)	36.63 (0.81)	36.54 (0.79)	36.77 (0.49)
Spo_2	85.78	86.90 (12.66)	83.38 (16.02)	87.47 (15.66)	96.00 (1.00)
Use of Medications					
Verapamil	0	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Amiodarone	5	1 (2.6%)	3 (5.8%)	1 (3.3%)	0 (0%)
ACE/ARB	33	8 (20.5%)	17 (32.7%)	7 (23.3%)	1 (33.3%)
Beta Blocker	33	9 (23.1%)	14 (26.9%)	9 (30.0%)	1 (33.3%)
Bronchodilator	28	7 (17.9%)	13 (25.0%)	7 (23.3%)	1 (33.3%)
PTB medications	6	2 (5.1%)	1 (1.9%)	1 (3.3%)	2 (66.7%)
CBC					
Leukocytosis (WBC >10.0)	61	20 9 (51.3%)	27 (51.9%)	14 (46.7%)	0 (0%)
Leukopenia (WBC <4.5)	7	1 (2.6%)	4 (7.7%)	2 (6.7%)	0 (0%)
Neutrophil to Lymphocyte Ratio	10.65	9.00 (7.49)	12.42 (16.67)	10.37 (9.59)	4.29 (3.44)
Anemia (Hgb <10.0)	4	4 (10.3%)	0 (0%)	0 (0%)	0 (0%)
Thrombocytopenia (Plt <150,000)	11	3 (7.7%)	5 (9.6%)	3 (10.0%)	0 (0%)
eGFR (mean±SD)		57.36 (32.40)	52.35 (24.90)	54.46 (36.74)	71.00 (55.57)
eGFR >90cc/1.73m^2	18	6 (16.2%)	5 (10.2%)	5 (20.0%)	2 (66.67%)
eGFR 60-89cc/1.73m^2	33	10 (27.0%)	15 (30.6%	8 (32.0%)	0 (0%)
eGFR 30-59cc/1.73m^2	36	14 (37.8%)	19 (38.8%)	3 (12.0%)	0 (0%)
eGFR 15-29cc/1.73m^2	25	4 (10.8%)	17 (14.3%)	4 (16.0%)	0 (0%)
eGFR <15cc/1.73m^2	12	3 (8.1%)	3 (6.1%)	5 (20.0%)	1 (33.3%)
Troponin I	0.54	0.60 (1.98)	0.51 (1.74)	0.57 (2.12)	0.01 (0.01)

Table 3. Distribution of parameters across pulmonary outcomes *(continued)*

Factors	N=355 No./Mean	ARF (n=39)	ARDS (n=52)	HAP/VAP (n=30)	Others (n=3)
		Frequency (%)			
Serum Electrolytes					
Sodium					
Hyponatremia	81	26 (66.7%)	33 (63.55)	21 (70%)	1 (33.3%)
Normal	37	11 (28.2%)	16 (30.85)	8 (26.7%)	2 (66.7%)
Hypernatremia	6	2 (5.1%)	3 (5.85)	1 (3.3)	0 (0%)
Potassium					
Hypokalemia	15	1 39 (0.3%)	5 (9.6%)	8 (26.7%)	1 (33.3%)
Normal	96	34 (87.2%)	42 (80.8%)	19 (63.3%)	1 (33.3%)
Hyperkalemia	13	4 (10.3%)	5 (9.6%)	3 (10.0%)	1 (33.3%)
Calcium					
Hypocalcemia	42	16 (43.2%)	17 (34.7%)	8 (28.6%)	1 (33.3%)
Normal	75	21 (56.8%)	32 (65.3%)	20 (71.4%)	2 (66.7%)
Hypercalcemia	0	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Magnesium					
Hypomagnesemia	12	1 (2.6%)	5 (9.8%)	4 (13.8%)	2 (66.7%)
Normal	94	27 (73.0%)	44 (86.3%)	22 (75.9%)	1 (33.3%)
Hypermagnesemia	9	4 (10.3%)	2 (3.9%)	3 (10.3%)	0 (0%)
12-Lead ECG					
Ischemic changes	22	14 (35.9%)	17 (32.7%)	8 (26.7%)	0 (0%)
LVH	9	1 (2.6%)	7 (13.5%)	1 (3.3%)	0 (0%)
Prolonged QT interval on admission	1	0 (0%)	1 (1.9%)	0 (0%)	0 (0%)
Corrected QT interval on admission	5	1 (2.6%)	3 (5.8%)	1 (3.4%)	0 (0%)
2D-Echo	80	22 (56.4%)	31 (59.6%)	25 (83.3%)	2 (66.7%)
Ejection fraction (by M Mode) (mean±SD)	62.88	62.41 (9.41)	61.87 (9.18)	63.96 (9.59)	75.50 (3.54)
Dilated chamber	12	0 (0%)	7 (22.6%)	4 (16.0%)	1 (50%)
Significant Valvular Heart disease	6	2 (9.5%)	2 (6.5%)	2 (8.0%)	0 (0%)
Segmental wall motion abnormality	8	5 (22.7%)	0 (0%)	3 (12.0%)	0 (0%)
RV dilatation	7	4 (18.2%)	2 (6.5%)	1 (4.0%)	0 (0%)
RA dilatation	10	3 (13.6%)	4 (12.9%)	2 (8.0%)	1 (50%)
Mechanically Ventilated					
Upon admission	48	13 (33.3%)	22 (42.3%)	13 (43.3%)	0 (0%)
Shifted in ward	46	15 (38.5%)	24 (46.2%)	7 (23.3%)	0 (0%)
With Oxygen Support					
High Flow Nasal Cannula	17	6 (22.2%)	6 (21.4%)	5 (29.4%)	0 (0%)
BIPAP	0	0 (0%)	0 (0%)	0 (0%)	0 (0%)
CPAP	0	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Nasal Cannula	42	17 (63.0%)	15 (53.6%)	9 (52.9%)	1 (50.0%)
Face Mask	5	0 (0%)	4 (14.3%)	1 (5.9%	0 (0%)
NRM	5	2 (7.4%)	3 (10.7%)	0 (0%)	0 (0%)

Table 2 shows the laboratory characteristics of included patients. 158 (44.6%) of the total number of patients (N=355) showed derangement in their WBC count with 121 (34.1%) showing elevated WBC count and 37 (10.4%) showing leukopenia. Most patients have normal WBC (55.4%), with a median Neutrophil to Lymphocyte ratio (NLR) of 8.25, normal hemoglobin levels (89.8%) and platelet count (92.6%). Most patients (N=116, 36.6%) have eGFR levels of 60-89cc/1.73m^2. Most patients were noted to have hyponatremia (N=228, 64.6%) and with normal potassium, calcium and magnesium levels. ECG results showed that 88 (24.8%) had ischemic changes, 18 (5.1%) had left ventricular hypertrophy, and only 11 (3.1%) has prolonged QT interval on admission. 2d Echocardiography results showed a median ejection fraction of 61.83% by M mode, 43 (28.1%) of these patients had dilated chamber, 9 (5.9%) had significant valvular heart disease, 22 (14.3%) had segmental wall motion abnormality, 14 (9.2%) had RV dilatation and 17 (11.1%) had RA dilatation.

Table 3 shows characteristics of patients with pulmonary outcomes. A total of 124 (34.9%) of patients were identified to have pulmonary outcomes. The most common pulmonary complication among these was ARDS (N=52, 41.9%), followed by ARF (N=39, 31.5%), HAP/VAP (N=30, 24.2%), and then others (N=3, 2.4%). The median age for patients with pulmonary outcomes was 63.25 years with most of these patients being male (N=81, 65%). Hypertension was the most common baseline co-morbidity (N=83,

66.9%) followed by diabetes mellitus (N=47, 37.9%). Patients who have pulmonary outcomes have normal BMI. MAP in these patients were normal with ranges from 93-98. Most patients were tachycardic (median HR=105) and hypoxemic (mean SpO_2=85%). Most of these patients were on ACE inhibitors, ARB's, and beta blockers prior to admission. Most patients with pulmonary outcomes have an eGFR 60-89cc/1.73m^2 (N=36, 26.8%) and hyponatremic. 31% of these patients were mechanically ventilated upon admission and 30% were intubated at the wards.

Table 4 shows patients with cardiovascular outcomes. A total of 26 (7.3%) patients were identified to have cardiovascular outcomes. Most of these patients had Acute Coronary Syndrome (ACS) (N=14, 53.8%), arrhythmia (N=6, 23%), venous thromboembolism (N=2, 7.6%) and (N=4, 15%) had sudden bradycardia. Most patients were male (N=19, 73%) with diabetes mellitus (40%) and hypertension (37%) as their baseline co-morbidities. Patients who had ACS were also identified to have a high likelihood of having diabetes (78.86%). Patients with cardiovascular outcomes had the following levels (mean: SBP=136, DBP=81, MAP=99.3, HR=105, temperature=36.8, and SpO_2=82.8%). Most of these patients had positive baseline Troponin I (range=0.04-2.65) and were taking ACEI/ARB (26%), and beta blockers (16%). Most patients had abnormal ECG findings (N=23, 88.5%). Of these patients, the majority had ischemic changes (N=18, 69%) and LVH (N=5, 19%). Patients with abnormal echocardiography findings showed a mean ejection fraction of 50.06%, with most of these patients having dilated chambers (N=9, 34%) and with RA dilatation (N=3, 11.5%) and RV dilatation (N=2, 7.6%).

Table 4. Distribution of parameters across cardiovascular outcomes

Factors	N=355 No./Mean	Arrythmia (n=6)	ACS/MI (n=14)	VTE (n=2)	Others (n=4)
		Frequency (%)			
Age (mean±SD)	64.0	62.33 (16.17)	66.86 (12.61)	54.50 (2.12)	61.0 (21.65)
18-40 yrs old	1	0 (0%)	0 (0%)	0 (0%)	1 (25.0%)
41-60 yrs old	9	3 (50.0%)	4 (28.6%)	2 (100%)	0 (0%)
61-80 yrs old	10	2 (33.3%)	8 (57.1%)	0 (0%)	3 (75.0%)
>80 yrs old	3	1 (16.6%)	2 (14.3%)	0 (0%)	0 (0%)
Gender					
Male	19	4 (66.7%)	12 (85.7%)	1 (50.0%)	2 (50.0%)
Female	7	2 (33.3%)	2 (14.3%)	1 (50.0%)	2 (50.0%)
Estimated BMI	21.3	-	22.52 (2.57)	-	20.70 (-)
Underweight <18.5	1	-	-	-	1 (100%)
Normal 18.5-<25	2	-	2 (100%)	-	-
Overweight >25-30	0	-	0 (0%)	-	-
Obese >30	0	-	0 (0%)	-	-
Co-morbidities					
Hypertension	17	4 (66.7%)	8 (57.1%)	2 (100%)	3 (75.0%)
DM type 2	18	3 (50.0%)	11 (78.6%)	0 (0%)	4 (100%)
Chronic kidney disease	2	0 (0%)	2 (14.3%)	0 (0%)	0 (0%)
COPD	0	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Asthma	2	0 (0%)	0 (0%)	1 (50.0%)	1 (25.0%)
History of CAD	3	0 (0%)	2 (14.3%)	0 (0%)	1 (25.0%)
History of CVD	1	1 (16.7%)	0 (0%)	0 (0%)	0 (0%)
Chronic Liver Disease		-	-	-	-
Malignancy	0	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Connective Tissue disease	0	0 (0%)	0 (0%)	0 (0%)	0 (0%)
PTB (history of PTB or if active)	2	1 (16.7%)	1 (7.1%)	0 (0%)	0 (0%)
HIV/AIDS	0	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Smoking history					
Smoker	7	4 (66.7%)	3.2 (25.0%)	0 (0%)	0 (0%)
Non-smoker	17	2 (33.3%)	9.2 (75.0%)	2 (100.0%)	4 (100.0%)
Initial vital signs					
Systolic Pressure	136.0	142.67 (23.31)	134.79 (26.44)	124.00 (5.66)	136.00 (33.03)
Diastolic Pressure	81	84.50 (8.94)	78.00 (15.30)	85.00 (7.07)	84.25 (17.10)
MAP	99.3	103.89 (12.22)	96.93 (17.70)	98.00 (6.60)	101.50 (22.18)
Heart Rate	105.0	108.17 (15.61)	102.36 (21.76)	111.00 (4.24)	106.25 (21.58)
Temperature	36.8	37.00 (0.79)	36.75 (0.79)	36.25 (0.35)	37.13 (1.08)
Spo_2	82.8	82.83 (14.58)	84.36 (11.41)	75.00 (21.21)	81.00 (12.57)

Table 4. Distribution of parameters across cardiovascular outcomes *(continued)*

Factors	N=355 No./Mean	Arrythmia (n=6)	ACS/MI (n=14)	VTE (n=2)	Others (n=4)
		Frequency (%)			
Use of Medications					
Verapamil	0	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Amiodarone	0	0 (0%)	0 (0%)	0 (0%)	0 (0%)
ACE/ARB	13	3 (50.0%)	7 (50.0%)	1 (50.0%)	2 (50.0%)
Beta Blocker	8	0 (0%)	5 (35.7%)	0 (0%)	3 (75.0%)
Bronchodilator	1	1 (16.7%)	0 (0%)	0 (0%)	0 (0%)
PTB medications	0	0 (0%)	0 (0%)	0 (0%)	0 (0%)
CBC					
Leukocytosis (WBC >10.0)	13	4 (66.7%)	6 (42.9%)	2 (100%)	1 (25.0%)
Leukopenia (WBC <4.5)	0	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Neutrophil to Lymphocyte Ratio	12.5	23.25 (31.02)	8.98 (7.79)	11.66 (8.11)	9.39 (5.85)
Anemia (Hgb <10.0)	2	0 (0%)	1 (7.1%)	0 (0%)	1 (25.0%)
Thrombocytopenia (Plt <150,000)	0	0 (0%)	0 (0%)	0 (0%)	0 (0%)
eGFR (mean±SD)	57.1	49.50 (36.05)	52.28 (7.79)	44.50 (19.09)	88.50 (28.10)
eGFR >90cc/1.73m^2	2	1 (20.0%)	0 3 (0%)	0 (0%)	1 (25.0%)
eGFR 60-89cc/1.73m^2	10	0 (0%)	7 3 (53.8%)	0 (0%)	3 (75.0%)
eGFR 30-59cc/1.73m^2	7	2 (40.0%)	3 3 (23.1%)	2 (100%)	0 (0%)
eGFR 15-29cc/1.73m^2	4	2 (40.0%)	2 3 (15.4%)	0 (0%)	0 (0%)
eGFR <15cc/1.73m^2	1	0 (0%)	1 3 (7.7%)	0 (0%)	0 (0%)
Troponin I	1.45	2.65 (4.71)	1.52 (3.08)	0.19 (0.26)	0.04 (0.03)
Serum Electrolytes					
Sodium					
Hyponatremia	18	2 (33.3%)	11 (78.6%)	2 (100%)	3 (75.0%)
Normal	7	4 (66.7%)	2 (14.3%)	0 (0%)	1 (25.0%)
Hypernatremia	1	0 (0%)	1 (7.1%)	0 (0%)	0 (0%)
Potassium					
Hypokalemia	2	0 (0%)	1 (7.1%)	0 (0%)	1 (25.0%)
Normal	21	4 (66.7%)	13 (92.9%)	1 (50.0%)	3 (75.0%)
Hyperkalemia	3	2 (33.3%)	00 (0%)	1 (50.0%)	0 (0%)
Calcium					
Hypocalcemia	6	3 (50.0%)	3 (21.4%)	0 (0%)	0 (0%)
Normal	20	3 (50.0%)	11 (78.6%)	2 (100%)	4 (100%)
Hypercalcemia	0	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Magnesium					
Hypomagnesemia	3	0 (0%)	2 (14.3%)	0 (0%)	1 (25.0%)
Normal	18	4 (66.7%)	9 (64.3%)	2 (100%)	3 (75.0%)
Hypermagnesemia	4	2 (33.3%)	2 (14.3%)	0 (0%)	0 (0%)
12-Lead ECG					
Ischemic changes	18	5 (83.3%)	10 (71.4%)	0 (0%)	3 (75.0%)
LVH	5	0 (0%)	4 (28.6%)	0 (0%)	1 (25.0%)
Prolonged QT interval on admission	0	0 (0%)	0 3 (0%)	0 (0%)	0 (0%)
Corrected QT interval on admission	0	0 (0%)	0 3 (0%)	0 (0%)	0 (0%)
2D-Echo	13	1 (16.7%)	8 (57.1%)	1 (50.0%)	3 (75.0%)
Ejection fraction (by M Mode) (mean±SD)	50.06	42.00 (-)	49.25 (18.24)	67.00 (-)	56.50 (7.85)
Dilated chamber	9	1 (100%)	5 (62.5%)	1 (100%)	2 (50.0%)
Significant Valvular Heart disease	0	0 (0%)	0 (0%)	-	0 (0%)
Segmental wall motion abnormality	0	0 (0%)	0 (0%)	0 (0%)	0 (0%)
RV dilatation	2	0 (0%)	1 (12.5%)	1 (100%)	0 (0%)
RA dilatation	3	0 (0%)	2 (25.0%)	1 (100%)	0 (0%)
Mechanically Ventilated					
Upon admission	10	3 (50.0%)	5 (35.7%)	1 (50.0%)	1 (25.0%)
Shifted in ward	9	3 (50.0%)	5 (35.7%)	0 (0%)	1 (25.0%)
With Oxygen Support					
High Flow Nasal Cannula	2	0 (0%)	1 (11.1%)	0 (0%)	1 (25.0%)
BIPAP	0	0 (0%)	0 (0%)	0 (0%)	0 (0%)
CPAP	0	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Nasal Cannula	13	3 (100%)	8 (88.9%)	1 (100%)	1 (25.0%)
Face Mask	1	0 (0%)	0 (0%)	0 (0%)	1 (25.0%)
NRM	0	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Table 5 shows the comparison of sociodemographic, clinical and laboratory factors of patients with and without pulmonary outcomes. Patients with pulmonary outcomes tend to be older in average (Mean=63 vs. 57 years, p=0.001) and hypertensive (p=0.001). Pulmonary outcomes were significantly greater (p<0.007) in patients with eGFR levels of 30-59 cc / 1.73 m^2 and 15-29 cc / 1.73 m^2 and with hyperkalemia (p=0.013). Proportion of patients with LVH findings in those with pulmonary outcomes were also significantly higher than those without (p=0.044). Systolic pressure (135.61 vs 127.21, p=<0.001), MAP (98.19 vs 94.52, p=0.019), heart rate (105.75 vs. 96.96; p=<0.001), leukocytosis and NLR (11.73 vs. 7.13, p=<0.001), were significantly higher for those with pulmonary outcomes. Also, significantly lower SpO_2 (86.15 vs. 90.47, p=0.003) and eGFR (56.70 vs. 70.74, p=0.001) were noted in these patients.

Patients with cardiovascular outcomes tend to be significantly older (Mean: 64 y.o. vs. 58 y.o., p=0.039) and had diabetes (66.7% vs. 32.3%, p=0.027), with the difference in proportions to be almost twice compared to non-cardiovascular patients (Table 6). The use of ACE/ARB (54.2% vs. 26.3%, p=0.003) and bronchodilator (4.2% vs. 21.8%, p=0.040) were significantly higher, almost twice, in patients with cardiovascular outcomes. The presence of hypermagnesemia was also significantly higher in these patients (16.7% vs. 5.5%, p=0.05). Patients with LVH (16.7% vs. 4.2%, p=0.007) and ischemic changes (66.7% vs. 21.8%, p=<0.001) via 12-LEAD ECG were significantly higher, almost three times more, in patients with cardiovascular outcomes. Patients diagnosed with dilated chamber (61.5% vs. 25%, p=0.005) and segmental wall motion abnormality (46.2% vs. 11.4%, p=0.001) via echocardiography yielded

Table 4. Distribution of parameters across cardiovascular outcomes

Factors	N=355 No./Mean	Arrythmia (n=6)	ACS/MI (n=14)	VTE (n=2)	Others (n=4)
		Frequency (%)			
Age (mean±SD)	64.0	62.33 (16.17)	66.86 (12.61)	54.50 (2.12)	61.0 (21.65)
18-40 yrs old	1	0 (0%)	0 (0%)	0 (0%)	1 (25.0%)
41-60 yrs old	9	3 (50.0%)	4 (28.6%)	2 (100%)	0 (0%)
61-80 yrs old	10	2 (33.3%)	8 (57.1%)	0 (0%)	3 (75.0%)
>80 yrs old	3	1 (16.6%)	2 (14.3%)	0 (0%)	0 (0%)
Gender					
Male	19	4 (66.7%)	12 (85.7%)	1 (50.0%)	2 (50.0%)
Female	7	2 (33.3%)	2 (14.3%)	1 (50.0%)	2 (50.0%)
Estimated BMI	21.3	-	22.52 (2.57)	-	20.70 (-)
Underweight <18.5	1	-	-	-	1 (100%)
Normal 18.5-<25	2	-	2 (100%)	-	-
Overweight >25-30	0	-	0 (0%)	-	-
Obese >30	0	-	0 (0%)	-	-
Co-morbidities					
Hypertension	17	4 (66.7%)	8 (57.1%)	2 (100%)	3 (75.0%)
DM type 2	18	3 (50.0%)	11 (78.6%)	0 (0%)	4 (100%)
Chronic kidney disease	2	0 (0%)	2 (14.3%)	0 (0%)	0 (0%)
COPD	0	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Asthma	2	0 (0%)	0 (0%)	1 (50.0%)	1 (25.0%)
History of CAD	3	0 (0%)	2 (14.3%)	0 (0%)	1 (25.0%)
History of CVD	1	1 (16.7%)	0 (0%)	0 (0%)	0 (0%)
Chronic Liver Disease		-	-	-	-
Malignancy	0	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Connective Tissue disease	0	0 (0%)	0 (0%)	0 (0%)	0 (0%)
PTB (history of PTB or if active)	2	1 (16.7%)	1 (7.1%)	0 (0%)	0 (0%)
HIV/AIDS	0	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Smoking history					
Smoker	7	4 (66.7%)	3.2 (25.0%)	0 (0%)	0 (0%)
Non-smoker	17	2 (33.3%)	9.2 (75.0%)	2 (100.0%)	4 (100.0%)
Initial vital signs					
Systolic Pressure	136.0	142.67 (23.31)	134.79 (26.44)	124.00 (5.66)	136.00 (33.03)
Diastolic Pressure	81	84.50 (8.94)	78.00 (15.30)	85.00 (7.07)	84.25 (17.10)
MAP	99.3	103.89 (12.22)	96.93 (17.70)	98.00 (6.60)	101.50 (22.18)
Heart Rate	105.0	108.17 (15.61)	102.36 (21.76)	111.00 (4.24)	106.25 (21.58)
Temperature	36.8	37.00 (0.79)	36.75 (0.79)	36.25 (0.35)	37.13 (1.08)
Spo_2	82.8	82.83 (14.58)	84.36 (11.41)	75.00 (21.21)	81.00 (12.57)

Table 4. Distribution of parameters across cardiovascular outcomes *(continued)*

Factors	N=355 No./Mean	Arrythmia (n=6)	ACS/MI (n=14)	VTE (n=2)	Others (n=4)
		Frequency (%)			
Use of Medications					
Verapamil	0	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Amiodarone	0	0 (0%)	0 (0%)	0 (0%)	0 (0%)
ACE/ARB	13	3 (50.0%)	7 (50.0%)	1 (50.0%)	2 (50.0%)
Beta Blocker	8	0 (0%)	5 (35.7%)	0 (0%)	3 (75.0%)
Bronchodilator	1	1 (16.7%)	0 (0%)	0 (0%)	0 (0%)
PTB medications	0	0 (0%)	0 (0%)	0 (0%)	0 (0%)
CBC					
Leukocytosis (WBC >10.0)	13	4 (66.7%)	6 (42.9%)	2 (100%)	1 (25.0%)
Leukopenia (WBC <4.5)	0	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Neutrophil to Lymphocyte Ratio	12.5	23.25 (31.02)	8.98 (7.79)	11.66 (8.11)	9.39 (5.85)
Anemia (Hgb <10.0)	2	0 (0%)	1 (7.1%)	0 (0%)	1 (25.0%)
Thrombocytopenia (Plt <150,000)	0	0 (0%)	0 (0%)	0 (0%)	0 (0%)
eGFR (mean±SD)	57.1	49.50 (36.05)	52.28 (7.79)	44.50 (19.09)	88.50 (28.10)
eGFR >90cc/1.73m^2	2	1 (20.0%)	0 3 (0%)	0 (0%)	1 (25.0%)
eGFR 60-89cc/1.73m^2	10	0 (0%)	7 3 (53.8%)	0 (0%)	3 (75.0%)
eGFR 30-59cc/1.73m^2	7	2 (40.0%)	3 3 (23.1%)	2 (100%)	0 (0%)
eGFR 15-29cc/1.73m^2	4	2 (40.0%)	2 3 (15.4%)	0 (0%)	0 (0%)
eGFR <15cc/1.73m^2	1	0 (0%)	1 3 (7.7%)	0 (0%)	0 (0%)
Troponin I	1.45	2.65 (4.71)	1.52 (3.08)	0.19 (0.26)	0.04 (0.03)
Serum Electrolytes					
Sodium					
Hyponatremia	18	2 (33.3%)	11 (78.6%)	2 (100%)	3 (75.0%)
Normal	7	4 (66.7%)	2 (14.3%)	0 (0%)	1 (25.0%)
Hypernatremia	1	0 (0%)	1 (7.1%)	0 (0%)	0 (0%)
Potassium					
Hypokalemia	2	0 (0%)	1 (7.1%)	0 (0%)	1 (25.0%)
Normal	21	4 (66.7%)	13 (92.9%)	1 (50.0%)	3 (75.0%)
Hyperkalemia	3	2 (33.3%)	00 (0%)	1 (50.0%)	0 (0%)
Calcium					
Hypocalcemia	6	3 (50.0%)	3 (21.4%)	0 (0%)	0 (0%)
Normal	20	3 (50.0%)	11 (78.6%)	2 (100%)	4 (100%)
Hypercalcemia	0	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Magnesium					
Hypomagnesemia	3	0 (0%)	2 (14.3%)	0 (0%)	1 (25.0%)
Normal	18	4 (66.7%)	9 (64.3%)	2 (100%)	3 (75.0%)
Hypermagnesemia	4	2 (33.3%)	2 (14.3%)	0 (0%)	0 (0%)
12-Lead ECG					
Ischemic changes	18	5 (83.3%)	10 (71.4%)	0 (0%)	3 (75.0%)
LVH	5	0 (0%)	4 (28.6%)	0 (0%)	1 (25.0%)
Prolonged QT interval on admission	0	0 (0%)	0 3 (0%)	0 (0%)	0 (0%)
Corrected QT interval on admission	0	0 (0%)	0 3 (0%)	0 (0%)	0 (0%)
2D-Echo	13	1 (16.7%)	8 (57.1%)	1 (50.0%)	3 (75.0%)
Ejection fraction (by M Mode) (mean±SD)	50.06	42.00 (-)	49.25 (18.24)	67.00 (-)	56.50 (7.85)
Dilated chamber	9	1 (100%)	5 (62.5%)	1 (100%)	2 (50.0%)
Significant Valvular Heart disease	0	0 (0%)	0 (0%)	-	0 (0%)
Segmental wall motion abnormality	0	0 (0%)	0 (0%)	0 (0%)	0 (0%)
RV dilatation	2	0 (0%)	1 (12.5%)	1 (100%)	0 (0%)
RA dilatation	3	0 (0%)	2 (25.0%)	1 (100%)	0 (0%)
Mechanically Ventilated					
Upon admission	10	3 (50.0%)	5 (35.7%)	1 (50.0%)	1 (25.0%)
Shifted in ward	9	3 (50.0%)	5 (35.7%)	0 (0%)	1 (25.0%)
With Oxygen Support					
High Flow Nasal Cannula	2	0 (0%)	1 (11.1%)	0 (0%)	1 (25.0%)
BIPAP	0	0 (0%)	0 (0%)	0 (0%)	0 (0%)
CPAP	0	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Nasal Cannula	13	3 (100%)	8 (88.9%)	1 (100%)	1 (25.0%)
Face Mask	1	0 (0%)	0 (0%)	0 (0%)	1 (25.0%)
NRM	0	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Table 6. Factors associated with cardiovascular outcomes in adult COVID-19 patients admitted at the LCP

	Total (N=355) No. (%) / Mean (SD)	With cardiovascular outcomes (n=24) No. (%) / Mean (SD)	Without cardiovascular outcomes (n=331) No. (%) / Mean (SD)	P value
Age (mean±SD)	58.28 (14.40)	64.17 (14.59)	57.86 (14.36)	0.039
18-40 yrs old	45 (12.7%)	1 (4.2%)	44 (13.3%)	0.170
41-60 yrs old	144 (40.6%)	8 (33.3%)	136 (41.1%)	
61-80 yrs old	148 (41.7%)	12 (50%)	136 (41.1%)	
>80 yrs old	18 (5.1%)	3 (12.5%)	15 (4.5%)	
Gender				
Male	226 (63.7%)	18 (75%)	208 (62.8%)	0.232
Female	129 (36.3%)	6 (25%)	123 (37.2%)	
Estimated BMI	23.68 (4.64)	22.52 (2.57)	23.76 (4.76)	0.721
Underweight <18.5	-	-	-	0.796
Normal 18.5-<25	28 (82.4%)	2 (100%)	26 (81.3%)	
Overweight >25-30	4 (11.8%)	0 (0%)	4 (12.5%)	
Obese >30	2 (5.9%)	0 (0%)	2 (6.3%)	
Co-morbidities				
Hypertension	202 (56.9%)	16 (66.7%)	186 (56.2%)	0.317
DM type 2	123 (34.6%)	16 (66.7%)	107 (32.3%)	0.001
Chronic kidney disease	24 (6.8%)	2 (8.3%)	22 (6.6%)	0.715
COPD	10 (2.8%)	0 (0%)	10 (3%)	0.388
Asthma	28 (7.9%)	2 (8.3%)	26 (7.9%)	0.933
History of CAD	30 (8.5%)	3 (12.5%)	27 (8.2%)	0.460
History of CVD	11 (3.1%)	1 (4.2%)	10 31 (3%)	0.542
Chronic Liver Disease	-	-	-	-
Malignancy	14 (3.9%)	0 (0%)	14 (4.2%)	0.304
Connective Tissue disease	1 (0.3%)	0 (0%)	1 (0.3%)	0.787
PTB (history of PTB or if active)	31 (8.7%)	2 (8.3%)	29 (8.8%)	0.523
HIV/AIDS	1 (0.3%)	0 (0%)	1 (0.3%)	0.787
Smoking history				
Smoker	95 (27.5%)	6 (27.3%)	89 (27.5%)	0.984
Non-smoker	251 (72.5%)	16 (72.7%)	235 (72.5%)	
Initial vital signs				
Systolic Pressure	129.27 (19.30)	133.96 (25.05)	128.93(18.82)	0.218
Diastolic Pressure	78.49 (12.12)	80.25 (13.62)	78.37(12.01)	0.463
MAP	95.42 (12.70)	98.15(16.22)	95.22 (12.41)	0.275
Heart Rate	99.11 (16.80)	105.33 (19.76)	98.66 (16.50)	0.060
Temperature	36.57 (2.08)	36.85 (0.83)	36.55 (2.14)	0.506
Spo_2	89.41 (11.94)	83.08 (12.87)	89.87 (11.76)	0.007
Use of Medications				
Verapamil	2 (0.6%)	0 (0%)	2 (0.6%)	0.703
Amiodarone	5 (1.4%)	0 (0%)	5 (1.5%)	0.544
ACE/ARB	100 (28.2%)	13 (54.2%)	87 (26.3%)	0.003
Beta Blocker	66 (18.6%)	7 (29.2%)	59 (17.8%)	0.168
Bronchodilator	73 (20.6%)	1 (4.2%)	72 (21.8%)	0.040
PTB medications	10 (2.8%)	0 (0%)	10 (3%)	0.388
CBC				
Leukocytosis (WBC >10.0)	121 (34.1%)	12 (50%)	109 (32.9%)	0.094
Leukopenia (WBC <4.5)	37 (10.4%)	0 (0%)	37 (11.2%)	
Neutrophil to Lymphocyte Ratio	8.25 (10.12)	12.82 (16.99)	7.92 (9.39)	0.022
Anemia (Hgb <10.0)	34 (9.6%)	2 (8.3%)	32 (9.7%)	0.823
Thrombocytopenia (Plt <150,000)	25 (7.1%)	0 (0%)	25 (7.6%)	0.162
eGFR (mean±SD)	67.28 (32.71)	56.24 (31.25)	68.09 (32.72)	0.101
eGFR >90cc/1.73m^2	87 (27.2%)	2 (9.1%)	85 (28.5%)	0.058
eGFR 60-89cc/1.73m^2	116 (36.3%)	9 (40.9%)	107 (35.9%)	
eGFR 30-59cc/1.73m^2	70 (21.9%)	6 (27.3%)	64 (21.5%)	
eGFR 15-29cc/1.73m^2	20 (6.3%)	4 (18.2%)	16 98 (5.4%)	
eGFR <15cc/1.73m^2	27 (8.4%)	1 (4.5%)	26 98 (8.7%)	
Troponin I	1.95 (26.47)	1.95 (3.35)	1.98 (27.50)	0.957

Table 6. Factors associated with cardiovascular outcomes in adult COVID-19 patients admitted at the LCP *(continued)*

	Total (N=355) No. (%) / Mean (SD)	With cardiovascular outcomes (n=24) No. (%) / Mean (SD)	Without cardiovascular outcomes (n=331) No. (%) / Mean (SD)	P value
Serum Electrolytes				
Sodium				
Hyponatremia	119 (33.8%)	7 (29.2%)	112 (34.1%)	0.462
Normal	5 (1.4%)	1 (4.2%)	4 (1.2%)	
Hypernatremia	228 (64.8%)	16 (66.7%)	212 (64.6%)	
Potassium				
Hypokalemia	251 (71.1%)	19 (79.2%)	232 (70.5%)	0.218
Normal	27 (7.6%)	3 (12.5%)	24 (7.3%)	
Hyperkalemia	75 (21.2%)	2 (8.3%)	73 (22.2%)	
Calcium				
Hypocalcemia	209 (63.9%)	18 (75%)	191 (63%)	0.454
Normal	5 (1.5%)	0 (0%)	5 (1.7%)	
Hypercalcemia	113 (34.6%)	6 (25%)	107 (35.3%)	
Magnesium				
Hypomagnesemia	247 (74.4%)	18 (75%)	229 (74.4%)	0.050
Normal	21 (6.3%)	4 (16.7%)	17 (5.5%)	
Hypermagnesemia	64 (19.3%)	2 (8.3%)	62 (20.1%)	
12-Lead ECG				
Ischemic changes	88 (24.8%)	16 (66.7%)	72 (21.8%)	<0.001
LVH	18 (5.1%)	4 (16.7%)	14 (4.2%)	0.007
Prolonged QT interval on admission	11 (3.1%)	0 (0%)	11 (3.3%)	0.374
Corrected QT interval on admission	13 (3.7%)	0 (0%)	13 (4%)	0.331
2D-Echo	155 (43.7%)	12 (50%)	143 (43.2%)	0.517
Ejection fraction (by M Mode) (mean±SD)	61.83 (12.06)	52.54 (15.65)	62.68 (11.37)	0.003
Dilated chamber	43 (28.1%)	8 (61.5%)	35 (25%)	0.005
Significant Valvular Heart disease	9 (5.9%)	0 (0%)	9 (6.4%)	0.365
Segmental wall motion abnormality	22 (14.4%)	6 (46.2%)	16 (11.4%)	0.001
RV dilatation	14 (9.2%)	2 (15.4%)	12 (8.6%)	0.415
RA dilatation	17 (11.1%)	3 (23.1%)	14 (10%)	0.151
Mechanically Ventilated				
Upon admission	75 (21.9%)	9 (37.5%)	66 (20.8%)	0.003
Shifted in ward	56 (16.4%)	8 (33.3%)	48 (15.1%)	
With Oxygen Support				
High Flow Nasal Cannula	24 (8.8%)	1 (6.3%)	23 (8.9%)	0.785
BIPAP	1 (0.4%)	0 (0%)	1 (0.4%)	
CPAP	1 (0.4%)	0 (0%)	1 (0.4%)	
Nasal Cannula	172 (63%)	13 (81.3%)	159 (61.9%)	
Face Mask	14 (5.1%)	1 (6.3%)	13 (5.1%)	
NRM	5 (1.8%)	0 (0%)	5 (1.9%)	

similar results. Mechanically ventilated patients were significantly higher, almost twice as likely, in patients with cardiovascular outcomes (33.3% vs. 15.1%, p=<0.003). Also, mean SpO_2 was significantly lower in these patients (83.08 vs. 89.87, p=0.007). NLR was found to be significantly higher (12.82 vs. 7.92, p=<0. 0.022) but ejection fraction levels (52.54 vs. 62.68, p=0.003) were noted to be significantly lower.

DISCUSSION

This study investigated the sociodemographic, clinical, and laboratory factors associated with pulmonary and cardiac outcomes among COVID-19 patients. ARDS and ACS were the most common pulmonary and cardiovascular outcomes, respectively. Factors that were significantly increased in patients with adverse pulmonary outcomes were age, male gender, hypertension, hyperkalemia, and lower eGFR levels. Cardiovascular outcomes were noted to be significantly increased in older patients, diabetics, ARB/ACEI, bronchodilator, leukocytosis, hyper magnesia, high neutrophil to lymphocyte count, LVH on ECG, low EF and segmental wall-motion abnormality on echocardiography and mechanical ventilation.

Similar to studies done earlier, ARDS was identified to be the most common pulmonary outcomes.[18,25] One explanation could be the immense cytokine cascade caused by COVID-19 which occurs at a short period causing critically ill patients to develop

ARDS and require oxygen support.18 On the other hand, ACS/myocardial infarction was the most common cardiovascular complication identified. This reflects previous studies wherein myocardial injury or acute myocardial infarction was also identified as the most common cardiac outcomes in COVID-19. The mechanism behind this was viral myocarditis and the cardiovascular effects of systemic inflammation.[25]

Hyponatremia was also found to be present in most patients (N=228, 64.6%) with COVID-19. The reason could be due to infectious diseases and severe inflammatory conditions being complicated by SIAD (Syndrome of Inappropriate Antidiuresis), with IL-6 inducing non-osmotic release of vasopressin causing hyponatremia.[27]

Pulmonary Outcomes

Patients who developed pulmonary outcomes were noted to be male, aged 41 to 60 years old, and hypertensive. Reduced susceptibility of females to viral infections was secondary to the protection conferred by the X chromosome and sex hormones which play an essential role in immunity.[5,28] Increased age was associated with death in COVID-19 possibly due to age-dependent defects in T-Cell and B-Cell function.17,29 Furthermore, excessive production of type 2 cytokines may result in a loss of viral replication control and a prolonged proinflammatory state, both of which can contribute to bad outcomes.[17] Hypertension and diabetes were common Co-morbidities possibly due to decreased immune system response in these patients making them more susceptible to infection.[15,16,18]

Results of laboratory parameters showed that patients with pulmonary outcomes had lower eGFR levels (30-59cc/1.73m^2 and 15-29cc/1.73m^2). This does not come as a surprise since kidney involvement was frequently encountered in COVID-19 with >40% of patients having proteinuria on admission.[30] The presence of viral particles was also reported to be present in renal endothelial cells indicating viremia as possible cause of damage to the endothelium and contributor to AKI and consequent hyperkalemia.[31]

Hyperkalemia, LVH on 2D-Echo, leukocytosis, and high NLR were also noted in patients with pulmonary outcomes. Baseline vital signs in these patients were also observed to have higher systolic pressure, MAP, heart rate but lower SpO_2 on admission.

The LVH on 2D-Echo along with the increased SBP, MAP, and HR were likely related to the increased age, HTN, and distressed state in patients with pulmonary outcomes. Impairment in lung mechanics, particularly ventilation and V/Q mismatch in pulmonary outcomes (e.g., ARDS, HAP/VAP) caused hypoxemia in these patients.

Cardiovascular Outcomes

Patients with cardiovascular outcomes tended to be older, of male gender, and diabetic. Diabetes causes an inefficient immune response due to chronic hyperglycemia and inflammation leading to decreased polymorphonuclear leukocyte mobilization, chemotaxis, phagocytic activity, decreased cytokine secretion in response to lipopolysaccharides, induction of T-Cell Tumor Necrosis Alpha (TNF-α) activity, and immunoglobulin glycation.[32,33] Cardiac effects of diabetes include the increase risk for the development of Vascular Calcification (VC) and blood vessel hardening and dysfunction.[34]

The use of ACE/ARB's, bronchodilators were also associated with cardiovascular outcomes. This was most likely due to the older patient profile, diabetes, and consequent maintenance medications these conditions require. In another study, patients with noted cardiovascular disease (CVD) prior to admission were noted to have higher mortality rates than patients without underlying CVD.[44] The presence of elevated Troponins however showed increased mortality for both patient groups regardless if they had underlying CVD or not, albeit higher when CVD was present.[35]

Cardiovascular outcomes were linked to hypermagnesemia and a high NLR. Patients with ischemia abnormalities on ECG, LVH, dilated chamber, segmental wall motion abnormality, and low ejection fraction on 2D-Echo had cardiac co-morbidities on admission and presumably even previously.

Magnesium levels do not appear to be controlled by hormonal systems but rather was dependent on intestinal absorption and renal excretion. Hypermagnesemia in CKD is caused by a reduction in eGFR, which leads to a rise in magnesium levels

as renal function declines.[36] The majority of patients with hypermagnesemia had impaired renal function (N=22 of 24 patients, 90.9 percent with eGFR 90), which was not represented in our tables. This could be due to the low number of patients with cardiovascular outcomes compared to the total population of patients in our study.

COVID-19 has been shown to cause cardiovascular morbidity by direct myocardial injury, microvascular damage due to DIC and thrombosis, direct viral entry to myocardial cells, and lastly due to hypoxemia in increased metabolic demands causing myocardial injury.[37] Hypoxemia and mechanically ventilated patients were more likely to have cardiovascular outcomes which was consistent with previous studies.[38] Older age, preexisting coronary conditions, and the severity of pneumonia at diagnosis were known risk factors for cardiac events in patients with pneumonia.[39]

CONCLUSIONS AND RECOMMENDATIONS

The results of study showed that age, male gender, hypertension, hyperkalemia, lower eGFR levels, were the factors significantly increased in number in patients with pulmonary outcomes. Cardiovascular outcomes were noted to be significantly increased in older patients, with diabetes, hypermagnesemia, use of ARB/ACE, bronchodilators, leukocytosis, high neutrophil to lymphocyte count, LVH on ECG, low EF, and segmental wall motion abnormality. Lastly, patients who were hooked to mechanical ventilator had increased cardiac complications.

Several limitations were encountered during the study related to its retrospective study design. Not all laboratory exams were done in all patients. Some tests like, inflammatory markers, though important were missing. Other data such as BMI upon admission were also not properly recorded.

For future research, we recommend investigating the other outcomes such as renal, neurological, as well as gastrointestinal outcomes. A multi-center study with multivariate analysis could give a stronger conclusion on which subset would be susceptible to complications, whether organ specific or multi organ, among hospitalized COVID-19 patients.

Authorship

All authors have certified fulfillment of Scientific Proceedings authorship criteria.

Disclosure of Conflicts of Interest

All authors have no conflict of interest to disclose.

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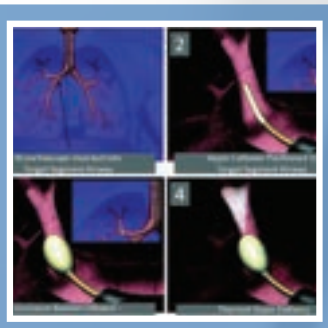

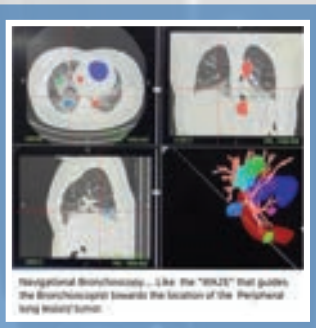

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The Outcomes of Evolving Treatment Regimens Among COVID-19 Confirmed Severe and Critical Cases Admitted at The Lung Center of The Philippines

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ABSTRACT

Objective. Few studies are available on the characteristics, management, and outcomes of patients with confirmed COVID-19. This study aims to describe the outcomes of evolving treatment regimens among COVID-19 confirmed severe and critical cases admitted at the Lung Center of the Philippines (LCP).

Methodology. A retrospective, cohort study conducted at the LCP from March 2020 to August 2020 that included 219 COVID-19 confirmed severe and critical patients.

Discussion. The mean age of patients was 62 years old and majority were males. The number of survivors is greatest among patients 50-59 years old (33.8%). Severe COVID-19 was associated with patients with chronic kidney disease (p=0.009). Most number of survivors is recorded for regimens with LCP Standard of Care 2 (antibiotic therapy, multivitamins + zinc, O_2 therapy, IV fluid, and management of co-morbidities + anticoagulant + dexamethasone) and high flow nasal cannula (HFNC). Combinations that included invasive ventilation showed an increased likelihood of death. Regression analysis on APACHE II score and PF ratio score showed that an increased APACHE II score increased the likelihood of death and an increased PF ratio score lessened the probability of death. Median length of hospital stay was 11 days.

Conclusions. Treatment regimens that included HFNC and LCP Standard of Care 2 in combination with either interferon, tocilizumab, hemoperfusion, proning, or remdesivir decreases the likelihood of death. Invasive ventilation simultaneously given with any of the regimens increases the likelihood of death. Patients with higher APACHE II scores and lower PaO_2/FiO_2 were non-survivors and in a more critical condition.

Keywords: treatment regimens, severe and critical COVID-19, treatment outcomes

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This study was included among the Most Outstanding PCP Researches for 2021 and won 1st place at The Philippine College of Physicians 51st Annual Congress for the Descriptive Category. It likewise garnered 3rd place at the Lung Center of the Philippines Annual Research Contest 2021, and was a finalist in the Department of Health 1st National Hospital Week Research Forum (2021). The paper was also presented at the Asian Pacific Society of Respirology 2021 Hybrid Congress in Kyoto, Japan.

INTRODUCTION

In December 2019, the novel coronavirus SARS-CoV-2 and its disease COVID-19 was diagnosed in a series of patients in Wuhan, China and has marked the start of a global pandemic. SARS-CoV-2 pneumonia may present as a mild case to critically ill. Earlier studies have only reported the overall clinicodemographic features, management, and outcomes of patients with confirmed COVID-19.[1-3] There are few studies available on the characteristics, management, and outcomes of the severe to critically ill patients.[4-16] As of August 20, 2020 there are more than 22 million COVID-19 confirmed cases and 781,932 deaths globally. In the Philippines, 173,774 cases and 2,795 deaths has been recorded.[17] The Lung Center of the Philippines (LCP) is one of the designated COVID-19 referral hospitals in the country. As of August 20, 2020, it has recorded a total of 1,344 COVID-19 confirmed cases with 256 COVID-19 confirmed deaths. The hospital has provided 48 ICU beds to accommodate COVID-19 critical patients.

Currently, there are limited studies available on the management strategies and outcomes of COVID-19 confirmed severe and critical cases admitted at the ICU. As of this writing, there are no locally recorded nor published studies made on the said population. This study aims to describe the outcomes of evolving treatment regimens among COVID-19 confirmed severe and critical cases admitted at the LCP.

OBJECTIVES

The study aims to describe the treatment outcomes of COVID-19 confirmed severe and critical cases admitted at the LCP. Specifically, the study shall: 1) determine the outcomes of severe and critical patients in terms of length of hospital stay, disposition at the time of discharge from the hospital (survival), 2) describe the demographic characteristics of the survivors and non-survivors in terms of age, sex, co-morbidities, 3) compare the proportion of severe and critical COVID-19 cases who underwent the treatment regimens in a combination of Standard of Care, antiviral therapy (remdesivir, lopinavir/ritonavir, oseltamivir, chloroquine/hydroxychloroquine), adjunctive interventions (corticosteroids, tocilizumab, hemoperfusion, interferon B1a), convalescent plasma, respiratory support (high flow nasal cannula [HFNC], invasive mechanical ventilation, proning), and anticoagulation, and 4) compare the difference of baseline severity between survivors and non-survivors under treatment regimen combination in terms of APACHE II score and PaO_2/FiO_2 ratio.

METHODOLOGY

Study site and Study Population

This is a retrospective, cohort study. The study was conducted at the LCP from March 2020 to August 2020. Patients included in the study were admitted COVID-19 confirmed cases by OPS/NPS RT-PCR or SARS-CoV-2 GeneXpert, aged 19 years old and above, who are classified based on the World Health Organization (WHO) case definition of Severe and Critical COVID-19 (Severe: with clinical signs of pneumonia plus one of the following: respiratory frequency >30 breaths per minute, severe respiratory distress, SpO_2 ≤90% on room air, and for Critical: with acute respiratory distress syndrome (ARDS), sepsis, or septic shock) within 24 hours of admission, and admitted at the ICU with known outcome. Patients with lost medical records were not included in the study.

Sample size

A minimum of 132 confirmed COVID-19 severe and critical patients satisfying the inclusion/exclusion criteria was required to have an 80% chance of determining, as significant at the 5% level, the treatment outcomes of severe and critical cases.

Data Collection and Processing

A total of 526 COVID-19 confirmed cases from the master list was obtained from the Hospital Epidemiologic Surveillance Unit, admitting and records section of LCP. There were 52 severe cases and 182 critical cases out of the 526 COVID-19 confirmed cases. There were 15 patients excluded from the study because of lost medical records. A total of 219 patients were included in the study (Figure 1). The primary researchers were responsible for collecting the following data from the medical records of the study subjects 1) demographic information including age, sex and co-morbidities; 2) treatment regimens and interventions; 3) baseline Acute Physiology and Chronic Health Evaluation II (APACHE II) score and

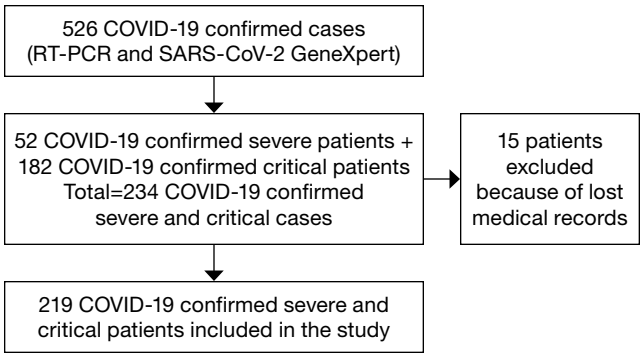


Figure 1. COVID-19 cases treated with hemoperfusion.

partial pressure of oxygen to FiO_2 (PaO_2/FiO_2 ratio); and 4) length of hospital stay and disposition at the time of discharge from the hospital. Baseline laboratories were extracted from the BizBox, an electronic health records and document management system. Baseline radiological images were reviewed using the Voyager PACS, a web enabled, server-based picture archiving and communication system (PACS). In this study, Standard of Care has evolved from LCP Standard of Care 1 consisting of antibiotic therapy, multivitamins + zinc, O_2 therapy, IV fluid, and management of co-morbidities to LCP Standard of Care 2 consisting of Standard of Care 1 + anticoagulant + dexamethasone. Treatment regimen used is a combination of any of the following: Standard of Care A or B, antiviral therapy, adjunctive interventions, convalescent plasma, respiratory support, and anticoagulation was identified for each patient. The length of hospital stay was computed from the day of ICU admission up to the time of hospital discharge. Patient's disposition upon discharge was categorized as survivor vs. non-survivor.

Statistical Analysis

Summary statistics are presented in tables or graphs and reported as mean standard deviation for continuous data with normal distribution or as median (inter-quartile range) for quantitative variables with skewed distribution (e.g., age in years, APACHE II score, P/F ratio, length of hospital stay) and as count (percent) for qualitative measures (e.g., sex, co-morbidity, antiviral therapy, antibacterial therapy, adjunctive interventions, convalescent plasma, respiratory support, respiratory support, circulatory support, multiple organ function support, anticoagulation, disposition, treatment regimen combination). Minimum and maximum values of continuous data are also be reported. One sample t-test or one sample Wilcoxon signed test were used to compare quantitative variables between survivors and non-survivors. The Cox-proportional hazards regression analysis was performed to determine factors associated with disposition at discharge (survivor or non-survivor) when patients were grouped based on treatment regimen combination. The hazard ratio at 95% confidence interval was estimated. Statistical significance was based on p-value<0.5. Data processing and analysis was performed using SPSS Statistics 22.

Ethical Considerations

This study was approved by the LCP IERB and followed the National Ethical Guidelines for Health and Health Related Research 2017 for health research. The patient's identity was anonymized using their initials. All study documents pertaining to this study are stored in a secured sealed envelope and are stored in a secured locker for 5 years and will be disposed of through shedding.

RESULTS

There was a total of 219 confirmed severe and critical cases from the month of March to August. Majority (29%) of the patients belonged to age group 60-69, followed by age group 50-59 (28%). Majority (70%) of the patients were male, 30% of the patients were female. Majority (63.5%) of the patients had hypertension, followed by diabetes mellitus (DM) (20%), 32% had other co-morbidities (PTB, HIV, etc.) Percent of non-survivors was greatest for aged 60-69 (29.2%), followed by 50-59 (27.4%) and 70-79 (21.0%). The number of survivors was greatest for 50-59 years old (33.8%). No significant association (p=0.111) was seen when proportions of survivors vs. non-survivor across the age range were compared. Majority of severe to critical COVID-19 patients were 60-69 years old. Severe and critical COVID-19 survival was found associated with patients with chronic kidney disease as to proportions of those who did not survive was higher than those did (11.7% vs. 0%, p=0.009) (Table 1A).

The average age of survivor and non-survivor were 63 and 59 years old with age of all patients ranging from 22 to 90 years old. There was a significant difference in the age of survivors and non-survivors. Difference was

Table 1A. Demographic and clinical characteristics of Severe to Critical COVID-19 patients

Characteristic	All Patients (n=219)	Non-Survivors (n=154)	Survivors (n=65)	p-value
Age in years				
18-29	2 out of 219 (0.9%)	1 out of 154 (0.6%)	1 out of 65 (1.5%)	0.106
30-39	9 out of 219 (4.1%)	8 out of 154 (5.2%)	1 out of 65 (1.5%)	
40-49	22 out of 219 (10%)	12 out of 154 (7.8%)	10 out of 65 (15.4%)	
50-59	60 out of 219 (27.4%)	38 out of 154 (24.7%)	22 out of 65 (33.8%)	
60-69	64 out of 219 (29.2%)	46 out of 154 (29.9%)	18 out of 65 (27.7%)	
70-79	46 out of 219 (21%)	34 out of 154 (22.1%)	12 out of 65 (18.5%)	
≥80	16 out of 219 (7.3%)	15 out of 154 (9.7%)	1 out of 65 (1.5%)	
Sex				
Male	154 out of 219 (70.3%)	104 out of 154 (67.5%)	50 out of 65 (76.9%)	0.165
Female	65 out of 219 (29.7%)	50 out of 154 (32.5%)	15 out of 65 (23.1%)	
Co-morbidity				
Any co-morbidity	191 out of 219 (87.2%)	135 out of 154 (87.7%)	56 out of 65 (86.2%)	0.760
Hypertension	139 out of 219 (63.5%)	98 out of 154 (63.6%)	41 out of 65 (63.1%)	0.937
Diabetes mellitus (DM)	74 out of 219 (33.8%)	55 out of 154 (35.7%)	19 out of 65 (29.2%)	0.354
Chronic obstructive pulmonary disease	8 out of 219 (3.7%)	6 out of 154 (3.9%)	2 out of 65 (3.1%)	1.000
Cardiovascular disease	18 out of 219 (8.2%)	13 out of 154 (8.4%)	5 out of 65 (7.7%)	0.854
Cerebrovascular disease	11 out of 219 (5%)	9 out of 154 (5.8%)	2 out of 65 (3.1%)	0.513
Chronic kidney disease (CKD)	18 out of 219 (8.2%)	18 out of 154 (11.7%)	0 out of 65 (0%)	0.009
Malignancy	10 out of 219 (4.6%)	9 out of 154 (5.8%)	1 out of 65 (1.5%)	0.288
Others	70 out of 219 (32%)	53 out of 154 (34.4%)	17 out of 65 (26.2%)	0.231

prominent across the middle age bracket as seen in Table 1C, wherein there were more non-survivors than survivor for patients with ages 40-60 years old. There was no difference in the survival and mortality rate of patients on the elderly and young adults (Table 1B, 1C).

There were 11 combinations of treatment regimens from the total 68 combinations that have significant difference in the proportion of survivor and non-survivor. TR 19 used Standard of Care 1 and of invasive ventilatory support had the greatest number of patients followed by TR 38, use of Standard of Care 2 + hemoperfusions + invasive ventilatory support. Among these 11, only 2 combinations, namely TR 19 and TR 38 were found to be significant predictor of hazard, in this case death. Positive coefficients and >1 hazard ratio implying that increase in use of such treatment will increase the likelihood of death and imply that patients will have lesser survival time. These were in agreement in the proportions of the survivor and non-survivor, wherein there were more non-survivor. *Note: Non-saturation of data for other combinations for the treatment regiments in the above table were not met thus it was not able to pass test for proportions. Therefore, it was better to anchor on the individual regiments that are significant predictor of survival (Table 2).*

Table 1B. Age of Survivors vs. Non-survivors of Severe and Critical COVID-19

Disposition	Survivor	Non-Survivor	Total	p-value
N	65.00	154.00	219.00	0.036*
Mean	59.05	62.78	61.67	
Minimum	27.00	22.00	22.00	
Maximum	82.00	90.00	90.00	
Std. Deviation	11.32	13.07	12.67	

* - significant difference at 0.05 level

Table 1C. Age Bracket of Survivors vs. Non-survivors of Severe and Critical COVID-19

Age Bracket	Disposition		Total
	Survivor	Non-Survivor	
Elderly (Above 60 years old)	29_a	90_a	119
Middle Age (40-60 years old)	34_a	55_b	89
Young Adults (18-39 years old)	2_a	9_a	11
Total	65	154	219

Each subscript letter denotes a subset of disposition categories whose column proportions do not differ significantly from each other at the 0.05 level.

The median APACHE II score among the patients was 12 with a minimum score of 0 and a maximum score of 39. There was a significant difference in the APACHE II scores of survivor and non-survivor wherein the median APACHE II score of non-survivors is higher (15) than survivors (8). The minimum and maximum were also higher for non-survivors. APACHE II score is a significant predictor of hazard such that the higher the APACHE II score is, there will be an increase in the likelihood of hazard, in this case death happening. In Table 3B, using the patients with

Table 2. Proportions and test on Treatment Regimens in Severe and Critical COVID-19

Treatment Regimens		Patient outcome			Test for proportions	Cox Regression	
		All Patients (N=219)	Survivor (N=65)	Non-Survivor (N=154)	p-value[b]	B[a]	p-value[b]
TR 19	S1+I	45 (20.55%)	0 (0%)	45 (29.22%)	0**	1.541	0
TR 60	S2	4 (1.83%)	3 (4.62%)	1 (0.65%)	0.045*	-1.288	0.201
TR 62	S2+IN	2 (0.91%)	2 (3.08%)	0 (0%)	0.029*	-13.586	0.985
TR 9	S2+HFNC	4 (1.83%)	4 (6.15%)	0 (0%)	0.002**	-13.595	0.975
TR 12	S2+P+HFNC	3 (1.37%)	3 (4.62%)	0 (0%)	0.007**	-13.588	0.983
TR 13	S2+R+HFNC	4 (1.83%)	4 (6.15%)	0 (0%)	0.002**	-13.591	0.978
TR 17	S2+T+HFNC	2 (0.91%)	2 (3.08%)	0 (0%)	0.029*	-13.597	0.985
TR 10	S2+HP+HFNC	5 (2.28%)	4 (6.15%)	1 (0.65%)	0.013**	-1.174	0.243
TR 14	S2+R+HP+HFNC	3 (1.37%)	3 (4.62%)	0 (0%)	0.007**	-13.604	0.983
TR 18	S2+T+HP+HFNC	2 (0.91%)	2 (3.08%)	0 (0%)	0.029*	-13.59	0.982
TR 38	S2+HP+I	19 (8.68%)	1 (1.54%)	18 (11.69%)	0.015**	0.56	0.032

Negative B means that there was an increase in hazard (death) for those without treatment as compared to those with treatment.
** - highly significant predictor of hazard; * - significant predictor of hazard; [ns] – not significant predictor of hazard

Hazard ratio that indicates multiplicative increase in the hazard as scores in predictors increase. EXP (B)=1 means no change in the hazard as scores in predictors increase; EXP (B) >1 means increase in likelihood of hazard as predictor increases; EXP (B) <1 means decrease in likelihood of hazard as predictor increases.

Table 3A. Over-all APACHE II Score of Severe to Critical COVID-19 patients

Disposition	Total Cases	Survivor	Non-Survivor	p-value
N	29	65	154	0.000**
Mean	12	8	15	
Minimum	0	0	2	
Maximum	39	16	39	
Interquartile Range	10	5	11	
Std. Deviation	7.9359	3.746	8.149	

Variables have skewed distribution.

** - highly significant difference of survivor and non-survivor (across all point categories) at 0.01 level

Table 3B. Survival Analysis based on APACHE II Score of Severe and Critical COVID-19

Cox Regression on APACHE II Score		
B[a]	p-value[b]	Exp(B)[c]
0.077	0.000**	1.080

Each subscript letter denotes a subset of disposition categories whose column proportions do not differ significantly from each other at the 0.05 level.

** - highly significant difference of survivor and non-survivor (across all point categories) at 0.01 level

APACHE II score of 0-4 as reference, the risk increases as APACHE II score such that risk becomes twice greater when APACHE II score is 15 and above. These were in the same tone as Table 3A wherein range of APACHE II score of survivors was 0 to 16 with an average of 8 (Table 3A, 3B, 3C).

Table 3C. APACHE II Score of Survivor vs. Non-survivor of Severe and Critical COVID-19

APACHE II	Disposition		Total	p-value	Risk Ratio
	Survivor	Non-Survivor			
0-4 points	8_a	6_b	14	<0.001**	1 (Ref)
5-9 points	29_a	31_b	60		1.21
10-14 points	24_a	34_b	58		1.37
15-19 points	4_a	35_b	39		2.09
20-24 points	0_a	20_b	20		2.33
25-29 points	0_a	19_b	19		2.33
30-34 points	0_a	4_a	4		2.33
≥35 points	0_a	5_a	5		2.33
Total	65	154	219		

Each subscript letter denotes a subset of disposition categories whose column proportions do not differ significantly from each other at the 0.05 level.

** - highly significant difference of survivor and non-survivor (across all point categories) at 0.01 level

There was 50% risk of non-survival if patients treated with TR 9 have ARDS as compared to patients treated with same combination but did not have ARDS. There was 10% risk of non-survival if patients treated with TR 38 have ARDS, consequently, if the patient have no ARDS, 90% of the risk of non-survival was decreased.

While there was no significant difference in the PF ratio of survivor and non-survivor at 95% level of confidence, it was almost possible. PF ratio was a

Table 4A. Over-all PF Ratio of Severe to Critical COVID-19 patients

Disposition	Total Cases	Survivor	Non-Survivor	p-value
N	219	65	154	0.053[ns]
Mean	155.3	188	141.55	
Minimum	36.3	43	36.3	
Maximum	485.7	476	485.7	
Interquartile Range	140.1	134	139.58	
Std. Deviation	7.9359	96.2198	104.5565	

Variables have skewed distribution.

[ns] - not significant difference of survivor and non-survivor (across all point categories) at 0.01 level

Table 4B. Survival Analysis based on PF Ratio of Severe and Critical COVID-19

Cox Regression on PF Ratio		
B[a]	p-value[b]	Exp(B)[c]
-0.002	0.029*	0.998

Each subscript letter denotes a subset of disposition categories whose column proportions do not differ significantly from each other at the 0.05 level.

* - significant difference at 0.05 level

Table 4C. PF Ratio of Survivors vs. Non-survivors of Severe and Critical COVID-19

Combination of Treatment		PF Ratio	Survivor	Non-Survivor	Risk Ratio
TR 19	S1+I	ARDS	0	40	1.078
		Not ARDS	0	5	
TR 60	S2	ARDS	3	0	0.167
		Not ARDS	0	1	
TR 62	S2+IN	ARDS	1	0	1
		Not ARDS	1	0	
TR 9	S2+HFNC	ARDS	3	0	0.5
		Not ARDS	1	0	
TR 12	S2+P+HFNC	ARDS	2	0	0.667
		Not ARDS	1	0	
TR 13	S2+R+HFNC	ARDS	4	0	0.2
		Not ARDS	0	0	
TR 17	S2+T+HFNC	ARDS	2	0	0.333
		Not ARDS	0	0	
TR 10	S2+HP+HFNC	ARDS	4	0	0.133
		Not ARDS	0	1	
TR 14	S2+R+HP+HFNC	ARDS	3	0	0.25
		Not ARDS	0	0	
TR 18	S2+T+HP+HFNC	ARDS	2	0	0.333
		Not ARDS	0	0	
TR 38	S2+HP+I	ARDS	1	16	1.1
		Not ARDS	0	2	

Risk Ratio: <1=Lesser likelihood of non-survival of patients who have ARDS and were treated with the combination of regimen than those who have no ARDS; >1=Greater likelihood of non-survival of patients who have ARDS and were treated with the combination of regimen than those who have no ARDS; 1=no difference in risk of non-survival between groups.

significant predictor of hazard such that the higher the PF ratio then the higher the likelihood of hazard decreasing, in this case the lesser the probability of death happening and survival time of the patients will likely increase (Table 4A, 4B, 4C).

Generally, there was a significant difference in the proportion of survivors and non-survivors for both the patients who have prolonged stay (more than 10 days) and patients who were discharged in 10 days or fewer. There was a 57% risk of non-survival when patients have prolonged hospital stay of more than 10 days. (Table 5A, 5B, 5C) E.g. There was a likelihood of 1.5 times of non-survival when the patients treated with TR 60 have prolonged (more than 10 days) hospital stay or there was more than 100% risk of non-survival when the patients treated with TR 10 (120%) and TR 60 (150%) have prolonged (more than 10 days) hospital stay.

Table 5A. Length of Hospital Stay of Severe to Critical COVID-19 patients

Disposition	Total Cases	Survivor	Non-Survivor	p-value
N	219	65	154	0.000*
Mean	11	17	9	
Minimum	0	7	0	
Maximum	72	55	72	
Interquartile Range	12	12.5	9.25	
Std. Deviation	11.9731	10.7841	11.4615	

* - significant difference at 0.01 level

Table 5B. Categories of Length of Hospital Stay of Severe to Critical COVID-19

Length of Hospital Stay	Disposition		Total	p-value	Risk Ratio
	Survivor	Non-Survivor			
≤10 days	9_a	93_b	102	<0.001**	0.57
>10 days	56_a	61_b	117		
Total	65	154	219		

Each subscript letter denotes a subset of disposition categories whose column proportions do not differ significantly from each other at the 0.05 level.

** - highly significant difference at 0.01 level

Table 5C. Length of Hospital Stay of Survivors vs. Non-survivors of Severe and Critical COVID-19

Combination of Treatment		Length of Hospital Stay	Survivor	Non-Survivor	Risk Ratio
TR 19	S1+I	≤10 days	0	5	0.928
		>10 days	0	40	
TR 60	S2	≤10 days	2	1	1.5
		>10 days	1	0	
TR 62	S2+IN	≤10 days	1	0	1
		>10 days	1	0	
TR 9	S2+HFNC	≤10 days	4	0	0.2
		>10 days	0	0	
TR 12	S2+P+HFNC	≤10 days	2	0	0.667
		>10 days	1	0	
TR 13	S2+R+HFNC	≤10 days	3	0	0.5
		>10 days	1	0	
TR 17	S2+T+HFNC	≤10 days	2	0	0.333
		>10 days	0	0	
TR 10	S2+HP+HFNC	≤10 days	3	1	1.2
		>10 days	1	0	
TR 14	S2+R+HP+HFNC	≤10 days	3	0	0.25
		>10 days	0	0	
TR 18	S2+T+HP+HFNC	≤10 days	2	0	0.333
		>10 days	0	0	
TR 38	S2+HP+I	≤10 days	1	8	0.89
		>10 days	0	10	

Risk Ratio: <1=Lesser likelihood of non-survival of patients who had prolonged (>10 days) hospital stay and were treated with the combination of regimen than those who stayed lesser days; >1=Greater likelihood of non-survival of patients who had prolonged (>10 days) hospital stay and were treated with the combination of regimen than those who stayed lesser days; 1=no difference in risk of non-survival between groups.

There were 85 patients treated with hemoperfusion from the months of May to August. Fifty-nine (69%) of these patients did not survive and this was significantly different to the proportion of patients who survived. (Figures 2 and 3). Seventy-two percent (61) of the patients were male and as seen in Table 6A, there was no significant difference in the mortality and survival rate of the male patients from female patients treated with hemoperfusion (Table 6A). Percentage of the patients who were 65 years old and below (56%) was slightly higher than those patients who were older than 65 years old. There was also no found significant difference in the mortality and survival rate of patients treated with hemoperfusion according to their age (Table 6B).

More than half of the patients treated with hemoperfusion were intubated (54%). There were also patients who were intubated at admission but were also treated with HFNC (8.24%) or nasal cannula (NC)

Table 6A. Sex of patients treated with hemoperfusion

Sex	Total	Disposition		p-value
		Survivor	Non-Survivor	
Male	61 (72%)	19_a	42_a	0.858^{ns}
Female	24 (28%)	7_a	17_a	
Total	85 (100%)	26	59	

Each subscript letter denotes a subset of disposition categories whose column proportions do not differ significantly from each other at the 0.05 level.

ns - no significant difference at 0.05 level

Table 6B. Comparison of survival and mortality rate by age bracket

Age Bracket	Total	Disposition		p-value
		Survivor	Non-Survivor	
≤65 years	48 (56%)	14_a	34_a	0.746^{ns}
>65 years	37 (44%)	12_a	25_a	
Total	85 (100%)	26	59	

Each subscript letter denotes a subset of disposition categories whose column proportions do not differ significantly from each other at the 0.05 level.

ns - no significant difference at 0.05 level

Table 7. Additional treatment to hemoperfusion

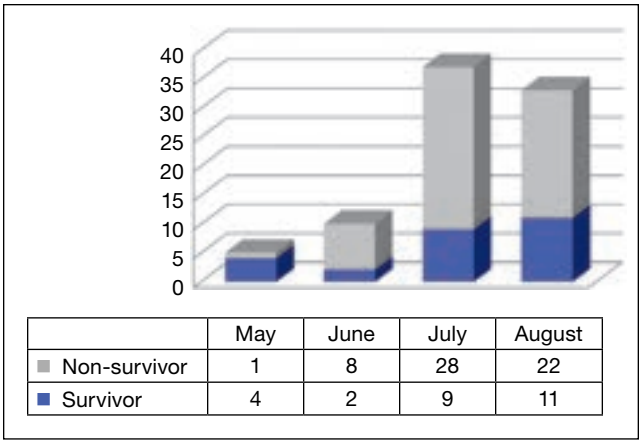
Treatment	Total	Disposition		p-value
		Survivor	Non-Survivor	
Face mask	3 (3.53%)	1_a	2_a	<0.001**
HFNC	14 (16.47%)	13_a	1_b	
Invasive ventilatory support	46 (54.12%)	7_a	39_b	
Invasive ventilatory support + HFNC	7 (8.24%)	0_a	7_a	
Invasive ventilatory support + NC	10 (11.76%)	2_a	8_a	
NC	5 (5.88%)	3_a	2_a	
Total	85 (100%)	26	59	

Each subscript letter denotes a subset of disposition categories whose column proportions do not differ significantly from each other at the 0.05 level.

**- highly significant difference at 0.01 level

HFNC - High Flow Nasal Cannula; NC - Nasal Cannula

(11.76%) during their stay at the hospital; 16.47% were not intubated and treated with HFNC and 5.88% were treated with NC. There were 3.53% who were only treated with hemoperfusion and advised to use face mask only. Over-all, the difference in the survival and mortality rate based on the treatment done was highly significant. The difference was more prominent



	May	June	July	August
Non-survivor	1	8	28	22
Survivor	4	2	9	11

Figure 2. COVID-19 cases treated with hemoperfusion.

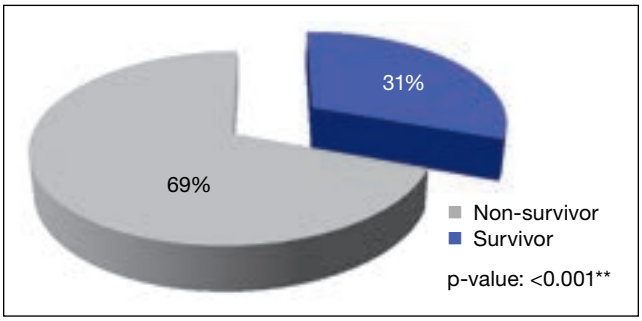


Figure 3. Mortality of COVID-19 cases treated with hemoperfusion.

in the patients treated with (i) HFNC and (ii) invasive ventilator support (Table 7).

Survival and mortality rate of the patients were compared based on their age and treatment. Following the result on treatment, survival and mortality rate across treatment and age bracket was also significant. For the patients who were 65 years old and below, significant difference in the survival and mortality rate was more noticeable for those who were treated with (i) HFNC, (ii) invasive ventilator support, and (iii) NC. On the results on Table 7, significant difference was not that prominent on NC for all patients treated with hemoperfusion, but with age brackets as additional sequence, significant difference became more noticeable. As for the patients who were more than 65 years old, it followed the result of the over-all, where significant difference was more noticeable for patients treated with (i) HFNC and (ii) invasive ventilator support (Table 8).

The month of March marked the earlier incidence of COVID-19. The trend for the number of treatment

Table 8. Comparison of COVID-19 cases based on age bracket and treatment

Age Bracket	Ventilation	Total	Disposition		p-value
			Survivor	Non-Survivor	
≤65 years	Face mask	1	0_a	1_a	<0.001**
	HFNC	6	6_a	0_b	
	Invasive ventilatory support	28	4_a	24_b	
	Invasive ventilatory support + HFNC	4	0_a	4_a	
	Invasive ventilatory support + NC	5	1_a	4_a	
	NC	4	3_a	1_b	
	Subtotal	48	14	34	
>65 years	Face mask	2	1_a	1_a	0.008**
	HFNC	8	7_a	1_b	
	Invasive ventilatory support	18	3_a	15_b	
	Invasive ventilatory support + HFNC	3	0_a	3_a	
	Invasive ventilatory support + NC	5	1_a	4_a	
	NC	1	0_a	1_a	
	Subtotal	37	12	25	

Each subscript letter denotes a subset of disposition categories whose column proportions do not differ significantly from each other at the 0.05 level.

**- highly significant difference at 0.01 level

HFNC - High Flow Nasal Cannula; NC - Nasal Cannula

combinations followed the same trend of the number of new cases. Number of treatment combinations administered was highest for the month of July and August. As the number of cases increase, the treatment combinations also evolved wherein for the month of March to August only, there were 68 treatment combinations formed (Figure 4).

DISCUSSION

This study retrospectively described the characteristics and outcomes of evolving treatment regimens of COVID-19 confirmed severe and critical cases admitted at the LCP. The mean age of survivor and non-survivor (63 and 59 years old) admitted at the ICU

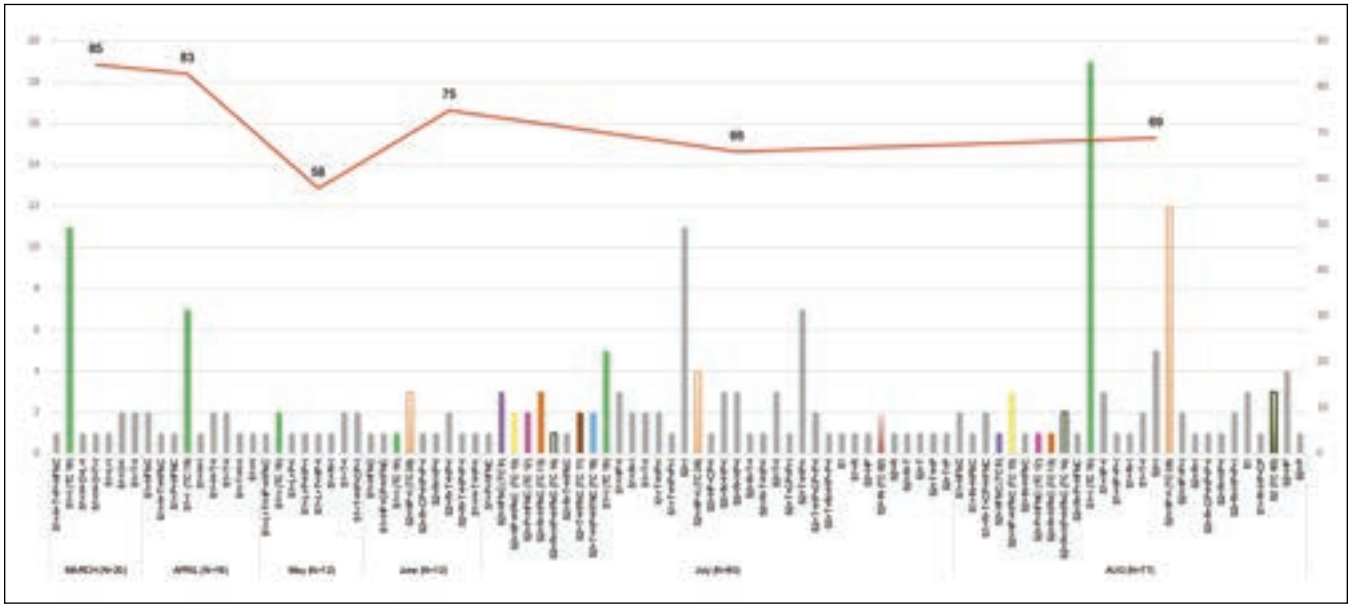


Figure 4. Evolution of treatment regimens in Severe to Critical COVID-19.

had similar findings found by previous studies.[10,19,20] Majority of the patients had hypertension and more than half of the non-survivors were hypertensive. A multivariate analysis showed that hypertension was not an independent factor associated with mortality.[19] In this study, severe and critical COVID-19 survival was found associated with patients with chronic kidney disease. Studies showed an increased risk of severity and mortality in COVID-19 patients with CKD.[21,22] The dysregulation of immune function in COVID-19 patients with CKD and the alterations in ACE2 receptor expression may explain the vulnerability of CKD patients to the SARS-CoV-2 virus.[21]

Patients included in our study were the most unwell, admitted and managed at the ICU, demonstrated by the very high proportions of patients who received invasive mechanical ventilation (70.32%). It has been observed that regardless of the simultaneous treatments, patients who received combinations with invasive ventilation were more likely to die. The use of HFNC in this study lessened the likelihood of death. In a retrospective observational study that included COVID-19 critically ill patients by Mukhtar, et al., the main finding was that the use of non-invasive ventilation is feasible with a high success rate and helped in avoiding invasive mechanical ventilation in 77% of patients with severe COVID-19 disease with an overall mortality rate of 18% against invasive mechanical ventilation (75%).[23] Panadero et al., concluded in their study that high-flow therapy is a useful treatment in ARDS in COVID-19 in the avoidance of intubation or as a bridge therapy.[24] Intubation and mechanical ventilation can be lifesaving but carries with it possible complications (complications of intubation, impaired host defense, effects of endotracheal tube, decreased cough efficacy, impaired mucociliary clearance, ventilator-induced diaphragmatic dysfunction, oxygen toxicity, hemodynamic compromise, and ventilator-induced lung injury).[25]

It was observed in this study that all patients received antibiotics. The study of G. Zhang, et al. showed a significant increase of coinfection with bacteria at 26.1% in severely affected patients with COVID-19 and that the coinfection rate was also higher in the death group with lymphocytopenia and the reduced host immune functions being the main reasons for nosocomial infections in critically ill.[26] According to the Italian Society of Anti-infective Therapy and the Italian Society of Pulmonology pending further studies, they suggest to empirically treat COVID-19 patients according to their clinical syndrome, choosing the best antimicrobial agent or agents on the basis of local guidelines and local antibiotic susceptibility patterns based on the facts that bacterial coinfection is common in patients with viral pneumonia and that it can potentially increase mortality.[27]

Standard of Care in this study has evolved from the combination of antibiotics, oxygen support, multivitamins + zinc, and management of co-morbidities with the addition of dexamethasone and anticoagulant. It can be seen, that all combinations with a decrease in likelihood of death included Standard of Care 2. Interim results of the RECOVERY trial provided evidence that treatment with dexamethasone at dose of 6 mg once daily for up to 10 days reduces 28-day mortality in patients with COVID-19 who are receiving respiratory support, however, there was no benefit and with the possibility of harm among who did not require oxygen. The trial also hypothesized that the greater mortality benefit of dexamethasone in patients with COVID-19 was likely due to immunomodulation of the proinflammatory response.[28] Previous studies showed that coagulopathy may complicate severe COVID-19 disease.[29,30] The finding that the incidence of thrombotic complications in critically ill patients with COVID-19 was high at 31% supports the recommendation of pharmacological thrombosis prophylaxis in all critical COVID-19 patients and the suggestion of high prophylactic doses.[29]

Simultaneous treatment with remdesivir, interferon, tocilizumab, proning, and hemoperfusion were also used in the combinations. Interim WHO Solidarity trial results showed that remdesivir and interferon had little or no effect on hospitalized patients with COVID-19, as indicated by overall mortality, initiation of ventilation, and duration of hospital stay.[31] Overall findings of a double-blind, randomized, placebo-controlled trial showed that a 10-day course of remdesivir had a shorter time to recovery and that remdesivir may have prevented the progression to more severe respiratory disease.[32] In another randomized, double blind, placebo-controlled, multicenter trial, it showed that remdesivir was not associated with statistically significant clinical benefits, but was associated with

a numerical reduction of 5 days in median time to clinical improvement.[33]

Sallard et al. in their research concluded that Interferon B1a may account for a safe and easy to upscale treatment against COVID-19 in the early stages of infection and in the late phases anti-interferon drugs may be used to mitigate the pathology.[34] A study made by Sheahan et al. showed that the combination of interferon-1 (IFN-1) with lopinavir/ritonavir, ribavirin or remdesivir could improve its efficacy.[35]

A single center retrospective study done in Wuhan, China supported the effectiveness of tocilizumab in the prevention or treatment of cytokine storms induced by COVID-19. It also suggested that a single dose of tocilizumab in combination with glucocorticoid seems to fail to improve the disease activity in critically ill. In addition, they found out that a single dose of tocilizumab is more likely to be effective than glucocorticoid in the treatment of COVID-19.[36]

The study of Hallifax RJ, et al. were first to demonstrate favorable clinical outcomes in patients who are able to awake prone, wherein successful proning was achieved in 36.7%, and semi-proning in 56.7% patients. The data demonstrate a significant association between full proning and reduced mortality.[37]

Case reports of a COVID-19 patients admitted at the ICU showed that the application of CRRT/HP in the early stages of ARDS prevented the progression of the disease, prevented intubation and improved clinical conditions.[38,39] The reason for COVID deaths is suspected to be the "cytokine storm," defined by Cron and Behrens as an activation cascade of auto-amplifying cytokine production due to unregulated host immune response to different triggers (infections, malignancy, rheumatic disorders, etc.)[40] The application of hemoperfusion may reduce the burden of cytokines cutting the peaks in a nonspecific way resulting to a less severe derangement of the immune system and to an improved level of host immune response.[41]

The median APACHE II score of all patients was 12. Cox regression analysis on APACHE II score and PF ratio score showed that an increased APACHE II score increased the likelihood of death and an increased PF ratio score lessened the probability of death. In this study, patients with increased APACHE II score and decreased PF ratio score received invasive ventilation and with a higher number of non-survivors as demonstrated by TR 19 (Standard of Care 1 and invasive ventilation) and TR 38 (Standard of Care 2 + hemoperfusion + invasive ventilation). These findings are supported by the study of Yang et al. that showed that PaO_2 to FiO_2 ratio was significantly lower in non-survivors and that based on APACHE II score non-survivors were in a more critical condition.[10] A study made by Grasselli et al. also showed that a low PaO_2/FiO_2 was an independent risk factor associated with mortality.[19]

Previous studies in critically ill patients which showed that median length of hospital stay were 7-14 days.[10,19] Based on length of hospital stay, combinations with invasive ventilation were found to be high predictors of death.

This study showed that from March 2020 to August 2020, the institution has used 68 treatment regimens in the management of severe and critical cases in COVID-19. A spike of new cases was observed for the months of July (80) and August (77). The spike occurred a month after (June 1, 2020) Metro Manila exited modified enhanced community quarantine and transitioned to general community quarantine. The evolving treatment regimen in general, has resulted in a significant decline in mortality rate (from 85% to 69%). The use of hydroxychloroquine/chloroquine, lopinavir/ritonavir and oseltamivir ceased by the month of June. Interim results of Solidarity trial and RECOVERY trial showed no definite effect on mortality of hospitalized patients.[41] A study on the clinical efficacy of hydroxychloroquine in patients with COVID-19 requiring oxygen found that 10% of the patients in the treatment group had electrocardiographic modifications that required discontinuation of treatment.[42] Tan, Q. et al., found that oseltamivir is ineffective against SARS-CoV-2 in vitro study and its use did not improve the patient's symptoms and signs and did not slow the disease progression.[43]

The institution's Standard of Care has evolved with the addition of dexamethasone and anticoagulant. This is compatible with studies that showed clinical benefits of adding dexamethasone and anticoagulant in the management of COVID-19.[28-30]

CONCLUSION

In this retrospective cohort study of treatment outcomes of evolving treatment regimens among severe and critical COVID-19 confirmed patients admitted at the LCP, a total of 68 regimens were used. Out of the 68 regimens that were used 11 combinations of treatment regimens have significant difference in the proportion of survivors and non-survivors. Patients in combinations that included invasive ventilation have higher APACHE II score, lower PF ratio score, shorter hospital stay and were more likely to die. Use of HFNC and Standard of Care with anticoagulant and dexamethasone decreased the likelihood of death.

Limitations and Recommendations

This is a retrospective study that relied on data that were recorded in medical charts by the attending physicians. The population is small for the number of treatment combinations obtained from this study. The authors recommend that a future study be undertaken focusing on the 11 combinations of treatment regimens that were found to have significant difference in the proportion of survivors and non-survivors for supportive evidence for potential treatments in COVID-19. A continuation of the study is also recommended to further describe the continuously evolving treatment regimens and its outcomes in severe and critical COVID-19 patients.

Supplementary Material

The complete table of the Test of Proportions is available upon request from the corresponding author.

Authorship

All authors have certified fulfillment of Scientific Proceedings authorship criteria.

Disclosure of Conflicts of Interest

All authors have no conflict of interest to disclose.

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LUNG CENTER OF THE PHILIPPINES
Scientific Proceedings

Clinical Course and Exposure Characteristics of COVID-19 Confirmed Healthcare Personnel at the Lung Center of the Philippines

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ABSTRACT

Introduction. Coronavirus disease 2019 (COVID-19) has been posing a public health threat worldwide since early 2020. The steep rise in the number of individuals who are infected in a short span of time, has led to widespread community lockdowns, and has overwhelmed health care systems around the globe. This has put healthcare personnel (HCP) at potential risk for acquiring and transmitting the infection. The Lung Center of the Philippines (LCP) was identified as a COVID-19 referral hospital at the start of the pandemic and no reports nor prior study were done previously on the prevalence and clinical presentation of coronavirus disease 2019 among HCP working on the frontlines.

Objective. The study aimed to describe the clinical characteristics and determine the exposure risks of HCP with COVID-19 at the LCP.

Methodology. This is a retrospective cohort study among HCP of the LCP, with laboratory-confirmed COVID-19 cases using conventional real time reverse transcription polymerase chain reaction (RT-PCR) testing or SARS-CoV-2 Xpert Xpress, done at LCP from March 1 to November 30, 2020.

Results. A total of 141 subjects were noted to have tested positive at least once for COVID-19. Fifty percent (50.4%) were females and 49.6% were males. Mean age was 37 years old while median age was at 33. Thirteen percent had at least one underlying illness, most common of which was hypertension. Ninety-five percent of infected healthcare personnel were non-smokers. Forty-seven percent (67/141) provided direct care and or had access to COVID-confirmed patients within the hospital, whereas 53% (74/141) were assigned to non-COVID units. Eighty percent (114/141) of all COVID-19 cases involving HCP were categorized as having the mild form of disease upon consult. Fifty-three percent of these were asymptomatic carriers, screened only through scheduled monthly routine testing. Moreover, 29% percent of these asymptomatic carriers eventually developed mild symptoms of myalgia, colds, headache, dizziness, non-productive cough at an average of 5 days after the result of swab test and were re-classified as presymptomatic. Thirty-nine percent (55/141) were admitted, 26% were sent to DOH-designated quarantine facility and only 35% were sent to self-quarantine at their respective own homes. Transmission routes identified were 41% community-acquired, 50% from occupational exposure (30% from direct patient contact, 20% from co-worker), and lastly 8% with unknown transmission source. All patients had favorable outcome.

Conclusion. Majority of the HCP who were infected with COVID-19 in the LCP belonged to a younger age group and were found to be asymptomatic, presymptomatic or with some form of mild disease. This study also showed that working in high-risk exposure units may not confer increased risk of infection, possibly due to adequate and efficient use of available measures of protection. The greatest risk to healthcare personnel may be individuals who are asymptomatic or presymptomatic in the early stages of COVID-19 infection, including their own work colleagues and family members at home.

Keywords: COVID-19, SARS-CoV-2, health personnel, transmission, occupational exposure

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) is brought about by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which was believed to have originated from animal reservoir hosts in a seafood market in Hubei province in China.[1,2]

Pandemic transmission of SARS-CoV-2 via respiratory droplet has already caused more than 3.1 million infections with more than 200,000 deaths globally over a period of 4 months. The steep rise in the number of individuals who are infected in a short span of time, has led to widespread community lockdown, and has overwhelmed health care systems around the globe. This has put healthcare personnel (HCP) at potential risk for acquiring and transmitting the infection.[3,4]

The Lung Center of the Philippines (LCP) was identified as a COVID-19 referral hospital at the start of the pandemic and no reports nor prior study were done previously on the prevalence and clinical presentation of coronavirus disease 2019 among HCP working on these frontlines.

Since January 2020, the LCP has started its preparations for the novel coronavirus outbreak. A team of physicians, nurses, engineers, and department heads, comprised the Emerging and re-emerging Infectious Diseases Task Force, whose role was to spearhead the policy and protocol development and response management and its implementation. The primary goal of the team was the timely and adequate management of suspeeted and confirmed cases. As of September 2020, in the Philippines, there are 248,947 COVID-19–confirmed cases nationwide, 120 thousand cases within Metro Manila and an estimated 59 thousand confirmed cases among HCP, this seemed to be congruent in the numbers seen in LCP, where approximately 121 healthcare workers (HCWs) have already been infected and the trend had been on the rise.

Several challenges have already been identified at the forefront. Among the most important were limited access to medical equipment, infrastructure, medical supplies and manpower scarcity. Concurrently, the personnel's safety and welfare are of topmost priority to ensure that the services be provided continuously.

This study aimed to determine the clinical characteristics and exposure risks of HCP with COVID-19 at the LCP. The results of this study shall provide understanding on the dynamics of HCP COVID-19 infections in the hospital setting and guide in hospital policy makers in creating measures in order to keep its HCP COVID-19 free.

METHODOLOGY

Study Design

This is a retrospective cohort study conducted at the LCP, a respiratory specialty center, which was identified by the Department of Health (DOH) last March 2020 as one of the COVID-19 referral centers to aid in the emergency outbreak. Currently, it has allotted 99 beds for moderate to critical COVID-19 patients. The study was completely descriptive and data were collected and described through mean percentages of the demographic variables, community exposure, workplace information, disease severity and outcome.

Subjects

The study subjects were LCP healthcare personnel, regardless of age and employment status, with laboratory-confirmed COVID-19 cases using conventional real time reverse transcription polymerase chain reaction (RT-PCR) testing or SARS-CoV-2 Xpert Xpress, done at LCP from March 1 to November 30, 2020.

Sampling

This study employed consecutive sampling and included all LCP healthcare personnel with laboratory-confirmed COVID-19 cases using RT-PCR testing or SARS-CoV-2 Xpert Xpress from March 1 to November 30, 2020.

Ethical Considerations

The study protocol was reviewed and approved by the LCP Technical Review Board (TRB) and Institutional Ethics Review Board (IERB). No informed consent was disseminated since the study was done through chart review. Patient confidentiality was maintained throughout the data collection. Data transcribing was done in a private room without any visible patient identifiers.

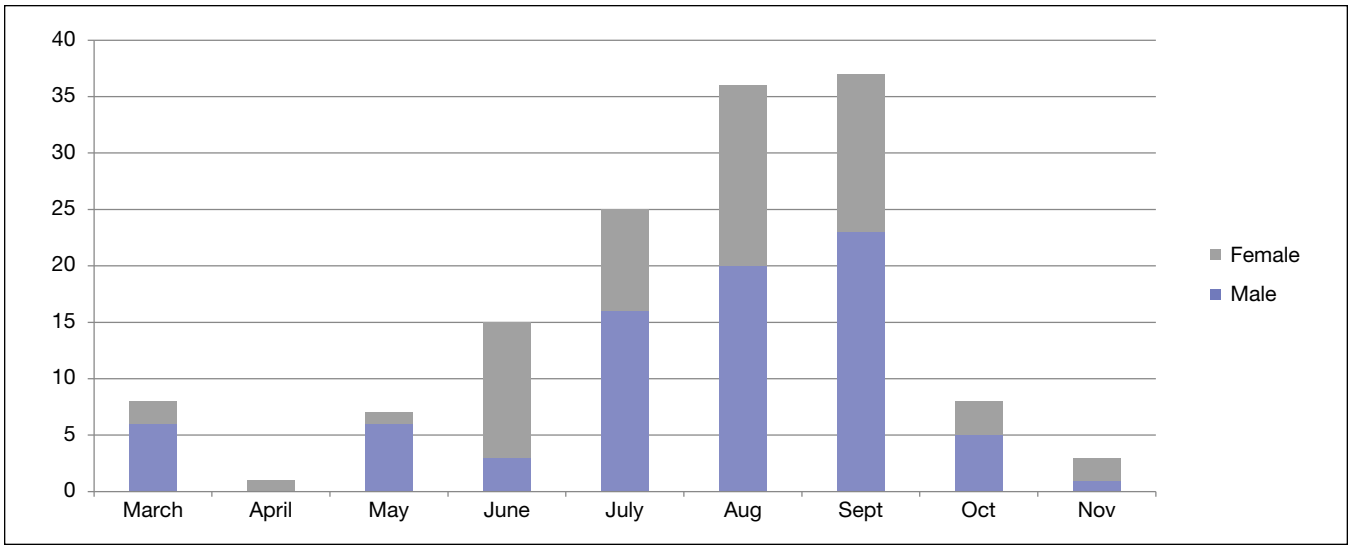

Figure 1. Gender distribution of healthcare personnel in LCP with COVID-19.

Data Review

Data from the Employees' Clinic of LCP were reviewed and collected to identify all LCP healthcare personnel diagnosed to have COVID-19 by RT-PCR or Xpert Xpress from March 1, 2020 to November 30, 2020. Inpatient charts were retrieved for those who were admitted at LCP. No informed consent form was employed since the study covered only chart and existing data review. Data were retrieved from the employees' clinic records and LCP medical records.

Statistical Analysis

Outcome measures included clinical characteristics in terms of the following: asymptomatic, presymptomatic and symptomatic, depending on the disease severity and course of COVID-19 positive HCP upon detection. Exposure risks were described in terms of area of assignment and severity of COVID-19 disease of patients being handled (high-risk and low-risk). Also, possible sources of infection were identified based on records of contact tracing and medical records. Clinical outcome of the subjects was tagged as either recovered or expired after com-pletion of prescribed duration of isolation/quarantine also identified from the subjects' charts (Appendix).

RESULTS

Baseline Characteristics

A total of 141 subjects were included in the study. From March 1 to November 30, 2020, out of 800 LCP employees, 141 (17.6%) subjects were noted to have tested positive at least once for COVID-19, whereas five HCWs tested positive twice on RT-PCR within the 9-month period. There is a near equal distribution of subjects between genders – 50.4% were females and 49.6% were males (Figure 1). Mean age was 37 years old while median age was at 33. Thirteen percent had at least one underlying illness, most common of which was hypertension. Ninety-five percent of infected HCP were non-smokers (Table 1).

Exposure Risk Based on HCP Classification and Work Assignment

Forty-seven percent (67/141) of HCWs who tested positive provided direct care and or had access to COVID-confirmed patients within the hospital, whereas 53% (74/141) were assigned to non-COVID units, performed tasks not related to providing direct care to COVID-confirmed patients (Figure 2, Table 2).

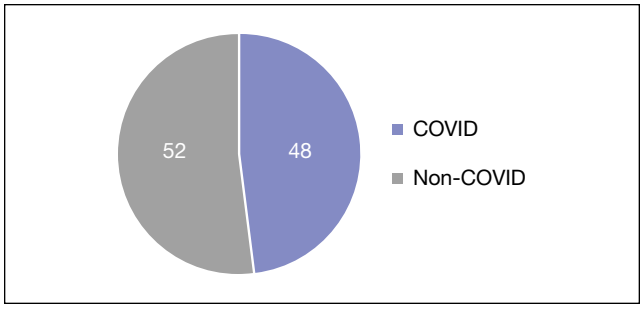

Figure 2. Work assignment of healthcare personnel with COVID-19 in LCP with COVID-19.

Table 1. Baseline characteristics of healthcare personnel in LCP with COVID-19

Characteristics	Number (%)
Age (years)	
Mean	37
Range	21-64
Median	33
18-30	18 (12.7)
31-40	66 (46.8)
41-50	23 (16.3)
51-60	11 (7.8)
>60	3 (2.12)
Sex	
Male	70 (49.6)
Female	71 (50.4)
Co-morbidities	
Hypertension	14(13)
Diabetes Mellitus	4 (4)
Bronchial Asthma	2 (2)
Pulmonary Tuberculosis	3 (3)
Smoking History	
Smoker	7 (5)
Non-Smoker	134 (95)

Table 2. Living and occupational risks of healthcare personnel in LCP with COVID-19

Characteristics	Number (%)
HCP Classification	
HCW First-Line	67 (47.5)
HCW Non-First Line	10 (7)
Non-HCW	64 (45)
Work Assignment	
COVID	67 (48)
Non-COVID	73 (52)
Administrative areas with exposure to COVID wards	9 (7)
Administrative areas without exposure to COVID wards	31 (22)
Employment Status	
LCP	107 (75.8)
DOH	34 (24.2)
Residence while in LCP	
Home	102 (72)
LCP shelter	39 (28)

Severity

Eighty percent (114/141) of all COVID-19 cases involving HCP were categorized as having the mild form of disease upon consult. Furthermore, 53% of these were asymptomatic carriers, screened only through scheduled monthly routine testing, 29% (11/49) of these asymptomatic carriers eventually developed mild symptoms of myalgia, colds, headache, dizziness, non-productive cough at an average of 5 days after the result of swab test and were later reclassified as presymptomatic. The remaining 47% were symptomatic and were noted to have sought consult 1-3 days after onset of mild. Most of the reported symptoms, were mild ranging from colds, low grade fever, myalgia, anosmia and ageusia (Figure 3).

Table 3. Clinical course of healthcare personnel with COVID-19 in LCP with COVID-19

Clinical Course	Number (%)
Clinical Presentation	
Asymptomatic	43%
Presymptomatic	11%
Symptomatic	46%
Disease classification	
Mild	88%
Moderate	11%
Severe	0%
Critical	1%
Place of Isolation	
Hospital	45%
Home	35%
Facility	20%
Outcome	
Recovered	100%
Expired	0%

Table 4. Possible exposure sources of healthcare personnel in LCP with COVID-19

Exposure Characteristics	Number (%)
Source	
Patient	39 (27.6)
Co-worker	23 (16)
Family	67 (41)
Unknown	12 (9.4)
Risk Category	
High	67 (48)
Low	73 (52)

Clinical Course

Thirty-nine percent (55/141) of COVID-confirmed HCP were admitted, 26% sent to DOH-designated quarantine facility and only 35% were sent to quarantine at their own homes outside of the LCP (Table 3). Seventy-five percent of these admitted cases were classified as mild, whereas 20% were moderate. Only 1 individual required invasive mechanical ventilation.

Possible Transmission Routes

Based on monthly tallies, April had the least number of cases with only 1 lone case of COVID-19 among HCWs whereas the number of cases increased markedly reaching its peak last August when 32% of the total number of affected HCWs were infected. Transmission routes identified were mostly from direct patient contact during March and April, and gradually became community-acquired from June to November (Table 4). Overall, 41% of infections recorded at the LCP were from the community (Figure 4).

DISCUSSION

The findings of this study were similar to the ones done in the United States during a similar period, 9,282 (19%) were identified as HCP, and (55%) reported contact with a COVID-19 patient only in health care settings.[5] Since then, the number of reported HCP with COVID-19 has increased tenfold. Most HCP with COVID-19 were female (79%), aged 16-44 years (57%), not hospitalized (92%), and without any underlying medical conditions. In the Netherlands, the noted patterns of transmissions were consistent with multiple introductions into the hospitals through community-acquired infections and local amplification in the community which were also seen in this study.[6] A summary report from China had suggested that transmission of the disease among HWs is associated with overcrowding, absence of isolation room facilities, and environmental contamination.[7] In a rapid review of 11 observational studies the following were identified as risk factors for acquiring COVID-19: lack of personal protective equipment (PPE), exposure to infected patients, work overload, poor infection control, and pre-existing medical conditions were identified as risk factors for COVID-19 among HWs.[8] Understanding SARS-CoV-2 infection among HCP and the risk factors for adverse outcomes is crucial not only for characterizing virus transmission patterns and risk factors for infection, but also for preventing future infection of essential human workforce and other patients, but also for informing and updating infection prevention and control measures at healthcare facility and hopefully at a national level.[9-12] After these data and changes in the infection control protocol were implemented in the LCP through the COVID-19 task force, a steady decline in the number of transmissions inside the hospital through direct patient contact was seen.

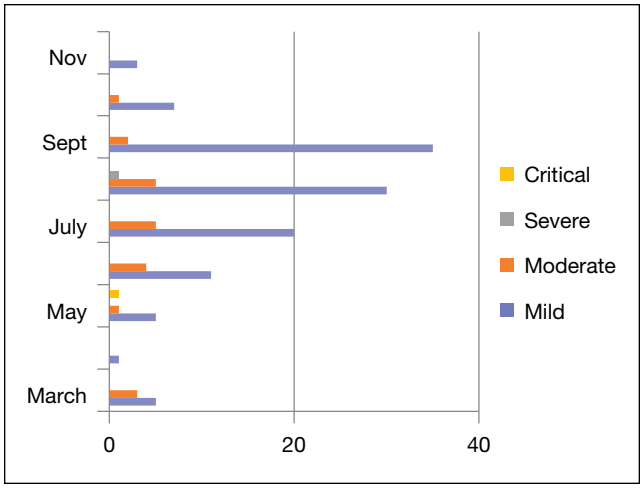

Figure 3. Severity of COVID-19 among affected healthcare personnel at the LCP.

Safety of HCP from COVID-19 infection is central for the resilience of our healthcare system in the face of a global pandemic such as COVID-19.[13,14] Noted exposure was from the community since there was a gap of knowledge and awareness among the general population during that time concerning the behavior of the disease. Identified route of exposure for these first 8 cases were mostly from direct contact

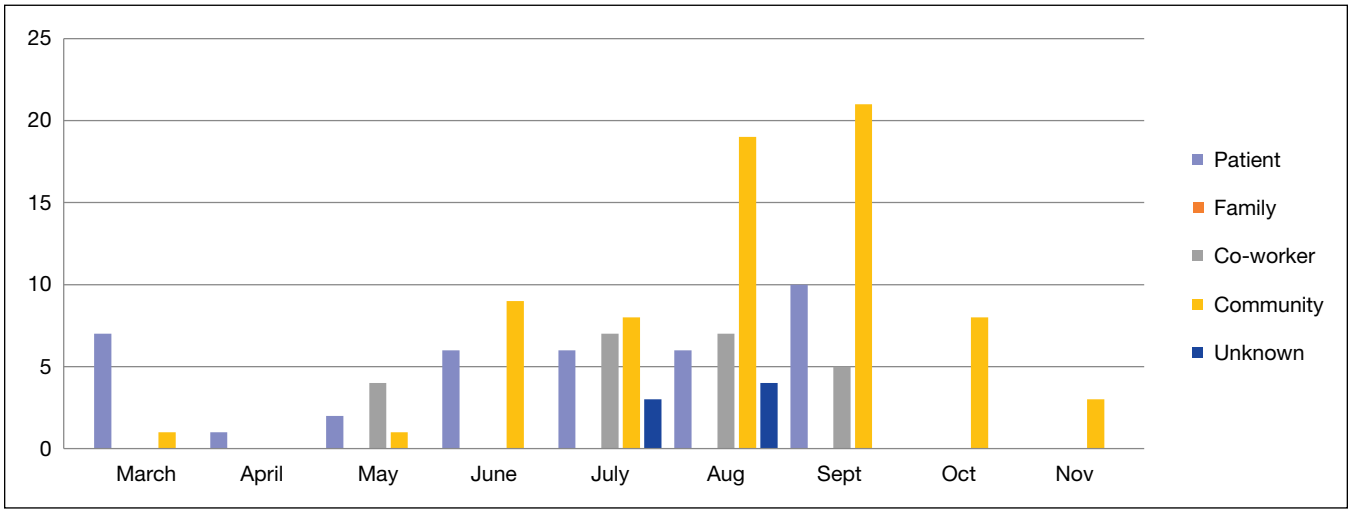

Figure 4. Transmission routes of infection of healthcare personnel in LCP with COVID-19.

to confirmed cases, since most were present during aerosol generating procedures, and hardly were compliant to prescribed PPE with likely a breach of a non-well-fitting mask. Figure 3 shows the monthly census of HCP in the LCP with COVID-19 from March to November 2020. The effect of the community lockdown coupled with concerted and timely efforts of the institution's task force has seemingly led to a significant decrease in new cases especially among its workforce. There was a silent period of 30 days straight, during when no new infection among HCP was recorded. Towards the rear end of the month of April, there was only one case of COVID-19. Case 9 who was a first-line HCW (respiratory therapist) assigned at the ER Triage and Extension. She was asymptomatic, and clinical course was uneventful and her case was only noted through routine testing. Again, a possible PPE breach was considered and donning and doffing procedures of the individual affected were checked and noted correct. A community source of transmission was thus entertained.

At this point, it was noteworthy that a higher rate of infection was found among those working in the high-risk areas during the early stage of the disease outbreak, especially among frontline HCP, most of whom had the milder form of disease state, with an asymptomatic carrier prevalence of 0.2%. This relatively low infection rate is suggestive that proper use of PPE, if and when available, can protect frontline HCWs directly caring for patients with COVID-19 and potentially curtail nosocomial transmission. This was similar to the findings of the studies done during the very early course of the pandemic.[15-17]

Concurrently, the apparent higher rate of infection among HCWs working in low-risk areas during the subsequent months especially after the community lockdown has been lifted then deserves further investigation (Figures 4 and 5). Possible reasons inferred why those HCWs with supposedly less exposure to the virus, had a bigger risk of contracting the virus could be non-compliance of infection control protocols among the hospital staff. By May 2020, there were only again 7 cases recorded. Cases 10-14 who were not involved in direct care of COVID-19 confirmed patients however their tasks included the installation of negative pressure rooms and vents for the COVID-19 units to function. The possible mode of exposure for this group of cases was at their shelter inside LCP premises where they were admittedly eating together, unknowingly disregarding social distancing and ultimately deviating from policy. After this reported incident, strict social distancing and timing of meals were implemented.

By June 2020, there was a slight increase in the number of cases among HCP in the institution albeit majority again from the community. Cases 17-25 and case 31 reported possible community exposures. Clusters of infection were traced from small family gatherings inside homes of reported cases, such as with cases 17, 18 and 25, whose respective family

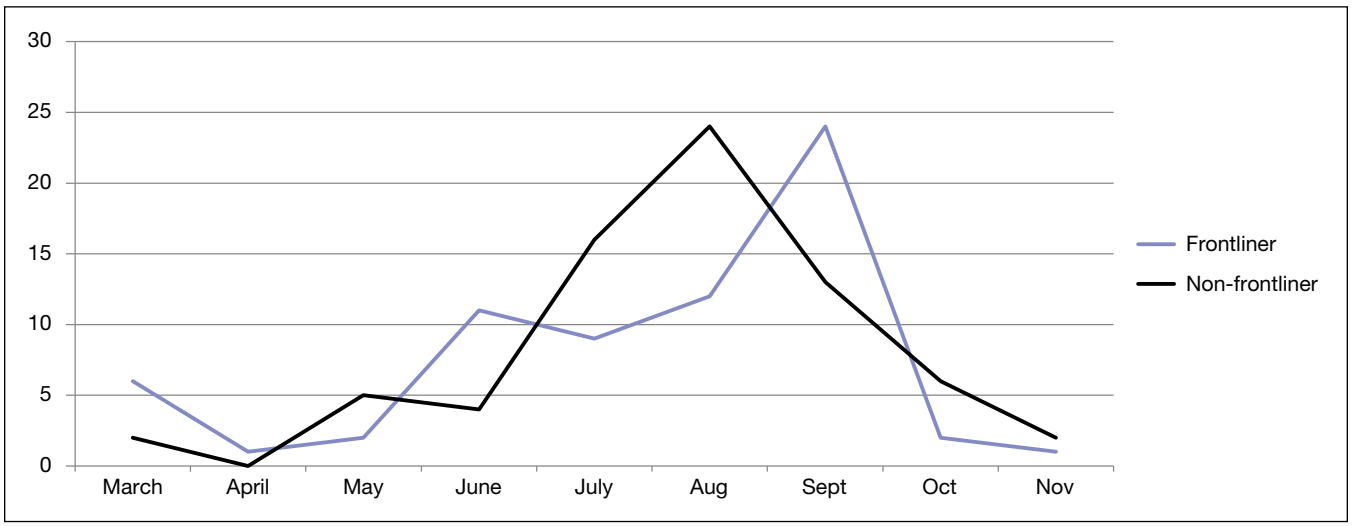

Figure 5. Monthly census of COVID-19 cases in LCP from March to November 2020.

members have subsequently been reported to be positive of the disease.

A continuous spike in the number of confirmed COVID-19 cases in our country was recorded in July 2020. At this point the COVID-19 bed occupancy rate was steadily increasing up to 47.8% nationwide, with the LCP reporting 100% bed occupancy almost daily. Among the HCP, there were 24 cases, 14 of which were acquired from community exposures with easing up of restrictions.

By August 2020, the steep rise in the number of cases both nationwide and among HCWs seemed to be unstoppable. There was a total of 36 cases recorded in August 2020, which clearly has increased from the previous month. The most common route of exposures recorded for this month were those from a HCP infected from the community then spreading the virus to his/her co-workers. Again, it is useful to mention that most of the HCP infected were not assigned in COVID-19 designated units. Possible reasons and were already mentioned previously were the seemingly lower rate of adherence to prescribed PPE at non-COVID-19 facilities, blunt complacency with imposed infection prevention precautions, and unrecognized/subclinical infection among patients and co-workers.

The WHO-China Joint Mission on COVID-19, summarized some reasons for such a high number of infected HCWs during the beginning of the SARS-CoV-2 emergency outbreak. First, inadequate personal protection of HCWs at the beginning of the epidemic was a central issue. The long-time exposure to large numbers of infected patients directly increased the risk of infection for HCWs, and also work intensity and lack of rest.[18] The reasons for the increase in the non-frontline risk as the months pass by have yet to be elucidated and we can only suggest that an attitude of complacency and non-compliance are both contributory.

The hospital and its staff have since adapted the mandatory use of the face shield worn together with face mask since August 15 to stem the workplace exposure. Ultimately, beyond the recognition of loopholes in our response in the ongoing pandemic and subsequent reassessment, the management of HCP exposed to COVID-19 virus will vary according to the risk categorization with the goal of keeping the valuable human workforce afloat.

In most hospitals, including the LCP, initial IPC responses to COVID-19 followed paradigms built for other respiratory viruses: identification of symptomatic cases meeting a clinical case definition, SARS-CoV-2 RT-PCR testing of upper respiratory samples, and isolation of these patients with enhanced IPC precautions.

Spearheaded by the hospital's Incident Command System, the changes implemented were: Engineering modifications in the wards, which included updating of the exhaust systems, barriers, and patient monitors to minimize HCW contact, mitigation efforts by IPC especially proper use of prescribed PPEs, and a focus on the immediate and accurate diagnosis of COVID-19 from efficient triage, to fast reliable testing and release of results. These measures may have been effective as the most recent numbers have begun to the decline, however the trend, which seemed to mirror that of the country on a national scale, there were still so many things to learn about the nature and behaviour of COVID-19 to say that we are seeing the tail end of the pandemic seems rather hopeful. It is more prudent therefore to reason that It takes concerted effort and commitment both by the hospital and the workforce to sustain the contingency plan into continuity.

CONCLUSION

Over a 9-month period, 141 HCP were noted to have tested positive at least once for COVID-19. Majority of the HCP who got infected with COVID-19 belong to the younger age-group and presented either as asymptomatic, presymptomatic, or with mild symptoms and had favorable outcome. This study also showed that working in high-risk exposure units may not confer increased risk of infection, possibly due to adequate and efficient use of available measures of protection. The transmission routes identified were person to person contact not necessarily inside the facility. The greatest risk to HCWs may be individuals who are asymptomatic or presymptomatic in the early stages of COVID-19 infection, including their own work colleagues and family members at home.

Authorship

All authors have certified fulfillment of Scientific Proceedings authorship criteria.

Disclosure of Conflicts of Interest

All authors have no conflict of interest to disclose.

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APPENDIX

LCP HCP Classification

- Healthcare Workers (HCW) – Individuals providing services related to health needs of patient either directly with contact or indirectly, with rotation inside the COVID-designated units
- Non-Healthcare Workers (NHCW) – Individuals whose tasks include completion of services not related to health needs of patients such as administrative and engineering work
- First Line – Healthcare personnel who have direct exposure, and/or involved in the direct care of patients, with access to COVID-19 confirmed patients or designated areas in the hospital / hot zones
- Non-First Line – Healthcare personnel who have direct exposure, access to COVID-19 confirmed patients or designated areas in the hospital / hot zones

Exposure characteristics based on risk categorization/Work Assignment

- High-risk – Exposure less than 2 meters and >15 minutes to a confirmed COVID-19 individual, HCP not wearing a respirator or facemask, eye protection, or if the person with COVID-19 was not wearing a cloth face covering or facemask. This also includes HCP not wearing all recommended PPE (i.e., gown, gloves, eye protection, respirator) while performing an aerosol-generating procedure, such as intubation, CPR and suctioning of secretions
- Low-risk – Those healthcare personnel with exposure risk other than described above

Area Classification

- COVID Areas – These are the areas where COVID-19 suspected and confirmed patients are received, admitted and grouped together to promote containment of the disease. Level 4 PPE was required to enter these identified zones. The healthcare workers in these areas were encouraged to stay within their allocated zone for their entire shift and not move into other zones. Appropriate and limited entry/access to the zones were instituted as well as adequate air filtration (HEPA) filters were attached to supplement existing air systems in these areas. In addition to a single room with its own bathroom, single negative pressure ventilation isolation rooms were made available. These included the following: Emergency Room / Triage Complex and Radiology department where patients were initially received and individually triaged prior to admission. These areas were also designated as the holding area for newly admitted COVID-suspect semi-private and pay ward patients while waiting for RT- PCR GeneXpert result. Critically ill COVID-confirmed patients were stationed at the critical care units of the hospital, these were spacious enough to accommodate mechanical ventilator and included the following: (St. Therese Unit, Respiratory Intensive Care Unit, Medical Intensive Care Unit and Ward 3B). All the other COVID-confirmed patients classified as mild, moderate and severe based on their oxygen requirement were stationed and admitted at wards 3A, 2A, 2B found on the second and third level of the hospital.
- Non-COVID Areas – These are zones/areas in the hospital where non-COVID individuals, verified by a negative RT-PCR were admitted. Patients were transferred to appropriate pre-assigned non-COVID rooms, which were basically the same hospital rooms available prior to the COVID-19 pandemic. These rooms had minimal changes done to them in terms of ventilation and procurement of filters. Level 3 PPE was encouraged to be used when staying in these identified areas. In the hospital, during the time the study was conducted, only 2 ward units both found in the third floor were utilized to accommodate non-COVID patients, hence the designation Ward 3C and 3D. Barriers were attached along the entry and exit points and a separate elevator car was used to transport patients and medical equipment in and out of these areas.

Exposure characteristics based on possible source

- Patient – Exposed/close contact with COVID-19 confirmed patient seen/ admitted in LCP
- Co-worker – Exposed/close contact with COVID-19 confirmed co-worker
- Family member – Exposed/close contact with COVID-19 confirmed family member

- Others – Exposed/close contact with COVID-19 confirmed case other that in-patient, co-worker, family member
- Unknown – Possible exposure/ source of infection cannot be identified

Clinical Course

- Asymptomatic – Absence of any COVID-19 related symptom upon knowledge of positive result and was asymptomatic from 2 days before testing and throughout the isolation period of 14 days
- Presymptomatic – Initial absence of any COVID-19 related symptoms up to 2 days prior and upon knowledge of positive result, but who later developed cough, fever, dyspnea, headache, malaise, anosmia, ageusia, throughout the isolation period
- Symptomatic – Presenting any symptoms related to COVID-19 during the time of testing/consult

Disease Severity classification (DOH)

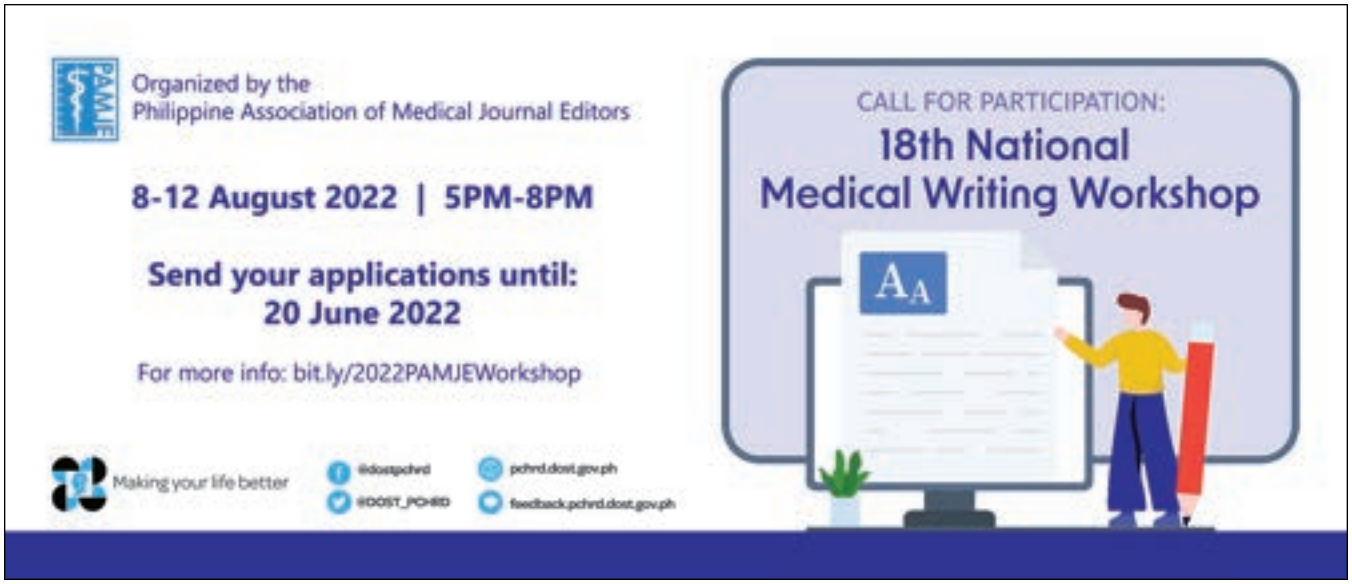
- Mild disease – Subjects with sore throat, anosmia, ageusia who are COVID-19 confirmed cases without evidence of viral pneumonia or hypoxia
- Moderate disease – Subjects with signs and symptoms of pneumonia (fever, cough, dyspnea, tachypnea)
- Severe disease – Subjects with clinical signs and symptoms of pneumonia upon arrival at the triage plus tachypnea or respiratory rate >30cpm, severe respiratory distress, or oxygen saturation <90% at room air
- Critical disease – Subjects with acute respiratory distress syndrome (ARDS), sepsis (life-threatening organ dysfunction caused by a dysregulated host response to infection with signs and symptoms of tachycardia, confusion/disorientation, fever, shortness of breath, and cold clammy skin), or septic shock (subset of sepsis with circulatory and cellular/metabolic dysfunction, which causes persisting hypotension requiring vasopressors to maintain a mean arterial pressure of 65 mmHg or higher and a serum lactate level greater than 2 mmol/L despite adequate volume resuscitation).

Place of Isolation

- Hospital – Healthcare personnel who were admitted in the hospital
- Home – Healthcare personnel assessed clear for home quarantine of those who opted to do home isolation and self-monitoring
- Facility – Healthcare personnel assessed clear for transfer to a designated isolation facility or those who opted to submit to facility isolation and self-monitoring

Outcome

- Recovered – Healthcare personnel who had improved symptoms upon discharge from isolation, or had completed the required number of days of isolation
- Expired – Healthcare personnel who succumbed to COVID-19 illness



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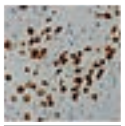
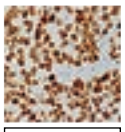


TTF-1 IHC Pulmonary Adenocarcinoma



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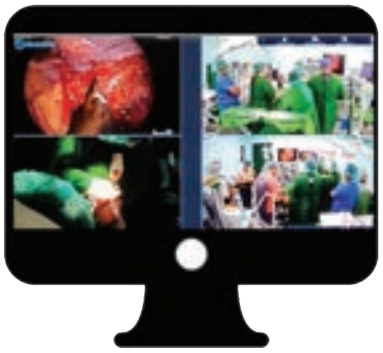

Submissions

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

Cover Letter

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

Author Form

The **Scientific Proceedings** Author Form (SPLCP-2021-AF-001) includes a certification of fulfillment of authorship criteria for all authors listed, declaration of conformity to publication ethics and ethical standards for experiments on human/animal subjects and approval by the appropriate ethics committee, disclosure of conflicts of interest where existing, and agreement to copyright transfer. Complete names of the authors, title indicating the highest educational attainment (e.g., MD, MSc, PhD), and name and location of not more than one (1) institutional affiliation, should be indicated.

Ethical Review Board Approval

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

Informed Consent Form

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

Article Categories

The **Scientific Proceedings** publishes articles in the following categories:

Original Articles	Original articles include clinical trials, laboratory investigations, clinical epidemiology, and evaluations of diagnostic and surgical techniques. Original articles should not exceed 25 typewritten pages (8.5 x 11 in., 1 in. margins at both sides, double spaced, excluding tables, figures, illustrations and references) or 6,000 words.
Systematic Review and Meta-Analysis	Review articles summarize and critically appraise current and relevant information on a particular topic. Reviews should not exceed 15 typewritten pages (8.5 x 11 in., 1 in. margins at both sides, double spaced, excluding tables, figures, illustrations and references) or 4,000 words.
Lectures, Symposium Proceedings, or Grand Rounds	Special articles summarizing and documenting lectures or symposium proceedings, as well as grand rounds, which include presentation of medical problems of a particular patient, evaluation and work-up, treatment and clinical course, discussion of key diagnostic and management points, and commentaries by specialty experts. A manuscript for grand rounds should not exceed 25 typewritten pages (excluding tables, figures, illustrations and references) or 6,000 words.
Case Reports and Case Series	Case reports or series focus on reportable cases encountered in practice, representing unusual or rare manifestations, presentations, or clinical course of disease. Case reports should not exceed 10 typewritten pages (8.5 x 11 in., 1 in. margins at both sides, double spaced, excluding tables, figures, illustrations and references) or 3,000 words.
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Letters and Correspondence	Scientific Proceedings welcomes feedback and comments on previously published articles in the form of Letters to the Editor. No abstract or keywords are necessary. A Letter to the Editor must not exceed 2 typewritten pages or 500 words and may include references following the Guide to Authors.
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Manuscript

Title Page

The title page should include:

- Complete title of the article which should be informative, concise, meaningful, and as brief as possible (no more than 20 words)
- Name of each author with highest academic degree(s) and complete address of one (1) institutional affiliation.
- Listing of any meeting(s)/conference(s) where the material is under consideration for presentation, has been previously presented, and/or has been awarded. Indicate title, place month and year of the meeting/conference.
- Corresponding author's name, mailing address, telephone, fax, and e-mail address. The corresponding author will be responsible for all questions about the manuscript. Only one author is to be designated as corresponding author and he/she does not need to be the first author on the manuscript.
- Appropriate footnotes for explanatory purposes or additional information may be placed with proper cross-referencing to the main text, in the following order of usage: *, **, ***
- Financial support, if any. Provide the agency name and city, company name and city, fellowship name and/or grant number.

Abstract

- Original Articles, Review Articles require a structured abstract of not more than 500 words, with the following four headings:
  - Objective/s: Briefly state the purpose/s or aim/s of the study.
  - Methodology: State the study design (e.g., randomized clinical trial, case-control study, cross-sectional study, systematic review), setting (multi-center, institutional, et cetera), study population. Additional modifiers can be stated (consecutive, retrospective, prospective,observational, interventional, non-consecutive, etc.)
  - Results: Briefly summarize the principal outcome measurements/data obtained. Results should be accompanied by data with confidence intervals and the exact level of statistical significance.
  - Conclusions: Provide brief and concise conclusion(s) directly supported by the data.

- Case Reports or Case Series do not require a structured abstract, with a maximum of 300 words.

Keywords

- At least 5 keywords listed in the Medical Subject Headings database ([MeSH] of the National Center for Biotechnology Information [NCBI] [https://www.ncbi.nlm.nih.gov/mesh/]) should be provided.

Body of the Text

- The manuscript should be written in IMRAD format (Introduction, Methodology, Results and Discussion, Conclusion).
- Organize and prepare the manuscript to include the following sections:
  - *Introduction:* The Introduction, without a heading, should refer only to the most pertinent past publications and should not be an extensive review of the literature. Include a brief background, the research question and/or rationale, objectives/purposes of the study, and major hypothesis to be tested if any.
  - *Methodology:* Methods should be written with sufficient detail to permit others to duplicate the work.
    Study Design: State the study design using a phrase such as randomized or nonrandomized clinical trial, case-control study, cross-sectional study, cohort study, case series, case report, systematic review, meta-analysis, review, experimental study, or historical manuscript; Setting: (e.g., multicenter, institutional, clinical practice); Participants, Patients, or Study Population: Number of patients, selection procedures, inclusion/exclusion criteria, randomization procedure and masking; Intervention or observation procedure(s); Main and secondary outcome measure(s); Data and statistical analyses, to include what software was used for the computations. For original articles, statements regarding adherence to the Declaration of Helsinki, approval by the Institutional Review Board (IRB)/Ethics Committee, and description of the informed consent process should be included.
  - *Results:* Results must be concise. Provide demographic data of the study population. Describe outcomes and measurements in an objective sequence with minimum discussion. Data should be accompanied by confidence intervals (usually at the 95% interval) and exact p-values or other indications of statistical significance.

- *Discussion:* The discussion should be restricted to the significant findings presented. Avoid excessive generalization and undue speculation. Elucidate on (but do not reiterate) the results, provide responses to other and contradictory literature, identify limitations or qualifications of the study, and state the conclusions that are directly supported by the data. Give equal emphasis to positive and negative findings, whether and what additional study is required, and conclude with the clinical applications or implications supported by the study.
- *Conclusion/s:* The conclusion(s) is/are should be directly supported by the results. Authors should avoid making statements on economic benefits and costs unless their manuscript includes economic data and analyses.

- Cite only published studies as references. Quote from the entire study, not the abstract. Authors may acknowledge "unpublished data" or submitted articles within parentheses in the text. Reference to a "personal communication" within parentheses in the text must be accompanied by a signed permission letter from the individual being cited.

Abbreviations

- Restrict abbreviations to those that are widely used and understood. Avoid abbreviations that have meaning only in the context of your specific manuscript.
- All abbreviations should be spelled out once (the first time they are mentioned in the text) followed by the abbreviation enclosed in parentheses.

Measurements

- All measurements and weights should be expressed in SI units.

Drugs, Instruments, Equipment

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

Conflicts of Interest

- There should be a statement disclosing conflicts of interest where existing, source of funding for the study and manuscript, and acknowledgements to individuals/groups of persons, or institution/s.

Funding Sources

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

Acknowledgments

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

Tables, Figures, Illustrations and Photographs

Tables

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

Figures (Graphs, Illustrations, and Photographs)

- Each final figure should be submitted as individual Joint Photographic Experts Group (JPEG), Portable Network Graphics (PNG), or Tag Image File Format (TIFF) files with appropriate labels (figure number, title).
- Submit the original, raw, and unedited files in the abovementioned formats in one (1) folder with labels that shall allow comparison with the final figures. Disclose If there are modifications, such as cropping, changes in color, orientation, or placement of arrows or shapes.
- Photographs (clinical photographs, fluorescein angiograms, computed tomography [CT] scans, magnetic resonance imaging [MRI], X-ray, photomicrographs, transmission/scanning electron micrographs [TEM/SEM], graphs, etc.) should have a resolution of at least 600 dpi.
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- Up to a maximum of five items only per type may be included.

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- Appendices should be used very sparingly. However, it is appropriate to provide survey forms, to list the members of a study group, or explain complex formulas or information. In studies involving a study group, the writing group authors should be listed along with the group name on the title page. Other group members should be listed in an appendix.

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- List only references that are pertinent to the manuscript.
- References should be numbered consecutively in the text and in the reference list. In the text, reference numbers are entered as superscripts. The references must be verified by the author(s) against the original documents. PubMed offers a useful reference checker. (http://www.ncbi.nlm.nih.gov)
- References to journal articles should include: the author or authors (for more than four authors, list only the first three followed by "et al."), title, journal name, (as abbreviated in Index Medicus), year, volume number, and inclusive page numbers. References to books should include: the author or authors, chapter title (if any), editor or editors (if any), book title, edition (other than the first), city of publication, publisher copyright year, and inclusive pages of the chapter or section cited.
- Website references must include author (or website owner), title of article, date article was posted, publication (if applicable), complete website address and date accessed.
- Examples:

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

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

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

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

  Chapter in Book

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

  Book

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

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

  Website

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

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

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2. Cover Letter • Included cover letter as an attachment, with complete title of the work, list of all authors, clear identification of the corresponding author with complete contact information (institutional mailing address, work telephone, fax number, and work e-mail address)	
3. Author Form • Ensured all authors have qualified as authors based on ICMJE authorship criteria • Ensured all authors have read and agreed to the Declaration • Ensured all authors have read and provided Disclosure of Conflicts of Interest where existing • Submitted a scanned copy of the fully accomplished Author Form	
4. Informed Consent Form • Submitted a scanned copy of the fully accomplished form (for Case Reports/Series) • If the subject for the case report/case series can no longer be contacted, the author/s should describe the attempts made to secure the Informed Consent.	
5. Title • Indicated the complete title of the manuscript • Included full names of the authors (first name and last name), highest educational attainment, and name and location (region, province, country only) of not more than 1 institutional affiliation per author • Indicated if presented in a scientific forum or conference through a footnote stating the name, location and date of presentation	
6. Abstract • Provided an abstract conforming with the Guide for Authors: structured for Original Articles, Review Articles: Objective/s, Methodology, Results, Conclusion; unstructured for Case Reports and Feature Articles • Did not place cross references within the abstract	
7. Key Words • Provided 3-6 keywords (listed in MeSH) *[https://www.ncbi.nlm.nih.gov/mesh/]*	
8. Content • Provided text/content in IMRAD format (Introduction, Methodology, Results and Discussion, Conclusion) • Made sure all abbreviations are spelled out once (the first time they are mentioned in the text) followed by the abbreviation enclosed in parentheses • Made sure all measurements and weights are expressed in SI units • Provided information on institutional review board / ethics review committee approval • Included a statement of conflicts of interest where existing, source of funding for the study and manuscript, and acknowledgments to individuals/groups of persons, or institution/s	
9. Funding Sources • Disclosed funding source/s for the study on which the manuscript is based, to include the writing of the manuscript.	
10. Acknowledgments • Listed all contributors to the work who do not fulfill the authorship criteria.	
11. References • Ensured that all references cited in the text are in numerical order using Hindu-Arabic numerals • Ensured that all references followed the prescribed format	
12. Tables, Figures, Illustrations and Photographs • Ensured that all tables, figures, illustrations and photographs are cited in the text, in numerical order per type • Provided separate files for tables, figures and illustrations with clear file names for reference • Provided a title and legend (if appropriate) for each table • Provided a title, legend (if appropriate), and caption for each figure and illustration (caption should be no longer than 15-20 words) *Note: If table, figure, or illustration is adapted, state so, include the reference and permission for use of the item.*	

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For submissions to the **Scientific Proceedings** of the Lung Center of the Philippines to be accepted, all authors must read and completely accomplish this Author Form consisting of: (1) the Authorship Certification, (2) the Author Declaration, (3) the Statement of Copyright Transfer, and (4) the ICMJE Form for Disclosure of Potential Conflicts of Interest. The completely accomplished Author Form shall be scanned and submitted along with the manuscript. No manuscript shall be received without the Author Form.

Complete Title of Manuscript

Authorship Certification

	Yes	No
In consideration of our submission to the **Scientific Proceedings** of the Lung Center of the Philippines, all of the undersigned author(s) of the manuscript hereby certify, that we have fulfilled the ICMJE Authorship criteria: (1) active and sufficient participation in the conception or design of the work, the acquisition, analysis and interpretation of data for the work; AND (2) drafting the work, revising it critically for important intellectual content; AND (3) responsibility for the final approval of the version to be published; AND (4) accountability for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.		

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The undersigned author(s) of the manuscript hereby declare:

	Yes	No
That the submitted manuscript represents original, exclusive and unpublished material.		
That it is not under simultaneous consideration for publication elsewhere.		
That it will not be submitted for publication in another journal, until a decision is conveyed regarding its acceptability for publication in the **Scientific Proceedings**.		
That the study on which the manuscript is based had conformed to ethical standards and/or had been reviewed by the appropriate ethics committee		
That the article had written/informed consent for publication from involved subjects (for case report/series only) and that in case the involved subject/s can no longer be contacted (i.e., retrospective studies, no contact information, et cetera), all means have been undertaken by the author(s) to obtain the consent.		

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No.	Author Name *(Last Name, First Name, Middle Name, Suffix)*	Signature	Date *(mm/dd/yy)*

Note: Use additional lines as necessary.

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Date: _____

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The following questions apply to the author's relationships/activities/interests as they relate to the **current manuscript only**.

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In item #1 below, report all support for the work reported in this manuscript without time limit. For all other items, the time frame for disclosure is the past 36 months.

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Time frame: Since the initial planning of the work			
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Subject matter of photograph or article (brief description):
(The subject matter of the photograph or article is hereafter termed as the "***Information***.")
Complete Title of Article:
Consent:

I, _____ , give my consent for this information about
[signature over complete name]

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- I can withdraw my consent at any time before publication, but once the Information has already been sent to press, it is my understanding that it will not be possible to revoke the consent.

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Witness:

Signed: _____ Date: _____
[signature over complete name]

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LUNG CENTER OF THE PHILIPPINES

Vision

The Lung Center of the Philippines is regionally competitive, locally responsive premier institution for lung and other chest diseases, providing quality healthcare through excellent service, training and research.

Mission

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

Core Values

Customer-focused
Commitment
Compassion
Creativity
Collaboration

Shared Values

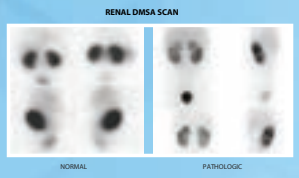
Concern and care for patients, employees and the institution
Responsibility and discipline
Commitment and dedication to excellence
Respect for individual worth
Integrity and honesty
Unity and teamwork
Creativity and innovativeness

LUNG CENTER OF THE PHILIPPINES

RADIOLOGY DEPARTMENT
NUCLEAR MEDICINE SECTION

Nuclear Medicine is a specialized area of radiology that uses very small amounts of radioactive substance, called a radionuclide (radiopharmaceutical or radioactive tracer) to diagnose, evaluate or treat a variety of diseases. Nuclear medicine imaging procedures are non-invasive, with the exception of intravenous injections, they are usually painless.

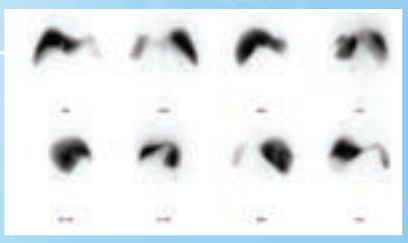
Scans are used to diagnose many medical conditions and diseases. Some of the most common tests include the following:



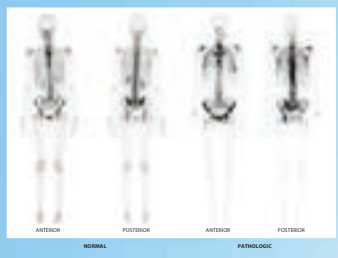
GENITOURINARY SYSTEM
(Renal Cortex Scintigraphy)

- To diagnose acute and chronic pyelonephritis (kidney function)
- To evaluate renal cortical scarring
- For the diagnosis of renal agenesis/ ectopia.

GASTROINTESTINAL SYSTEM
(Liver and Spleen Scintigraphy)



- Assessing the size, shape, and position of the liver and spleen.
- Detecting, measuring and monitoring masses of the liver and/or spleen.
- Differentiating hepatic hemangiomas and focal nodular hyperplasia from other liver lesions.
- Evaluating hepatic function in acute or chronic liver disease.
- Evaluating suspected functional asplenia.

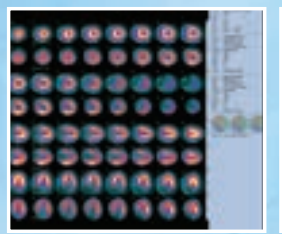


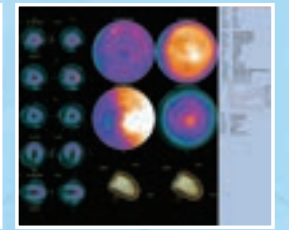
SKELETAL SYSTEM
(Bone Scintigraphy)

- For the detection of bone metastasis from a primary extraskeletal malignancy
- Follow-up study after metastatic cancer therapy
- For the evaluation of musculoskeletal trauma and infections
- For the evaluation of primary benign and malignant bone lesions
- For diagnosis of reflex sympathetic dystrophy
- For evaluation of heterotrophic ossifications

ENDOCRINE SYSTEM
(Thyroid Scintigraphy)

- To assess general thyroid configuration and function
- To determine degree of function of a palpable thyroid nodule
- To differentiate thyroiditis from Graves' disease and other forms of hyperthyroidism
- To locate ectopic thyroid tissue or evaluate a neck or substernal mass
- To assist in the evaluation of congenital hypothyroidism





CARDIAC SYSTEM
(Myocardial Perfusion Scintigraphy - MPS)

- To diagnose coronary artery disease (CAD)
- To evaluate patency of the coronary artery bypass grafts (CABG) or percutaneous transluminal coronary angioplasty (PTCA)
- For post myocardial infarction (MI) viability assessment or risk stratification
- For pre-operative risk assessment
- For evaluation of patients with abnormal or equivocal stress electrocardiogram (ECG)

RESPIRATORY SYSTEM
(Lung Perfusion/ Ventilation Scintigraphy)

- To diagnose and quantify pulmonary function
- To diagnose pulmonary embolism, even after anti-coagulant therapy
- To assess perfusion change secondary to lung tumour
- For pre-operative evaluation post pneumonectomy, post-operative assessment

SERVICES OFFERED

A. Scintigraphic (Diagnostic) Procedures
- **1. Genitourinary system**
  - 1.1 GFR scan
  - 1.2 Renal scan
  - 1.3 Diuretic scan
  - 1.4 Renal Cortex scan
- **2. Gastrointestinal system**
  - 2.1 Liver / Spleen scan
  - 2.2 Hepatobiliary scan
  - 2.3 Meckels Diverticulum
  - 2.4 Gastrointestinal Bleeding
- **3. Endocrine system**
  - 3.1 Thyroid scan and Uptake (Tc99m / I-131)
  - 3.2 Parathyroid scan (Dual Phase / Dual Isotope)
- **4. Skeletal system**
  - 4.1 Bone scan
- **5. Cardiac system**
  - 5.1 Myocardial Perfusion Imaging (Treadmill / Dipyridamole)
    - · Thallium - 201
    - · Tc99m Sestamibi
  - 5.2 MUGA scan
- **6. Respiratory system**
  - 6.1 Lung VQ scan (Perfusion / Ventilation)
- **7. Oncology**
  - 7.1 Whole Body Scans (I-131, Ga-67, Tl201, MIBG I-131)
- **8. Lymphatic System**
  - 8.1 Lymphoscintigraphy
  - 8.2 Sentinel Node scan
- **9. Infectious / Inflammation**
  - 9.1 WBC Imaging with or without Bone Marrow imaging
  - 9.2 Three-Phase Bone scan (Bone infection)
- **10. Others**
  - 10.1 Scintimammography
  - 10.2 Salivary scan
  - 10.3 Testicular scan
  - 10.4 Dacryoscintigraphy

B. Therapeutic Procedures
- **1. Low Doses I-131 RAI Therapy**
- **2. High Doses I-131 RAI Therapy**

C. Radioimmuno Assay Test (RIA)
- **C.1 Thyroid Functions**
  - Anti-Thyroglobulin
  - Thyroglobulin
  - TSH
  - FT4
  - FT3
- **C.2 Tumour Markers**
  - CA 19-9
  - CA 125

D. Bone Densitometry Procedures
- **D.1 L-spine + Hips (routine)**
- **D.2 Routine + Forearm**
- **D.3 Routine + Wholebody**
- **D.4 Routine + FA + WB**

LUNG CENTER OF THE PHILIPPINES

Quezon Avenue Extension, Quezon City, Philippines 1100

LUNG CANCER SCREENING

ARE YOU ELIGIBLE?

AGE?

YOU ARE

50-79

YEARS OLD

SMOKE?

YOU CURRENTLY SMOKE

OR

HAVE QUIT WITHIN THE PAST 15 YEARS

CALCULATE YOUR PACK YEARS

NUMBER OF PACKS OF CIGARETTES SMOKE PER DAY

X

NUMBER OF YEARS YOU SMOKED

YOU HAVE A **20** PACK YEAR OR GREATER HISTORY OF SMOKING

FAMILY HISTORY

FIRST DEGREE RELATIVE

(PARENTS, BROTHER OR SISTER, CHILDREN)

WHO IS A NON-SMOKER WITH LUNG CANCER

TREATMENT?

YOU ARE

WILLING & ABLE

TO HAVE TREATMENT

DID YOU ANSWER YES?

A 15 MIN LOW-DOSE CT SCAN CAN DETECT SUSPICIOUS NODULES THAT MAY LEAD TO EARLY DETECTION OF LUNG CANCER

- PAINLESS
- NON-INVASIVE
- NO PREPARATIONv

EARLY DETECTION SAVES LIVES 90% OF THE TIME

THE BEST WAY TO REDUCE YOUR RISK OF LUNG CANCER IS TO **STOP SMOKING**

TALK TO YOUR LUNG DOCTOR

ABOUT YOUR RISK FOR LUNG CANCER AND THE BENEFITS OF SCREENING!

For further inquiries or support, you may call the LCP Early Lung Center Detection & Treatment Program Team at 8924 6101 ext. 1324 during office hours.