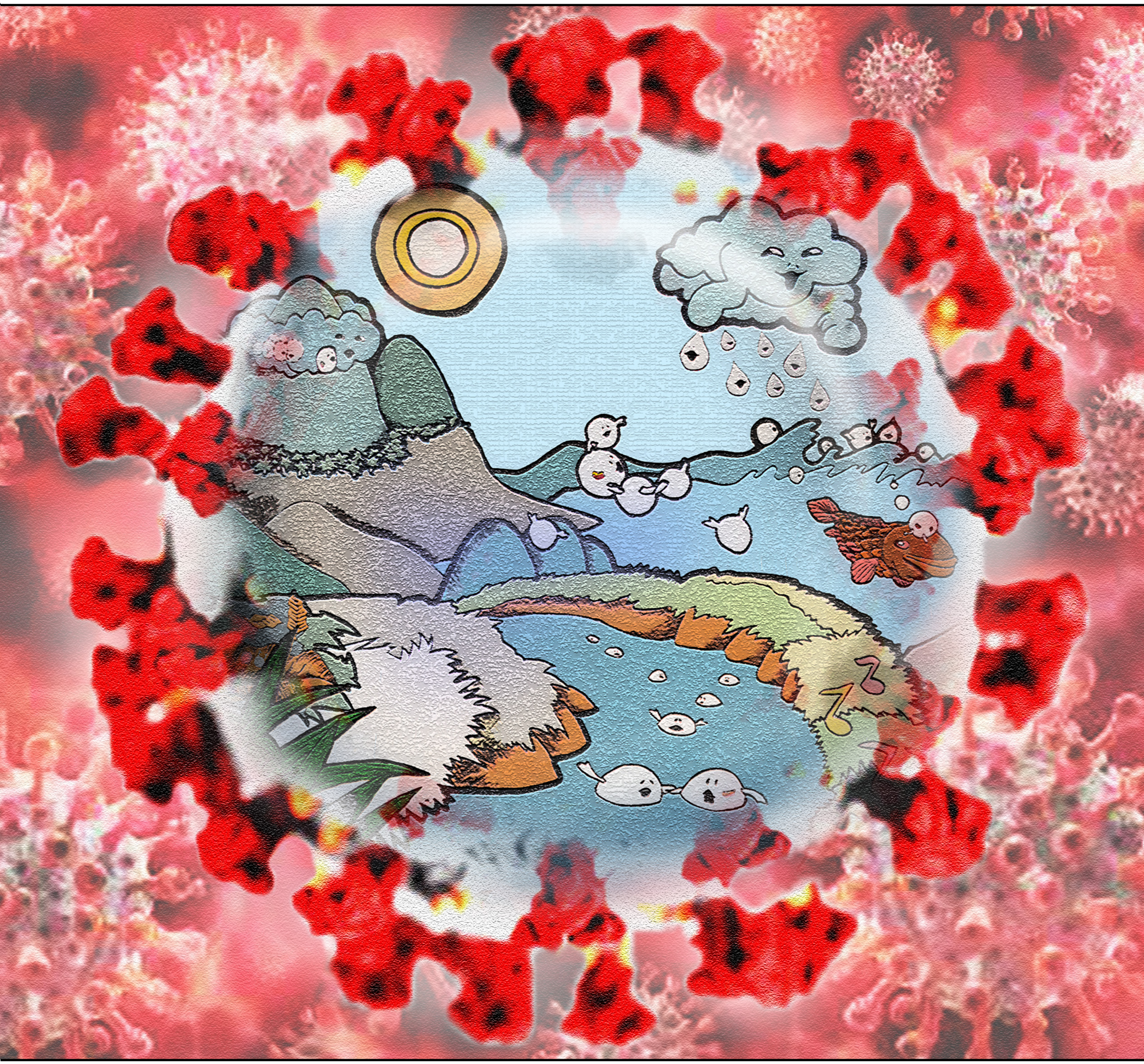
The PCMC Journal

Vol. 18 No.1 June 2022

Official Publication of the
Philippine Children's Medical Center
Quezon Avenue, Diliman, Quezon City 1100
ISSN No.: 0117-3774
e-ISSN No.: 2704-3665



The PCMC Journal

An Official Publication of the Philippine Children's Medical Center

Editorial:

Welcome to this special issue on COVID-19!

Going over the 8 articles in this issue will give the reader a very good idea of the breadth of research that is being done by our trainees, of course under the guidance and support of the consultant staff of the hospital. We have articles on the manifestations of COVID and a case series focusing on its neurologic manifestations. There are articles on the KAP toward COVID of our medical frontliners, as well as concerns of caregivers of children with neurodevelopmental concerns. We also have articles focusing on diagnostic tests (validation of a rapid antigen test, a meta-analysis comparing saliva and nasopharyngeal RT-PCR, and the clinical utility of cycle threshold values. Finally we also have an analysis of hospitalization costs of pediatric patients with COVID.

All these should show the commitment of PCMC in studying and unraveling the major medical story of our time. Here's to yet more relevant research to come!

The PCMC Journal

An Official Publication of the Philippine Children's Medical Center

CONTENTS

DIAGNOSTIC ACCURACY OF SALIVA REVERSE TRANSCRIPTION POLYMERASE CHAIN REACTION (RT-PCR) COMPARED TO NASOPHARYNGEAL SWAB REVERSE TRANSCRIPTION POLYMERASE CHAIN REACTION (RT-PCR) IN THE DETECTION OF SARS-COV-2 IN PEDIATRIC PATIENTS AGES 0-18 YEARS OLD : A META-ANALYSIS

JAZZTINE V. DEL ROSARIO, M.D, MARIA EVA I. JOPSON, M.D

ABSTRACT

OBJECTIVES: To determine the diagnostic accuracy of Saliva RT-PCR in the detection of SARS-COV-2 in pediatric patients ages 0-18 years old, compared to the nasopharyngeal RT-PCR swab.

METHODOLOGY: A metanalysis was done to synthesize the diagnostic accuracy of saliva RT-PCR compared to the nasopharyngeal RT-PCR in the detection of SARS-COV 2 in pediatric patients ages 0-18 years old. Five studies published from January to September 2021 were analyzed using the "midas" command of STATA14. MIDAS command is a comprehensive program of statistical and graphical routines for undertaking meta-analysis of diagnostic test performance in Stata. The index and reference tests (gold standard) are dichotomous. Primary data synthesis is performed within the bivariate mixed-effects regression framework focused on making inferences about average sensitivity and specificity.

RESULTS: The World Health Organization's acceptable sensitivity and specificity for products used in COVID-19 diagnostics is ≥ 80% and ≥ 97% respectively. The results of this metanalysis showed the pooled sensitivity of Saliva RT-PCR as compared to the Nasopharyngeal RT-PCR is at 87% (81-92% at 95% CI) and the pooled specificity is at 97% (95% CI: 96-98%).

CONCLUSIONS: This metanalysis demonstrates that saliva can be used as an alternative specimen for SARS-COV-2 diagnostic testing in children. Aside from the acceptable pooled specificity and sensitivity, the use of saliva offers several advantages. However, the authors recommend to include more studies for future metanalysis research, to further increase sample size, and to include both symptomatic and asymptomatic pediatric age group participants. A future prospective research study comparing the two diagnostic modalities is likewise recommended

Keywords: *COVID-19, SARS-COV-2, Nasopharyngeal RT-PCR, Saliva RT-PCR, Children, 0-18 years old*

INTRODUCTION

A day before the start of 2020, an atypical respiratory disease similar to pneumonia and/or influenza was reported to the World Health Organization (WHO) Country Office in China. It was first detected in clusters in Wuhan City, Hubei Province, China. Later, it was discovered that this disease is caused by the Severe Acute Respiratory Syndrome Coronary Virus 2 (SARS COV-2)[(1)]. Within a month, the new virus was discovered to be highly-contagious and rapidly spread into many countries, with approximately 6000+ confirmed cases by January 2020. In January 30, 2020, the WHO declared the outbreak to be a Public Health Emergency of International Concern and by March 11, it was escalated as a pandemic upon the declaration of the WHO Director General. The WHO[(2)] officially named the new coronavirus disease as COVID-19 by February 11, 2020 and, not long after, confirmed cases spread across the globe, causing countries to enforce lockdowns to curb infection and deaths.

Testing has become a main defense tactic against the COVID-19 virus, with the reverse-transcriptase polymerase chain reaction (RT-PCR)[(3)] test through nasopharyngeal swab specimen as the main method currently utilized. An accurate diagnosis is important in the management and prevention of transmission of COVID-19 both in the adult and pediatric population. Like other parts of the world, the Philippines has been facing challenges in fighting COVID-19. Apart from the lack of easy and universal access to treatments and vaccines, Nasopharyngeal RT-PCR, which is the current gold standard in the diagnosis of COVID-19, has some several drawbacks starting from sample collection that usually causes pain and discomfort especially in the children and elderly up to the increased risk for viral transmission to the healthcare worker brought about by reflex sneezing or coughing.

Nasopharyngeal sampling requires significant human resources, time, and preparation, resulting in testing bottlenecks and the risk of transmission in overcrowded testing sites. Furthermore, the unpleasantness of the procedure and the long wait times for swab collection and results may deter some people from getting tested or from repeating negative tests. Thus, innovative testing techniques that utilize the tried and tested RT-PCR method are urgently needed to quickly classify cases, reduce waiting times, and promote mass screening.

A novel testing technique that can be a viable alternative to nasopharyngeal swab is saliva sampling. The pathophysiology behind the use of saliva for testing lies in the high salivary gland expression of host angiotensin-converting enzyme, which regulates the host receptor-cellular entry of SARS-CoV-2[(25)]. In addition, It has the advantage of being simple and painless to obtain, requiring no qualified personnel and even possibly allowing self-sampling. However, comparisons between real-time PCR results from salivary and nasopharyngeal samples show variations, with most finding greater sensitivity and lower RT-PCR counts in nasopharyngeal swab samples[(4-6)], while others find greater sensitivity in saliva samples[(7-8)].

A study done by El-Sharkawy, et.al published last March 2022 compared the performance of saliva and upper respiratory swab in the detection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Paired saliva and anterior nares specimens were collected from a largely asymptomatic cohort of students, faculty, and staff from the University of Pennsylvania. Paired saliva and combined nasopharyngeal/oropharyngeal (NP/OP) specimens were also collected from hospitalized patients with symptomatic COVID-19 following confirmatory testing. All study samples were tested by real-time PCR in the Hospital of the University of Pennsylvania. In the university cohort, positivity rates were 37 of 2500 for saliva (sensitivity, 86.1%) and 36 of 2500 for anterior nares (sensitivity, 83.7%), with an overall agreement of 99.6%. In the hospital study cohort, positivity rates were 35 of 49 for saliva (sensitivity, 89.3%) and 28 of 49 for NP/OP (sensitivity, 75.8%), with an overall agreement of 75.6%. A larger proportion of saliva than NP/OP samples tested positive after 4 days of symptom onset in hospitalized patients. This showed that saliva has an acceptable sensitivity and is comparable to upper respiratory swab, supporting the use of saliva for SARS-CoV-2 detection in both symptomatic and asymptomatic populations.

However, a study by Mestdagh, Et. Al[27] published last July 2021 also compared saliva specimens and nasopharyngeal (NP) swabs with respect to sensitivity in detecting SARS-CoV-2. In this study, a nasopharyngeal and two saliva specimens (collected by spitting or oral swabbing) were obtained from >2500 individuals. All samples were tested by RT-qPCR, detecting RNA of SARS-CoV-2. The test sensitivity was compared on the two saliva collections with the nasopharyngeal specimen for all subjects and stratified by symptom status and viral load, of the 2850 patients for whom all three samples were available, 105 were positive on NP swab, whereas 32 and 23 were also positive on saliva spitting and saliva swabbing samples, respectively. The sensitivity of the RT-qPCR to detect SARS-CoV-2 among NP-positive patients was 30.5% (95% CI, 1.9%e40.2%) for saliva spitting and 21.9% (95% CI, 14.4%e31.0%) for saliva swabbing. However, when focusing on subjects with medium to high viral load, sensitivity on saliva increased substantially: 93.9% (95% CI, 79.8%e99.3%) and 76.9% (95% CI, 56.4%e91.0%) for spitting and swabbing, respectively, regardless of symptomatic status. This result suggests that saliva cannot readily replace nasopharyngeal sampling for SARS-CoV-2 diagnostics but may enable identification of the most contagious cases with medium to high viral loads.

Given the conflicting findings in both in the adult and pediatric population, a meta-analysis is warranted to find consensus on the diagnostic accuracy of saliva sample versus nasopharyngeal swab.

This study summarizes existing literatures which compared the diagnostic accuracy of saliva as compared to the nasopharyngeal swab RT-PCR in detecting SARS-CoV-2 in the pediatric population ages 0-18 years old. A favorable result from this study will provide additional information to the current guidelines used in the diagnosis of COVID-19 in the pediatric population which in turn can bring us a step closer in ending this Pandemic.

This study aims to determine the diagnostic accuracy of Saliva RT-PCR in the detection of SARS-COV2 in pediatric patients ages 0-18 years old as compared to the Nasopharyngeal RT-PCR swab.

MATERIALS AND METHODS

Research Design

A meta-analysis was done to compare the diagnostic accuracy of saliva RT-PCR and nasopharyngeal RT-PCR in the detection of SARS-COV 2 in pediatric patients ages 0-18 years old.

Search Strategy and Study Identification

Pubmed, Medline, Google Scholar (first 1000 articles), and ResearchGate were searched using keywords (saliva) AND (nasopharyngeal OR nasopharynx) AND (RT-PCR OR "Reverse transcription polymerase chain reaction") AND (COVID-19 OR SARS-COV-2) AND (Children 0-18 years old OR Pediatric population). Forward search of literatures citing the included studies were done for possible additional studies. Backward review of other references cited in included studies were also done. Searches covered all studies published until September 15, 2021.

Eligibility Criteria

I. Types of studies

Diagnostic accuracy studies which described the sensitivity and specificity of saliva RT-PCR when compared to nasopharyngeal swab as gold standard in detecting SARS-CoV-2 were included. All studies until September 15, 2021and available in the English language were included. Excluded were studies which included both adult and children.

II. Types of participants

Only studies which involved individuals ages 0-18 years old diagnosed or suspected to have COVID-19, and those screened before surgery and other procedures, were considered eligible for this analysis.

DATA COLLECTION AND DATA ANALYSIS

Selection of studies and quality assessment

Two review authors screened the titles and abstracts of articles identified by the search strategy as relevant using the inclusion criteria. Studies deemed applicable for possible inclusion were then evaluated using full article copies in terms of objectives, methodology, reporting of outcomes and appropriateness for final inclusion.

Study quality was assessed using QUADAS-2 tool (quality assessment for diagnostic accuracy study) of the Review Manager version 5.4 software. Using this tool, each study was assessed in terms of representativeness of samples, selection criteria, reference standard, and flow/timing of outcome confirmation.

Data extraction and management

Data from studies were extracted into Microsoft Excel and STATA14. Information included were author, year of publication, setting, total sample size, number of patients included, sensitivity, specificity, and outcomes reported (true positives, true negatives, false positives, and false negatives). Two reviewers performed the data extraction and disputes were broken by a third reviewer's decision.

Statistical Analysis and data synthesis

The studies were analyzed using the "midas" command of STATA14. Midas is a comprehensive program of statistical and graphical routines for undertaking meta-analysis of diagnostic test performance in Stata. The index and reference tests were dichotomous. Primary data synthesis was performed within the bivariate mixed-effects regression framework focused on making inferences about average sensitivity and specificity. The pooled ROC for all studies were presented. The following guidelines was used for the interpretation of intermediate area under ROC values: low (0.5>= AUC <= 0.7), moderate (0.7 >= AUC <= 0.9), or high (0.9 >= AUC <= 1) accuracy.

RESULTS

In the primary search through databases, a total of 986 abstracts was screened, while 949 were excluded. Out of the 37 full-text articles reviewed, only five studies satisfied the inclusion and exclusion criteria of the study.

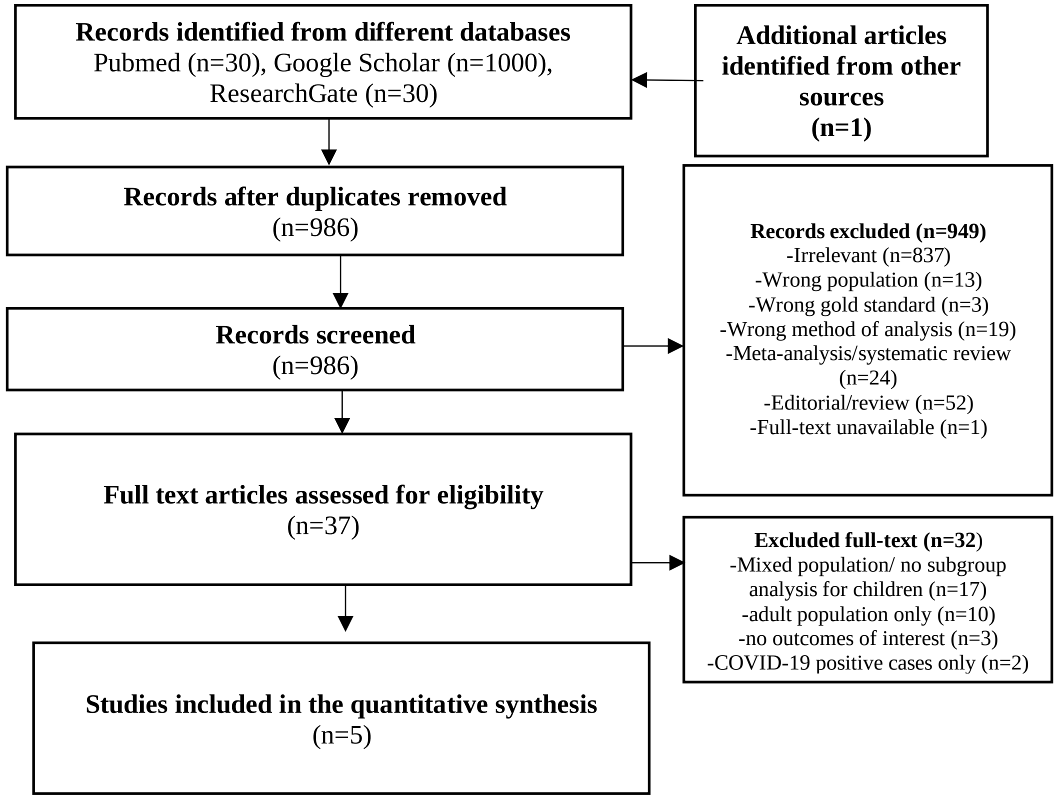


Figure 1. PRISMA Flow Chart of Literature Search

Study Characteristics

The characteristics of the studies included are presented in Table 1. All studies were published in 2021 coming from five different countries. The total number of patients is 937 with a total sample of 946. The mean age ranges from 3.8 to 13 years old. Males comprised 46-58.2% of the population. All saliva specimens were collected on the same day of the nasopharyngeal swab except for one study (Alenquer, 2021) as shown in Table 2.

Table 1. Characteristics Of Included Studies

Author, Year	Country	Population	No. of patients	No. of samples	Mean age (Range)	% male
Al Suwaidi, 2021	UAE	Presenting for COVID-19 screening: confirmed COVID-19 patients, presence of presumptive symptoms or testing for return to school.	476	485	10.8 (3-18)	58.2%
Alenquer, 2021	Portugal	Admitted to hospital for COVID-19 symptoms or causes non-related to COVID-19	85	85	3.8 (<10)	54.1%
Felix, 2021	Brazil	Suspected COVID-19 (mild symptoms)	50	50	10.24 (range not specified)	46%
Huber, 2021	Switzerland	Patients with COVID-19 symptoms and asymptomatic patients with relevant exposure to COVID-19 Excluded hospitalized patients	170	170	Median: 13 (5-17)	51.8%
Laura, 2021	Mexico	Hospitalized patients who showed respiratory symptoms while recovering from a disease other than COVID-19, and non-probable COVID-19 patients who attended to the hospital for routine clinical analyses before a programmed surgery	156	156	Median: 11 (5-18)	50%

Table 2. Specimen Collection Details

	Saliva specimen	**Timing of assessment: Saliva and NP swab specimen**
Al Suwaidi, 2021	-Abstinence from food or drink for at least 30 minutes -1-3 ml saliva, self-collected -Participants were asked to close their mouths, allow saliva to pool in the mouth for 1-2 minutes, and gently spit into the provided sterile container	Same day
Alenquer, 2021	-Abstinence from food or drink for at least 30 minutes -At least 1ml saliva collected with help of a healthcare worker -Participants were asked to pool saliva in the mouth and gently spit it into a sterile container without coughing or clearing their throats. For children under the age of 1 year, saliva was gently aspirated from the mouth with a suction tube.	Saliva samples collected within 24 or 48 hours from NP swab collection
Felix, 2021	-1 ml of saliva spit into a sterile container	Same day
Huber, 2021	-Abstinence from food or drink not performed -0.5-1 ml saliva -“Basic”: clear throat thoroughly and collect saliva one or two times into the same tube -“Enhanced”: clear throat three times and collect saliva into the same tube	Same day
Laura, 2021	-spit 5 times into a sterile container -not instructed to cough out or try to enrich samples with sputum	Same day

Table 3 shows the results of the various studies in terms of Specificity, Sensitivity, True Positive, False Positive, False Negative and True negatives. As prevalence increases, Positive Predictive Value (PPV) increases and Negative Predictive Value (NPV) decreases. In this metanalysis, we can see that the study done by (Al-Suwaidi,2021) has the lowest PPV since it is the only study that included asymptomatic individuals unlike the other remaining studies which mostly tested for symptomatic patients or close contact of COVID-19 patients.

Table 3. Results of Included Studies

Author, Year	Sensitivity	Specificity	TP	FP	FN	TN
Al Suwaidi, 2021	87.7% (95% CI: 78.5-93.9)	98.5% (95% CI: 96.8-99.5)	71	6	10	398
Alenquer, 2021	84.8% (95% CI: 71.8-92.4)	100% (95% CI: 91-100)	39	0	7	39
Felix, 2021	75% (95% CI: 35-97)	95.2% (95% CI: 84-99)	6	2	2	40
Huber, 2021	93.3% (95% CI: 78-99)	96.4% (95% CI: 92-99)	28	5	2	135
Laura, 2021	82.3% (95% CI: 56.6-96.2)	95.6% (90.8-98.4)	14	6	3	133

Figure 2 shows Pooled sensitivity of 87% (95% CI: 81-91%) while Pooled specificity of 97% (95% CI: 96-98%).The WHO's acceptable sensitivity and specificity for products used in COVID-19diagnostics is ≥ 80% and ≥ 97% respectively. On the other hand, minimal heterogeneity (I2=0%) was observed for sensitivity, and moderate heterogeneity (I2=35%) for specificity. Both are not considered significant and does not affect the overall study

.

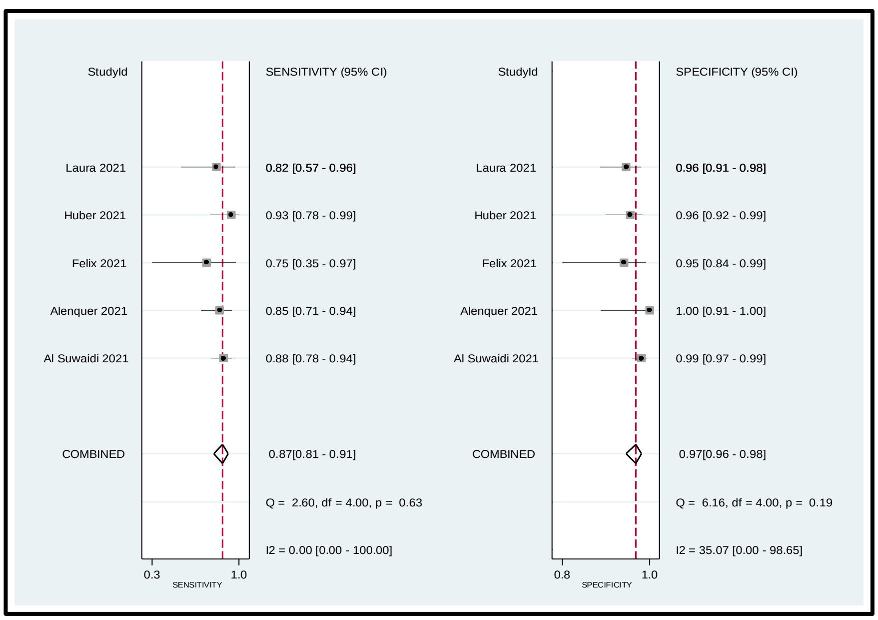


Figure 2 Forest plot showing the sensitivity and specificity of saliva RT-PCR in detecting COVID-19

Figure 3 shows that pooled AUC has high accuracy of 0.91 (95% CI: 0.88-93) while Figure 4 reveals that the pooled AUC despite the Alenquer study being excluded in the analysis. AUC remained high at 0.91 (0.88-0.93)

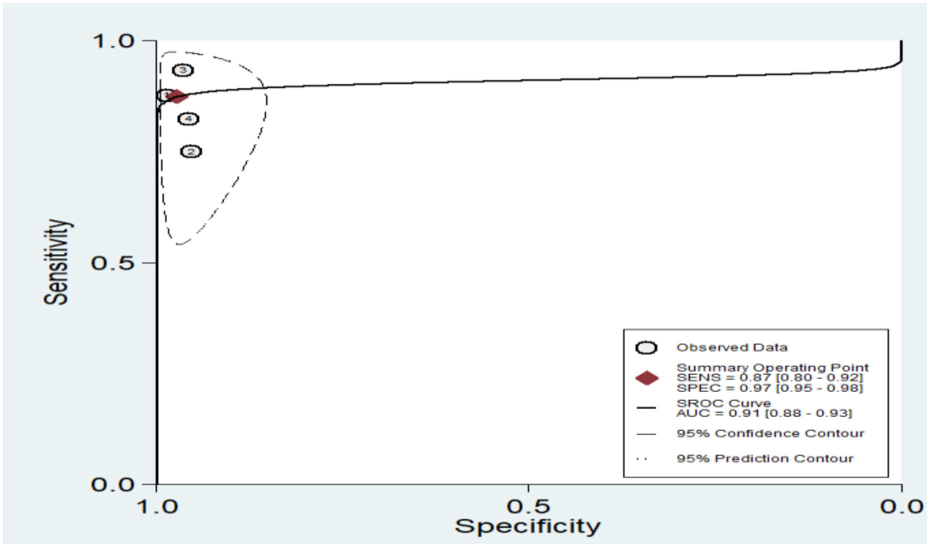


Figure 3. Pooled Area under the curve of 0.91 (95% CI: 0.88-093)

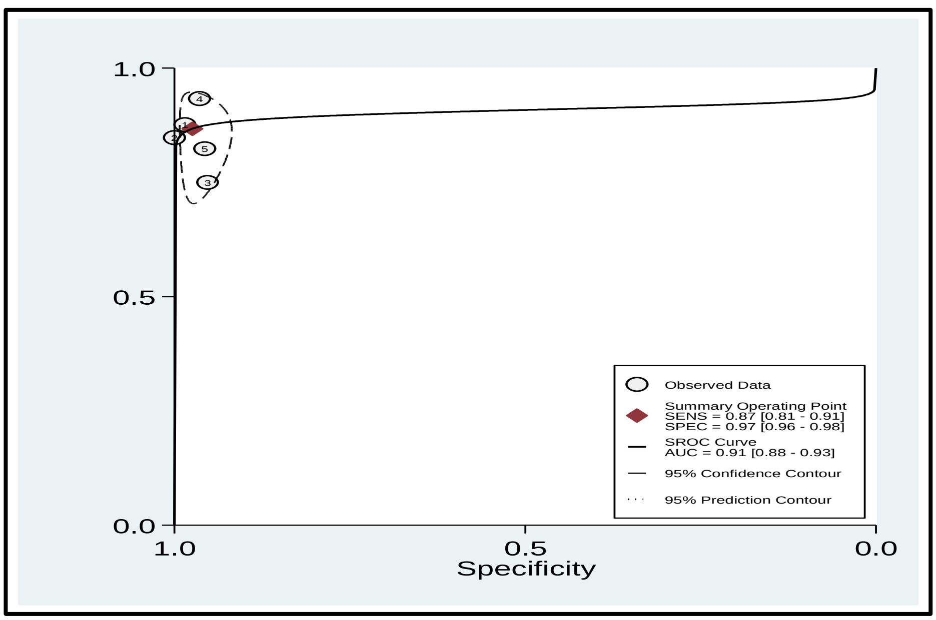


Figure 4. Pooled Area under the curve after the Alenquer study was excluded in the analysis.

Risk of bias

Figure 5 and 6 shows the risk bias and applicability of the study. Regarding patient selection, only two studies had low risk of bias, and only one study had low concern in terms of applicability. Risk of bias for the index test was low for three studies, and applicability concerns were low for four studies. Risk of bias for the reference standard was unclear from one study. However, all studies showed low concern for applicability. Only one study had high risk of bias for flow and timing.

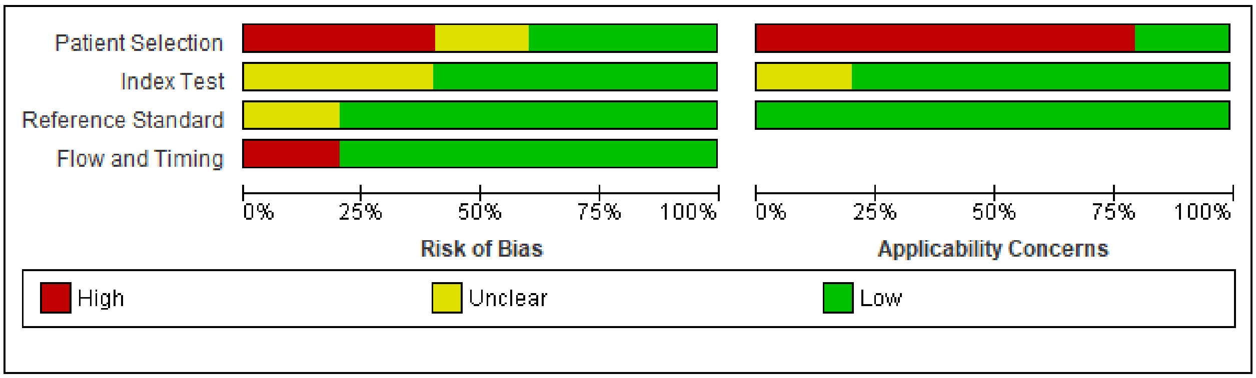


Figure 5 Risk of bias and applicability concerns graph: review authors' judgments about each domain presented as percentages across included studies

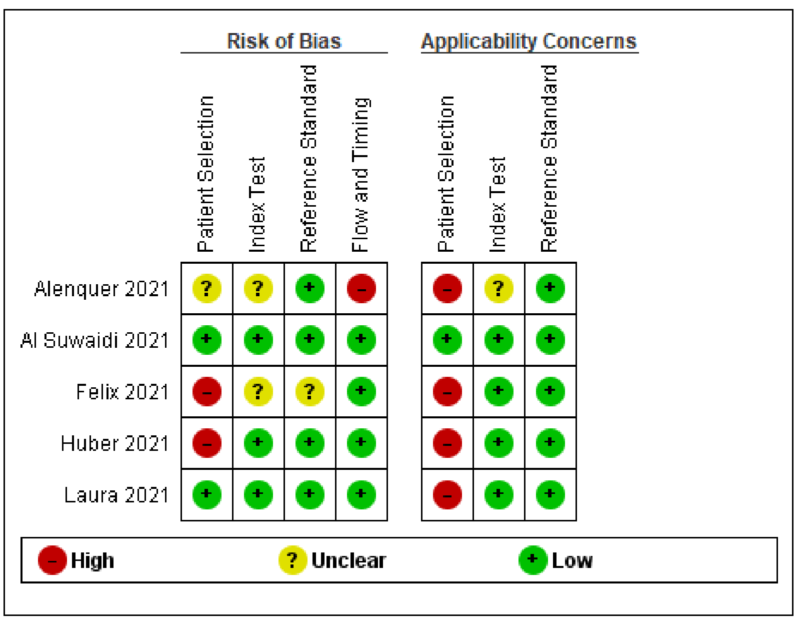


Figure 6 Risk of bias and applicability concerns summary: review authors' judgments about each domain for each included study

The Funnel plot as shown in Figure 7, revealed an asymmetric test results which signifies a Publication bias. However, it must be noted that this metanalysis only included less than 10 studies hence the power of the test may be too low to distinguish chance from true asymmetry.

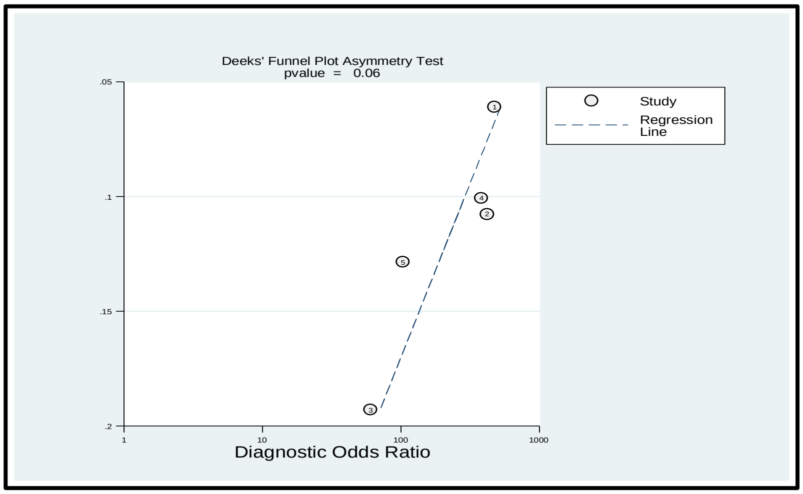


Figure 7. Deek's funnel plot asymmetry test

DISCUSSION

Accuracy of Saliva RT-PCR compared to Nasopharyngeal RT-PCR

The WHO's acceptable sensitivity for products used in COVID-19diagnostics is ≥ 80%. In this metanalysis, It was noted that pooled sensitivity of Saliva RT-PCR as compared to the Nasopharyngeal RT-PCR is at 87% (81-92% at 95% CI) which is within the acceptable range.

In terms of specificity, the standard set by the WHO is at ≥ 97%. In this study, it can be seen that the pooled specificity of saliva RT-PCR is at 97% which falls within the acceptable specificity set by the WHO.

Strengths and weaknesses

Heterogeneity of studies

Heterogeneity is defined as the variation in study outcomes between studies which is usually caused by differences in population characteristics, methodology, and other factors. It is determined by analyzing the sensitivity and specificity results. In this metanalysis, the pooled sensitivity showed minimal heterogeneity ($p = 0.19$). This can also be seen in the Forrest plot (Figure 2) which shows that sensitivity points are not distant to each other showing low variation and consistency within the results.

On the other hand, there is noted heterogeneity (12=359%) on the specificity analysis. As seen in the Forrest plot (Figure 2), the specificities of each study are inconsistent as shown by the distance of specificity values of each study. Significance of heterogeneity can be tested by measuring its p-value. A p-value of >0. 1 (0.19 on this metanalysis) is considered not significant. Therefore, it can be stated that heterogeneity, though present, is not significant and will not affect the overall study.

The predictive value quantifies the probability that a positive test result correctly identifies the presence of infection and a negative test result correctly identifies the absence of infection. This requires knowledge of not only the sensitivity and specificity of the test but the prevalence of the condition. The effect of prevalence on predictive values is considerable. As prevalence increases, Positive Predictive Value (PPV) increases and Negative Predictive Value (NPV) decreases. In this metanalysis, we can see that the study done by (Al-Suwaidi,2021) has the lowest PPV since it is the only study that included asymptomatic individuals unlike the other remaining studies which mostly tested for symptomatic patients.

Risk of bias

Some risks of bias are identified among the selected studies. In terms of patient selection, most of the studies focused on testing symptomatic parents. This may pose as risk for bias since symptomatic patients have higher probability of testing positive for COVID-19.This may also affect the applicability in testing asymptomatic patients. Only one study (Al-Suwaidi,2021) tested asymptomatic patients. Hence it is recommended to perform diagnostic studies which will cater to both symptomatic and asymptomatic patients.

A publication bias was also observed based on the Deek's funnel asymmetry test, however, since there were only less than 10 studies included in this metanalysis, the power of the test may be too low to distinguish chance from true asymmetry.

CONCLUSION AND RECOMMENDATIONS

Despite the strengths and weaknesses presented, the data gathered from the metanalysis demonstrate that saliva specimen can be used as an alternative for SARS-COV-2 diagnostic testing in children as demonstrated by the pooled specificity and sensitivity. However, the acceptable positive and negative predictive of the studies included in the metanalysis may not be reflective of the general pediatric population since most patients tested were symptomatic or close contacts of COVID-19 patients.

There are limitations identified considering the number of studies included. The authors recommend to include more studies for future metanalysis research, to further increase sample size, and to include both symptomatic and asymptomatic pediatric age group participants. A future prospective research study comparing the two diagnostic modalities is likewise recommended.

REFERENCES

1. World Health Organization. (n.d.). *Who western pacific*. World Health Organization. Retrieved May 27, 2021, from https://www.who.int/westernpacific/emergencies/covid-19
2. *Novel corona virus update 29 January 2020 background*. (n.d.). Retrieved May 27, 2021, from https://www.who.int/docs/default-source/maldives/novel-corona-virus-update-mav-30jan.pdf?sfvrsn=a10dfb7b_2
3. Tang Y. W, Schmitz JE, Persing DH, Stratton CW. Laboratory diagnosis of COVID-19: current issues and challenges. J Clin Microbiol. 2020;58(6):e00512-20.
4. Chen JH, Yip CC, Poon RW, Chan KH, Cheng VC, Hung IF, Chan JF, Yuen KY, To KK. Evaluating the use of posterior oropharyngeal saliva in a point-of-care assay for the detection of SARS-CoV-2. Emerging microbes & infections. 2020 Jan 1;9(1):1356-9.
5. Migueres M, Mengelle C, Dimeglio C, Didier A, Alvarez M, Delobel P, Mansuy JM, Izopet J. Saliva sampling for diagnosing SARS-CoV-2 infections in symptomatic patients and asymptomatic carriers. Journal of Clinical Virology. 2020 Sep 1;130:104580.

6. Williams E, Bond K, Zhang B, Putland M, Williamson DA. Saliva as a noninvasive specimen for detection of SARS-CoV-2. Journal of clinical microbiology. 2020 Jul 23;58(8):e00776-20.
7. Rao M, Rashid FA, Sabri FS, Jamil NN, Zain R, Hashim R, Amran F, Kok HT, Samad MA, Ahmad N. Comparing nasopharyngeal swab and early morning saliva for the identification of SARS-CoV-2 [published online ahead of print, 2020 Aug 6]. Clin Infect Dis. https://doi.org/10.1093/cid/ciaa1156. 2020.
8. Wyllie AL, Fournier J, Casanovas-Massana A, Campbell M, Tokuyama M, Vijayakumar P, Warren JL, Geng B, Muenker MC, Moore AJ, Vogels CB. Saliva or nasopharyngeal swab specimens for detection of SARS-CoV-2. New England Journal of Medicine. 2020 Sep 24;383(13):1283-6.
9. Hanson KE, Altayar O, Caliendo AM, Arias CA, Englund JA, Hayden MK, Lee MJ, Loeb M, Patel R, El Alayli A, Sultan S. The Infectious Diseases Society of America Guidelines on the Diagnosis of Coronavirus Disease 2019 (COVID-19): Antigen Testing. Clinical Infectious Diseases. 2021 Jun 23.
10. Ranney ML, Griffeth V, Jha AK. Critical supply shortages—the need for ventilators and personal protective equipment during the Covid-19 pandemic. New England Journal of Medicine. 2020 Apr 30;382(18):e41.
11. Sueki A, Matsuda K, Yamaguchi A, Uehara M, Sugano M, Uehara T, Honda T. Evaluation of saliva as diagnostic materials for influenza virus infection by PCR-based assays. Clinica Chimica Acta. 2016 Jan 30;453:71-4.
12. To KK, Yip CC, Lai CY, Wong CK, Ho DT, Pang PK, Ng AC, Leung KH, Poon RW, Chan KH, Cheng VC. Saliva as a diagnostic specimen for testing respiratory virus by a point-of-care molecular assay: a diagnostic validity study. Clinical Microbiology and Infection. 2019 Mar 1;25(3):372-8.
13. Kim YG, Yun SG, Kim MY, Park K, Cho CH, Yoon SY, Nam MH, Lee CK, Cho YJ, Lim CS. Comparison between saliva and nasopharyngeal swab specimens for detection of respiratory viruses by multiplex reverse transcription-PCR. Journal of clinical microbiology. 2017 Jan;55(1):226-33.
14. Azzi L, Carcano G, Gianfagna F, Grossi P, Dalla Gasperina D, Genoni A, Fasano

M, Sessa F, Tettamanti L, Carinci F, Maurino V. Saliva is a reliable tool to detect SARS-CoV-2. Journal of Infection. 2020 Jul 1;81(1):e45-50.

15. Pasomsub E, Watcharananan SP, Boonyawat K, Janchompoo P, Wongtabtim G, Suksuwan W, Sungkanuparph S, Phuphuakrat A. Saliva sample as a non-invasive specimen for the diagnosis of coronavirus disease 2019: a cross-sectional study. Clinical Microbiology and Infection. 2021 Feb 1;27(2):285-e1.
16. Williams E, Bond K, Zhang B, Putland M, Williamson DA. Saliva as a noninvasive specimen for detection of SARS-CoV-2. Journal of clinical microbiology. 2020 Jul 23;58(8):e00776-20.
17. Uwamino Y, Nagata M, Aoki W, Fujimori Y, Nakagawa T, Yokota H, Sakai-Tagawa Y, Iwatsuki-Horimoto K, Shiraki T, Uchida S, Uno S. Accuracy and stability of saliva as a sample for reverse transcription PCR detection of SARS-CoV-2. Journal of clinical pathology. 2021 Jan 1;74(1):67-8.
18. Yee R, Truong TT, Pannaraj PS, Eubanks N, Gai E, Jumarang J, Turner L, Peralta A, Lee Y, Dien Bard J. Saliva is a promising alternative specimen for the detection of SARS-CoV-2 in children and adults. Journal of clinical microbiology. 2021 Jan 21;59(2):e02686-20.
19. Buban JM, Villanueva PN, Gregorio GE. Should RT-PCR of saliva samples be used for diagnosis of COVID.
20. Al Suwaidi H, Senok A, Varghese R, Deesi Z, Khansaheb H, Pokasirakath S, Chacko B, Abufara I, Loney T, Alsheikh-Ali A. Saliva for molecular detection of SARS-CoV-2 in school-age children. Clinical Microbiology and Infection. 2021 Sep 1;27(9):1330-5.
21. Alenquer M, Silva TM, Akpogheneta O, Ferreira F, Vale-Costa S, Medina-Lopes M, Batista F, Garcia AM, Barreto VM, Paulino C, Costa J. Saliva molecular testing bypassing RNA extraction is suitable for monitoring and diagnosing SARS-CoV-2 infection in children. medRxiv. 2021 Jan 1.
22. Felix AC, De Paula AV, Ribeiro AC, Inemami M, Costa AA, Leal CO, Figueiredo WM, Sarmento DJ, Sassaki TA, Pannuti CS, Braz-Silva PH. Saliva as a reliable sample for COVID-19
23. diagnosis in paediatric patients. medRxiv. 2021 Jan 1.

24. Huber M, Schreiber PW, Scheier T, Audigé A, Buonomano R, Rudiger A, Braun DL, Eich G, Keller DI, Hasse B, Böni J. High efficacy of saliva in detecting SARS-CoV-2 by RT-PCR in adults and children. Microorganisms. 2021 Mar;9(3):642.
25. Ana Laura GO, Abraham Josue NR, Briceida LM, Israel PO, Tania AF, Nancy MR, Lourdes JB, Daniela DL, Fernando OR, Carlos Mauricio JE, Sergio Rene BP. Sensitivity of the molecular test in saliva for detection of COVID-19 in pediatric patients with concurrent conditions. Frontiers in Pediatrics. 2021 Apr 12;9:293.
26. Okoturo E, Amure M. SARS-CoV-2 saliva testing using reverse transcriptase-polymerase chain reaction (RT-PCR): A Systematic Review. International Journal of Infectious Diseases. 2022 May 13.
27. El-Sharkawy F, Tang CN, Fitzgerald AS, Khatib LA, Graham-Wooten J, Glaser L, Collman RG, Van Deerlin VM, Herlihy SE. Saliva versus Upper Respiratory Swabs: Equivalent for Severe Acute Respiratory Syndrome Coronavirus 2 University Screening while Saliva Positivity Is Prolonged After Symptom Onset in Coronavirus Disease 2019 Hospitalized Patients. The Journal of Molecular Diagnostics.
28. Mestdagh P, Gillard M, Dhillon SK, Pirnay JP, Poels J, Hellemans J, Hutse V, Vermeiren C, Boutier M, De Wever V, Soentjens P. Evaluating Diagnostic Accuracy of Saliva Sampling Methods for Severe Acute Respiratory Syndrome Coronavirus 2 Reveals Differential Sensitivity and Association with Viral Load. The Journal of Molecular Diagnostics. 2021 Oct 1;23(10):1249-58.

COST OF HOSPITALIZATION OF PEDIATRIC COVID-19 PATIENTS IN A TERTIARY PEDIATRIC HOSPITAL IN THE PHILIPPINES

ANGELO MARTIN B. CATACUTAN, MD, MBA, CARIDAD SANTOS, MD

ABSTRACT

BACKGROUND:

Out of pocket expenses still comprises a major share in health financing. A reactive approach in COVID-19 treatment may be problematic for the patient's finances. National health insurance systems like PHIC have COVID-related care benefits, but whether these offer sufficient coverage is unknown.

OBJECTIVES:

This study aims to describe the hospitalization costs incurred by pediatric COVID-19 patients admitted at a Filipino tertiary pediatric hospital, to determine the major cost drivers of hospitalization, and to determine how various payment methods provide coverage in paying for hospitalizations costs.

METHODS:

Financial statements of pediatric COVID-19 patients were reviewed, from which costs were categorized. Deductions were also compared with total hospitalization to determine adequacy of various financial assistance programs.

RESULTS:

Fifty-six charts and financial statements were reviewed for a 9-month period. Majority of the patients are of the 1-month to 6-year-old group (39.3%), of critical severity (66.1%), and with comorbidities (76.8%). Aggregated hospitalization costs of all COVID-19 patients amounted to PHP 9.5 million; medical costs accounted for the majority of the hospital costs at 35.40%. Mean total hospitalization cost per patient was determined to be PHP 170,170 and mean daily cost was

PHP 16,870. PHIC COVID-19 packages may provide deducted as much as 90.56% of the overall costs, but only 28.6% of patients were able to avail of this privilege. Out-of-pocket expenditure remains at 33% of the total hospitalization cost.

CONCLUSIONS:
COVID-19 hospitalization in this institution mainly consists of the 1-month to 6 years old, and the costs in the average can reach up approximately PHP 170,000, as basic medical fees drive the majority of the costs. Patients with no known comorbids tend to have higher costs of care but more data is needed to elaborate on the trend. Availing PHIC packages can greatly ameliorate the financial burden of hospitalization. However, checks in timely and accurate filing of claims should be in place to assure those that can avail this assistance are rightfully supported.

RECOMMENDATION:
A larger patient base with equal representation of patient categories is recommended in order to determine more comprehensive cost patterns and make significant associations.

Keywords: COVID-19, hospitalization costs, PHIC, Health Financing

INTRODUCTION

Coronavirus Disease 2019 (COVID-19) is a lingering global pandemic that has afflicted millions of people worldwide, 1.14 million of which, as of writing of this study, are Filipinos. However, as all treatment and preventive approaches continue to be experimental, management of the disease continues to be reactive – positing a risk to order more tests and medicines, which could possibly then lead to overcharging.

There is a paucity of information when it comes to the costs of care of COVID-19 patients. The Kaiser Family Foundation, a non-profit organization that deals with health policy analyses, made a projection that the cost of treatment for COVID-19 patients can go as high as USD 20,000 (PHP 1 million) and over USD 88,000 (PHP 4.4 million) if this patient would require mechanical ventilation. FAIR Health, another non-profit organization, had a higher projection of USD 38,221 (PHP 1.9 million) (Rae, et al. 2020).

A Korean study made a comprehensive investigation on 145 pediatric COVID-19 admissions in 2020. The mean hospitalization period was noted to be at 10.38 days, which tend to increase with the age of the child: 4.63 days for 0-5 years old, 10.87 days for 6-10 years, 14.88 days for 11-15 years, and 15.81 days for 16-19 years (Lee, et al. 2020). Total medical cost for all 145 children summed to USD 317,802 (PHP 15.9 million), and mean individual cost was USD 2,192 (PHP 109,600). Mean individual cost also appeared to be lower in the younger age group where patients at 0-5 years spent an average of USD 749 versus patients aged 16-19 years at USD 3,655. Out of the total costs, 99.19% was comprised of medical costs and prescription drugs were less than 1%. Furthermore, 88.13% of the total medical costs was shouldered by the Korean National Health Insurance Service. Unfortunately, there is still no other locally published data on pediatric COVID-19 costs as of writing.

This study was undertaken to describe the hospitalization costs incurred by pediatric COVID-19 patients admitted at a Filipino tertiary pediatric hospital in Quezon City, Philippines. The objectives of this study included (1) describing the demographic and clinical characteristics of pediatric COVID-19 admitted at the said institution, (2) determining hospitalization expenses and its breakdown, (3) determining the association of demographic and clinical factors with the cost of hospitalization, and (4) determining cost coverage by payment schemes employed by patients.

METHODOLOGY

A list of patients of age 1 month to <19 years old admitted for symptoms of COVID-19 and confirmed with a positive SARS CoV 2 RNA via RT-PCR admitted at PCMC from March 1 to December 31, 2020 was obtained from the hospital Infection Control Committee for inclusion in the study. Excluded were patients discharged against medical advice, transferred to other institutions, those who were asymptomatic during the time of admission, had healthcare associated COVID-19 infection, and neonatal COVID-19 infection.

Account statements were accessed via Bizbox™ with permission from the hospital's Billing Section. Disease severity was based on PIDSP Interim COVID-19 Guidelines wherein:

- Moderate COVID – is defined as symptomatic patients with clinical signs of non-severe pneumonia.
- Severe COVID – defined as symptomatic patients with clinical signs of pneumonia with one of the following, age-specific tachypnea, cyanosis or hypoxia, lethargy or unconsciousness, or inability to drink or feed.
- Critical pneumonia – symptomatic patients consistent with severe COVID, along with signs of acute respiratory distress syndrome (ARDS) or sepsis.

On the other hand, sources of payment were classified as follows:

- COVID Case Rate / Package – coverage provided by PhilHealth specifically for patients diagnosed COVID-19 disease, under the guidelines published in PhilHealth's Circular 2020-0009
- Non-COVID Case Rates – coverages by PhilHealth that are granted based on the final diagnosis written on the Claim Form 2 (CF2), other than those pertaining to COVID-19 disease
- C3 Discounts – discounts given to indigent patient as per classification of the hospital's Social Service Office. Although there are no actual payments made in the case of "discounts" granted to patients, it will be defined as "a mode of payment" for the purposes of this study.
- Guaranteed Hospital Bills – coverages granted to patients by funding entities functioning externally from the hospital, such as government agencies, non-government organizations, charity institutions, and the likes.

The Institutional Research Ethics Committee (IR-EC) approved all study-related procedures. Patient confidentiality in accordance with data privacy laws throughout the study duration was observed.

Data was encoded using Microsoft Excel 2019. Statistical analysis such as measures of central tendencies and analysis of variance were done using the same program, and verified using GraphPad Prism 8.

RESULTS

Fifty-six patients were included based on set inclusion and exclusion criteria. Demographic and clinical profile are listed below in Table 1. There was an equal proportion of male and female patients. Majority were below 6 years of age (39.3%), had Critical COVID-19 (66.1%), had comorbid illnesses prior to admission (76.8%), and encountered severe complications during admission (71.4%). Mean length of stay was 12 days, ranging from overnight admissions to long admissions of approximately 44 days.

Table 2 describes the composition of costs based on specific cost categories. The aggregated hospitalization cost of all 56 admitted patients during the 9-month study period amounted to PHP 9,529,738.14. Median total hospital costs per patient approximated to PHP 98,000.

Majority of the expenditures were from the medical costs category which included room rates, professional fees, and use of nursing facilities. It is then followed by laboratory and pharmacy costs which covers all laboratory tests and pharmaceutical agents respectively. Other costs, comprised of radiologic and other subspecialized care only accounted a minor percentage of the total costs.

Table 3 below describes the total and daily hospital costs of pediatric COVID-19 patients categorized by demographic and clinical characteristics. Middle adolescent groups appear to have the highest hospital costs among different age groups, but due to a high p-value, a further representation of each group should be done so as to establish significance. As for disease severity, progressing severity follows an increasing trend of costs, which is similarly found with the data obtained in regards to presence of complications. On the other hand, the absence of a comorbid illness tends to incur higher costs than having a known comorbid (p-value = 0.001).

Table 1 Demographic and Clinical profile of subjects (N=56)

Demographic and Clinical Characteristics	Frequency	%
Sex		
Male	28	50.0
Female	28	50.0
Age Groups (y)		
1mo to <6	22	39.3
6 to < 11	15	26.8
11 to < 16	12	21.4
16 to < 19	7	12.5
Social Classification		
Pay / Private	1	1.79
Charity	55	98.21
Disease Severity**		
Mild	10	17.9
Moderate	7	12.5
Severe	2	3.6
Critical	37	66.1
Presence of Comorbid Illness		
Without	13	23.2
With	43	76.8
Presence of Complications		
Without	16	28.6
With	40	71.4
Discharge Status		
Discharged	43	76.8
Expired	13	23.2
Source of Payment		
PhilHealth (COVID Case Rate)	16	28.6
C19I P2 (Moderate)	11	19.6
C19I P3 (Severe)	5	8.9
PhilHealth (Non-COVID Rates)	28	50
C3 Discounts	40	71.4
Guaranteed Hospital Bills	21	37.5
	Mean	**Range**
Length of Stay (days)	12	1 – 44

Table 2 Breakdown of hospitalization costs of pediatric COVID-19 patients (n = 56)

Cost Categories	Amount (x1000PHP)		Percentage of Hospitalization Costs
	Mean	Range	
Medical Cost	60.24	2.87 – 216.86	35.40
Other Cost (Radiology, ICU, etc)	51.24	0 – 218.60	30.10
Laboratory Cost	38.04	1.02 – 169.96	22.36
Pharmacy Cost	20.65	0.65 – 661.44	12.14
Total Hospitalization Cost	170.17	4.54 – 1029.12	100

Table 3 Mean total and daily hospitalization costs of pediatric COVID-19 admissions based on demographic and clinical diagnosis. (n=56)

Demographic/ Clinical Characteristics	Mean Hospital Costs X1000 PHP (Range)	p value	Mean Daily Hospital Costs (Range)	p value
Age Groups (y)				
1mo to < 6 (n=22)	118.35 (21.20 – 506.50)	0.38	17.14 (5.37 – 40.30)	0.46
6 to < 11 (n=15)	195.21 (4.54 – 781.12)		14.26 (4.54 – 29.70)	
11 to < 16 (n=12)	233.54 (25.17 – 1029.12)		22.09 (6.98 – 102.91)	
16 to < 19 (n=7)	170.78 (28.28 – 400.72)		12.64 (5.88 – 28.28)	
Disease Severity				
Mild (n=10)	83.24 (4.54 – 219.28)	0.24	12.48 (4.54 – 22.31)	0.20
Moderate (n=7)	142.73 (75.35 – 245.13)		10.41 (7.65 – 17.54)	
Severe / Critical (n=39)	197.33 (16.94 – 1029.12)		19.15 (5.39 – 19.15)	
Presence of Comorbid Illness				
Without (n=13)	220.19 (25.17 – 1029.12)	0.32	27.66 (5.39 – 102.91)	0.001
With (n=43)	155.05 (4.54 – 781.112)		13.61 (4.54 – 40.30)	
Presence of Complications				
Without (n=16)	102.86 (4.54 – 102.86)	0.10	11.18 (4.54 – 21.20)	0.18
With (n=40)	197.10 (16.94 – 1029.12)		16.36 (8.75 – 40.30)	
Overall	170.17 (4.54 – 1029.12)		16.87 (4.54 – 102.91)	

Table 4 and Figure 1 below describes the various payment sources available to pay for the hospital's COVID-19 admissions. Approximately PHP 3.14 million (33%) of this was accounted from receivables from PhilHealth reimbursements, consisting of combined COVID and non-COVID case rates. On the other hand, about 20% of these costs were granted as C3 discounts, on which no receivables are to be expected. The remaining 47% are classified as patient-shared expenses, which were shouldered by the patients, either as out-of-pocket payments (34%) or guaranteed hospital bills (14%).

Table 4 Breakdown of payment sources for overall hospitalization costs for pediatric COVID-19 admissions.

Reimbursement Source	**Patients availed n (%)**	**Hospitalization Cost Covered (x1000PHP)**
Total PHIC Coverage	44 (78.57%)	3,142.37
COVID Case Rates	16 (28.57%)	2,422.51
Non-COVID Rates	28 (50.00%)	719.86
C3 (Social Service) Discounts	40 (60.61%)	1,862.39
Guaranteed Hospital Bills	21 (37.50%)	1,326.83
Actual Payments (out of pocket)	33 (58.93%)	3,198.15
TOTAL		***9,529.74***

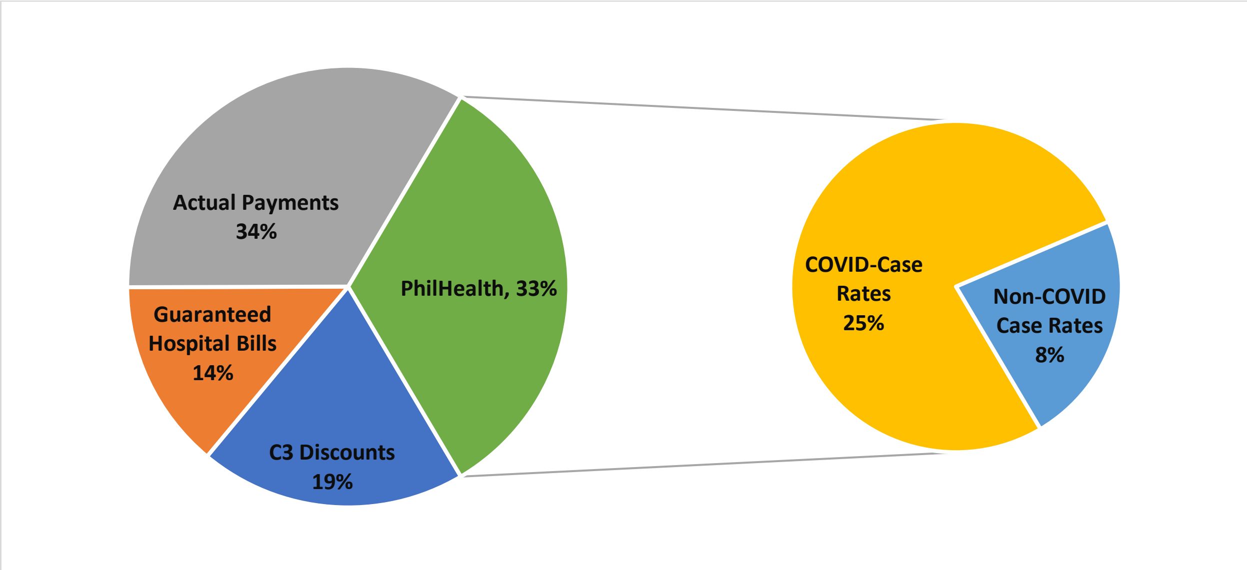


Figure 1 Breakdown of payment sources to compensate for overall hospitalization costs for pediatric COVID-19 admissions.

Table 5 describes how these available payment schemes can potentially contribute in financing the hospitalization costs of each patient. PhilHealth's COVID-19 case rates, on the average, can provide for about 90% coverage in the patient's total hospital costs. In some cases, wherein the expenses were relatively lower, PHIC COVID-19 packages can even reach full coverage of hospitalization expenses. Non-COVID rates by PhilHealth, on the other hand, can only provide for about a quarter of the hospitalization costs. Social service or C3 discounts take away approximately a third of the total costs, while guaranteed bills or non-institutional financial aids provide about a 45% coverage. Fortunately for the patient, these payment modes and deductions are not mutually exclusive, and can concurrently be availed by one patient.

Table 5 Mean percentage of hospitalization cost covered by each payment source per patient account.

Payment Source	**Mean Percentage of Hospitalization Cost Covered per Patient (%)**
PhilHealth	
COVID Case Rate (n=16)	90.56
Non-COVID Case Rate (n=28)	23.22
C3 Discounts (n=40)	32.36
Guaranteed Hospital Bills (n=21)	43.43

Discussion

The mean total hospitalization costs of admitted pediatric COVID-19 patients in this institution was PHP 170,170.00 (USD 3,403.40; PHP 50 = USD 1) which appears higher than the computed results of Lee et. al. of USD 2,192. Medical cost was noted to be the major cost driver as COVID-19 disease requires a specialized type of care as per hospital's infection control guidelines. This is similar to the outcomes in the study of Lee et. al. The cost of personal protective equipment (PPE), tedious sanitation requirements, among others fall into this cost category. Other costs which are comprised of subspecialty care charges (such as Radiology, Pulmonology, and Intensive Care) comes second in the overall costs. Charges falling into category are mostly found in patients with severe or critical course of the disease – those that required ICU admission and mechanical ventilation. Laboratory costs rank third as minimal laboratory tests are done on COVID-19 patients after obtaining baseline laboratory parameters. Higher laboratory costs seem are more apparent on patients with complicated course of disease, especially those who are candidates for Multisystem Inflammatory Syndrome in Children (MIS-C) – requiring specialized, thus more expensive, tests that may need to be sent out to an off-site laboratory. As the backbone of management of COVID-19 disease is still supportive care, medicines were only prescribed based on patient-specific problems, which is mostly related on the patient's comorbid disease, rather than COVID-19 disease itself. Hence pharmacy costs are relatively taking a lower share of the costs.

Pediatric COVID-19 patients belonging to the early and middle adolescents appear to incur higher hospitalization costs as shown in Table 3. However, due to the uneven distribution of patients per age group, significant associations cannot be statistically established. Hospitalization costs appear to follow an increasing trend as the course becomes more complicated.

The presence of comorbid illnesses ironically has a negative correlation to the hospitalization costs than those with known comorbid illnesses (p=0.001). However, this finding may have been confounded by other patient factors. One notable feature of these patients, who had no known comorbidities, is that most of these had a severe or critical course of COVID-19 disease. Alternatively, one reason why patients with known comorbids had lower costs, may have been due to the fact that these are old, or known, patients of the study institution, hence these patients already had established baseline workups which may compel the care team to treat more conservatively rather than an all-out approach to diagnostics and therapeutics. Unfortunately, cost breakdown studies are lacking at the time of writing of this study, further probing on this is recommended.

Inconsistencies become apparent when the focus of the discussion is shifted towards the payment of these hospitalization costs. As described in Table 5, PHIC's COVID-19 packages have the potential to provide an almost 90% coverage of the patient's bills, reducing patient-shared expenses to only 10%. Unfortunately, this only applies to the 16 (28.57%) patients who were able to successfully avail of the said care package. Twenty-eight (50%) patients, though eligible to claim, were not able to avail of the privilege, and was granted a different case rate which had a lower cost coverage that only covers approximately 23% of their hospitalization expenses. This explains the findings in Table 4 – that despite great sum of coverage offered by PHIC COVID-19 case rates, it only paid for PHP 2.42 million (25%) of the actual aggregated hospitalization costs for COVID-19 admissions. As for those patients that were not able to rightfully claim COVID-19 packages, their case rates only provided for 8% of the aggregated hospitalization costs.

Upon further investigation, these inconsistencies rose from the logistic lapses in the filing of PHIC's claim forms during the period when the COVID-19 case packages were fairly new. As COVID-19 disease is mainly a disease that affects the respiratory system, and PHIC claim forms rely on a "per diagnosis" system, majority of unsuccessful COVID-19 package claims ended up being written off as "pneumonia, unspecified" or whichever comorbid condition the patient had prior to acquiring COVID-19. Unfortunately, the coverage rates for these diseases were significantly lower than the COVID-19 packages. One example is the case rate for moderate risk pneumonia which is PHP 10,500 according to PHIC's updated rates as of 2017, compared to moderate COVID-19-related pneumonia which is PHP 143,267 (Philippine Health Insurance Corporation 2017).

Fortunately for patients, they are not confined in subscribing only to one form of payment source when financing their hospital bills. Table 5 above summarized how much each payment scheme can potentially cover for a patient's expenses. By mixing and matching one payment source and another, with the exception of PHIC benefits as they can only subscribe to one package per admission – oftentimes based on the diagnosis with the highest case rate, a patient can potentially achieve full coverage for his hospitalization, without even paying a single peso. However, that is not always the case in all patients. Going back to Table 4, out-of-pocket (OOP) costs of COVID-19 admissions were found to be at 34%, even slightly higher than what PHIC was able to cover. Even with the capability to concurrently subscribe to multiple payment sources, some patients still ended up paying a significant share of their bills. On a positive note, a 34% out-of-pocket spending is still relatively lower to the 44.7% OOP payments for financing health expenditures in 2020, as recently reported by the PSA (Philippine Statistics Authrority 2021).

CONCLUSION

COVID-19 hospitalization in this institution mainly consists of the 1-month to 6 years old, and the costs in the average can reach up approximately PHP 170,000, as basic medical fees drive the majority of the costs. Patients with no known comorbids tend to have higher costs of care but more data is needed to elaborate on the trend. Availing PHIC packages can greatly ameliorate the financial burden of hospitalization. However, checks in timely and accurate filing of claims should be in place to assure those that can avail this assistance are rightfully supported.

REFERENCES

1. Connecticut Children's Medical Center. 2020. "Emergency Department and Inpatient COVID-19 Algorithm." Accessed December 12, 2020. https://www.connecticutchildrens.org/wp-content/uploads/2020/12/COVID19-Ed-Inpatient-12.9.20.pdf.

2. Dong, Yuanyuan, Xi Mo, Yabin Hu, Xin Qi, Fang Jiang, Zhongyi Jiang, and Shilu Tong. 2020. "Epidemiological Characteristics of 2143 Pediatric Patients with 2019 Coronavirus Disease in China." *Pediatrics.*

3. Hassan, Syed Adeel, Fahad N Sheikh, Somia Jamal, Jude K Ezeh, and Jude Akhtar. 2020. "Coronovirus (COVID-19): A Review of Clinical Features, Diagnosis, and Treatment." *Cureus.* Accessed October 1, 2020. doi:10.7759/cureus.7355.

4. Lee, Joon Kee, Byuk Ok Kwak, Jae Hong Choi, Eun Hwa Choi, Jong-hyun Kim, and Dong Hyun Kim. 2020. "Financial Burden of Hospitalization of Children with Coronavirus Disease 2019 under the National Health Insurance Service in Korea." *J Korean Med* e224.

5. Ludvigsson, Jonas F. 2020. "Systematic review of COVID-19 in children shows milder cases and a better prognosis than adults." *Acta Pediatrica* 109: 1088-1095.

6. Magsambol, Bonz. 2020. *Getting treated for coronavirus comes with a hefty price tag.*

April 17. Accessed December 29, 2020. https://www.rappler.com/newsbreak/iq/getting-treated-coronavirus-price-tag.

7. Pediatric Infectious Disease Society of the Philippines. 2020. "Interim Guidelines on the Screening, Assessment, and Management of Pediatric Patients with Suspected or Confirmed Coronavirus Disease 2019 version 3.1." August. Accessed December 13, 2020. http://www.pidsphil.org/home/themencode-pdf-viewer/?file=http://www.pidsphil.org/home/wp-content/uploads/2020/09/1598932106977519.pdf.

8. Philippine Health Insurance Corporation. 2020. "Benefit packages for inpatient care of probable and confirmed COVID-10 developing severe illness/outcomes." *PhilHealth Circulars.* Accessed October 2, 2020. https://www.philhealth.gov.ph/circulars/2020/#gsc.tab=0.

9. —. 2017. *List of Medical Case Rates.* February. Accessed November 5, 2021. https://www.philhealth.gov.ph/circulars/2017/annexes/0019/AnnexA-MedicalCaseRates.pdf.

10. Philippine Statistics Authrority. 2021. *Health Spending Registered 12.6 Percent Growth, Share of Health to Economy Went Up to 5.6 Percent in 2020.* October 14. Accessed November 5, 2021. https://psa.gov.ph/content/health-spending-registered-126-percent-growth-share-health-economy-went-56-percent-2020.

11. Rae, Matthew, Gary Claxton, Nisha Kurani, Daniel McDermott, and Cynthia Cox. 2020. *Potential costs of COVID-19 treatment for people with employer coverage.* March 13. Accessed October 2, 2020. https://www.healthsystemtracker.org/brief/potential-costs-of-coronavirus-treatment-for-people-with-employer-coverage/.

THE QUALITY OF LIFE, SITUATIONS AND EMERGING CONCERNS OF PARENTS OF CHILDREN WITH NEURODEVELOPMENTAL DISORDERS IN PHILIPPINE CHILDREN'S MEDICAL CENTER DURING THE COVID-19 PANDEMIC

ANNELYN FATIMA M. LOPEZ, MD, ERMENILDA L. AVENDAÑO, M.D., AILEEN MARIE O. VARGAS, M.D., LARA C. BAYLON, M.D., RORILEE Q. ANGELES, M.D.

ABSTRACT

BACKGROUND: COVID-19 resulted in a public health emergency and quarantine measures which may negatively impact vulnerable populations.

OBJECTIVES: This study intends to determine the quality of life, situations and emerging concerns of parents of children with neurodevelopmental disorders during the ongoing pandemic.

METHODOLOGY: A cross-sectional survey using a socio-demographic questionnaire, situations and emerging concerns during the coronavirus pandemic and WHOQOL-BREF (Filipino version) for parental quality of life was documented via Google Forms. Parents of patients aged 2-18 years seen at the PCMC Neurodevelopmental Pediatrics OPD during July to December 2019 were recruited.

RESULTS: Data from 115 respondents showed a lower score in the environmental domain. Child characteristics comparable with QoL scores include sex, severity of ID and ADHD while parent characteristics comparable with the QoL scores include educational attainment, monthly family income, father's employment status and family structure (P-value <0.05). Most respondents reported situations of physical distancing (82.61%) and curfew (80.87%). Inability to access essential services (43.48-74.48%) were further compounded by limited financial resources (51.30%) and public transport (60%). Government policy received included quarantine pass (90.43%), food allowance or relief package (86.09%), disinfection (60.87%), DSWD-SAP (42.61%) and cash distribution (41.74%).

Concerns include socio-environmental issues: no available transportation (73.04%), impaired ability to work or earn (70.43%), inadequate rations (50.43%), disruptions in basic social services (47.83%); and patient concerns: access to education (64.35%), medical (44.74%), developmental (33.04%), behavioral (31.3%), nutrition (20%) and sleep (19.13%).

RECOMMENDATIONS: Programs and policies should be planned accordingly to provide improvement of quality of life to parents and their child with neurodevelopmental disorder.

Keywords: Neurodevelopmental Disorder, Neurodevelopmental Pediatrics, Parental Quality of Life, WHOQOL-BREF, COVID-19, coronavirus

INTRODUCTION

The coronavirus disease (COVID-19), a systemic infection caused by a novel strain of coronavirus emerged from an outbreak in Wuhan, China in December 2019 and in a matter of months has been declared a global pandemic and public health emergency.[1] Toward the end of October 2020, there have been more than 40 million cases of COVID-19 reported in 215 countries and territories resulting in more than one million deaths yet the numbers are still rising.[2] To respond to this crisis, the government and health agencies have recommended limitation of social contact, practicing proper personal hygiene and travel restrictions.[3] Beginning March 16, 2020, the Philippine Government imposed community quarantine measures covering strict lockdown restrictions, suspension of mass public transportation, face-to-face school interactions, and closure of all private establishments, except for those providing essential goods and services.[4] In an effort to decongest health facilities and observe physical distancing, many outpatient services and private clinics were limited or closed during the lockdown, instead offering telehealth or remote consultation services.[5]

This encroachment affects not only social, economic and political resources but also instigates a sudden and drastic change in the life condition of families. Among vulnerable populations, children with neurodevelopmental disorders are of particular interest because of their unique and specialized needs. Children are dependent on others to provide for food, shelter, transportation and medical care.[6] This is magnified with a concomitant neurodevelopmental disorder for whose spectrum of illnesses include ASD, ADHD, CP, GDD, ID, Learning Disorders and Sensory Impairments.[7] These diverse group of chronic conditions present with early onset neurocognitive deficits causing a disturbance in the developmental process and persisting throughout an individual's lifetime as a form of disability in personal, social, academic, or occupational functioning.[8,9] Other difficulties that may arise in the current public health situation include transport concerns, need for continuous medical assistance and support services, limitations in communication and trouble with transitioning to different situations.[10] They are also at risk for serious behavioral and emotional concerns that may be brought about by the stress and uncertainty of the quarantine measures implemented.

This burden is much more palpable and long-lasting to their parents who spend most of their time and resources in caring for a child with a neurodevelopmental disorder thereby impacting their psychosocial health. Studies indicate lower quality of life for these parents usually correlated to the functional dependence of their child and increasing stress levels.[11,12] This high level of caregiving is in itself a daunting challenge on a day to day basis but add to that, a global medical phenomenon of disastrous proportions, may trigger a breaking point. The quarantine, health services and transport established for the COVID-19 response may fail to accommodate the needs of their children and even create obstacles to earn wages, access health and education services.[13,14] Discrimination and stigma already contribute to these systemic and societal barriers that may also negatively influence the psychosocial and environmental dynamics for their parents. The intersectionality of disability with demographic factors and exposure to disaster can multiply the stigma, discrimination and disadvantage that persons with disabilities experience.[15]

There is limited research as to the psychosocial effects of disaster and pandemics on this special population of pediatric patients and their families.[13, 16, 17] Since a pandemic of this scope and scale has not been experienced for more than a century, this becomes an opportunity to look into the varied and far-reaching impact that this global event has brought about. This study aims to determine the quality of life, situations and emerging concerns of parents of children with neurodevelopmental disorders during the ongoing coronavirus pandemic. In this vein, the elicited quality of life scores will be correlated to the socio-demographic data. The knowledge gained from this study will benefit families of children with neurodevelopmental disorders as it will provide health care professionals with information regarding how the current global pandemic may impact the families of our patients, specifically the parents' quality of life, situations and emerging concerns. This knowledge may be used to create appropriate interventions and programs that may improve how families can adapt to the changes brought about by COVID-19 pandemic and assimilate into their "new normal" lives.

METHODOLOGY

a. Study Design and Participants

With approval by the Institutional Research-Ethics Committee of PCMC (PCMC IR-EC 2020-036), this cross-sectional survey on parents of patients seen at the PCMC Neurodevelopmental Pediatrics OPD Clinic for the period of July 2019 – December 2019 due for a follow-up schedule were invited to join the study through phone call. To encourage participation, an advertisement was also sent to online support groups of PCMC patients. The patients' ages ranged from 2 to 18 years and had at least one confirmed neurodevelopmental disorder diagnosed at least 6 months prior to recruitment. Parents who had more than one child with a neurodevelopmental disorder, unable to understand conversational English or Tagalog and residing outside of the Philippines were excluded from the study.

Parents who agreed to join were given the option to fill up the same Google Forms either in the clinic, via phone interview or online survey to ensure their participation because of the community quarantine restrictions and technological limitation. A written consult was provided to all participants – for those who were interviewed over the phone, verbal consent was initially recorded but were subsequently sent written documents for signing via a courier service. There was no monetary compensation for participating but resources to psychosocial counselling were provided.

The number of participants was sufficient for the computed sample size of 85, based on 0.3 desired correlation coefficient of any parent's or child's characteristics as well as situations and emerging concerns of the children with neurodevelopmental disorders with the QoL scores of parents of children with neurodevelopmental disorders, 5% level of significance and 80% power. [21] This is based on the data of the previous study done in our center.

b. Outcome Assessments

Socio-demographic questionnaire:

A socio-demographic questionnaire was administered which included pertinent information such as parent demographics and patient characteristics.

WHOQOL-BREF (Filipino version):

The WHOQOL-BREF Filipino version was used to measure the quality of life of parents of children with neurodevelopmental disabilities. The WHOQOL-BREF is a condensed form of the WHOQOL-100 containing 26 items rated individually on a 5-point Likert scale and identifying four domains: Physical Health, Psychological, Social Relationships and Environment. The Filipino version is cross-culturally valid and has been used for similar populations in local studies: particularly parents of children with special needs and parents of children with ASD. [19,20,21]

Situations and Emerging Concerns during the COVID-19 pandemic:

A survey on situations and emerging concerns was adapted from the online survey on the Needs and Situations of Children with Disabilities in the Context of COVID-19 by the Sub-committee on Children with Disability of the Council for the welfare of Children, a government agency to include specific developmental and behavioral concerns.[22] The members of this committee are experts in their field and represented agencies such as Commission on Human Rights, Department of Education, ECCD Council, UNICEF, Norfil Foundation and many others. Permission was obtained from the members of the sub-committee to modify the questionnaire by adding specific concerns such as behaviors, sleep and nutrition. The survey included current measures implemented or services provided as a response to COVID-19, reasons and difficulties in accessing needs or services, and emerging issues or concerns which have surfaced. The questions had an option for open-ended responses if the participants had something to add aside from the choices presented.

The adapted survey was piloted by sending the Google Forms thru facebook messenger to 17 subjects – all parents who have children who were previously seen at the outpatient clinics of the Child Neuroscience Division. Item analysis was done resulting in a Cronbach's Alpha of .820.

c. Statistical analysis

Descriptive statistics was used to summarize the demographic and clinical characteristics of the patients. Frequency and proportion was used for categorical variables, median and inter quartile range for non-normally distributed continuous variables, and mean and SD for normally distributed continuous variables. Independent sample T-test and One-way analysis of variance was used to determine the difference between two and three groups, respectively, in terms of Quality of Life scores. Pearson product moment or Spearman correlation was used to determine the linear and rank correlation between QoL scores of parents of children with neurodevelopmental disorders and different parameters. All statistical tests was two tailed. Shapiro-Wilk was used to test the normality of the continuous variables. Missing values was neither replaced nor estimated. STATA 13.1 was used for data analysis.

RESULTS

A total of 115 final respondents were culled from 198 parents after application of the selection criteria. Table 1 and 2 show the child and parent characteristics.

The proportion of the primary neurodevelopmental diagnosis in the child's characteristics approximate the figures seen in the section's annual patient census which would further support an adequate sampling of subjects. Out of the patients whose primary neurodevelopmental diagnosis was either Global Developmental Delay or Intellectual Disability, there were 9 (7.8%) who had a neurologic malformation such as congenital hydrocephalus or Chiari 2 malfunction, 7 (6%) who had Down Syndrome or Trisomy 21, and 6 (5.2%) who had epilepsy.

There were 56 respondents (48.7 %) who reported that they had to discontinue interventions of their children due to the lockdown restrictions. The timing of data collection may have influenced the results of education as the resumption of classes in public schools occurred in the following month.

Most of the respondents were from the National Capital Region (66.08%) with 30 out of the 76 residing in Quezon City. Of those from Region III, majority (12 respondents) were from Bulacan province and of those from Region IV-A, majority (21 respondents) were from Rizal province.

A majority (96.65%) of the respondents were mothers, most of whom were unemployed (64.91%) but were the primary caregivers (38.28%).

Table 3 details the WHOQOL-BREF scores across the different domains. A study using the WHOQOL-BREF proposed the critical value of 60 as a cut-off point for assessing QoL.[28] The parental quality of life showed acceptable scores in the physical, psychological and social relationships domains with a lower score (less than 60) for the environmental domain. The WHOQOL-BREF uses a Likert scale with 5 as the highest score; the first 2 questions reflect ratings for over-all quality of life (Mean=3.06) and over-all perception of health (Mean=3.37).

Table 4 relays the concerns of the parents caring for their children who have neurodevelopmental disorders during the pandemic. Most participants were concerned about social distancing (82.61%) and the curfew (80.87%) among the current measures being implemented during the COVID-19 pandemic. Of the 20 who answered Other: 9 participants named specific measures such as the wearing of face masks and face shields outside of the home; 7 named stricter restrictions for minors and senior citizens; 4 named proper hand hygiene and disinfection while answers such as liquor ban, designated time for marketing or stricter security measures in private subdivisions were also mentioned.

When asked about how they had been affected by the quarantine measures, options on the inability to access rehabilitative, developmental, educational, and medical services were chosen (74.78%, 67.57% 45.22% and 43.48% respectively). 75 respondents (65.22%) specified loss of income or employment as a consequence of the quarantine measures. Domestic and child abuse were rarely chosen with a frequency of 4.35% and 2.61% respectively. Of the 13 who answered "Other": 7 mentioned the limitation of medical services; 2 respondents each elaborated on the decreased source of income, lack of recreational activities for their child and restrictions on public transport.

The majority of the reasons for limited access to services and necessities were those of limited or absence of financial resources and absence of public transport. Of the 20 who answered "Other": 9 respondents mentioned the closure of many establishments such as schools, clinics and therapy centers and 6 respondents mentioned fear of contracting the virus in public places.

The more common services or assistances received included quarantine pass (90.43%), food allowance or relief package (86.09%), disinfection of areas (60.87%), DSWD Social Amelioration Package (SAP) (42.61%) and cash distribution from City or Barangay (41.47%). Of the 9 who answered "Other": 3 respondents each answered oral polio vaccination and other sources of cash assistance such as SSS and the 4Ps program; one respondent remarked that they were able to avail of the first round of SAP dole-outs but not the second.

Regarding issues or concerns that have surfaced during the implementation of quarantine measures, these options can be grouped into socio-environmental issues and patient concerns. For socio-environmental issues, respondents more frequently chose no available transportation (73.04%), effect of the quarantine on ability to work or earn (70.43%), violations on distancing (54.78%), inadequate food/medicine rations (50.43%), disruptions in basic social services (47.83%) and non-compliance to set curfew time (40.87%). For patient concerns, the frequency of respondents' choices were as follows: access to education (64.35%), medical (44.74%), developmental (33.04%), behavioral (31.3%), nutritional (20%) and sleep (19.13%).

Table 5 shows the comparison of the child characteristics against the QoL mean score for each domain. P-value with <0.05 (**bold**) were significantly different between the group in their respective row (variable). Thus, there was a statistical difference seen in 2 variables in terms of their Environmental QoL score. Parents had higher QoL score in the environmental domain when their child was male (59.24 $\pm$ 13.78) compared to when their child was female (54.08 $\pm$ 11.88). This difference was also seen when a child with Intellectual Disability had severe classification (66.67 $\pm$ 9.71) compared to one classified to have moderate severity (51.71 $\pm$ 6.68). In terms of the QoL score under Social Relationships, there was a statistical difference seen in the classification of Attention-Deficit/Hyperactivity Disorder. Parents had a higher Social Relationships QoL score when their child with ADHD was classified with moderate severity (80.29 $\pm$ 9.14) compared to a child with ADHD having a severe classification (59.5 $\pm$ 13.44). None of the other characteristics were seen to have a significant difference when compared against the QoL scores of the parents.

Table 6 shows the comparison of the parent characteristics against the QoL mean score for each domain. P-value with <0.05 (**bold**) were significantly different between the group in their respective row (variable). The variables marked with an asterisk (*), shows positive correlation. Of these factors, educational attainment, monthly family income, father's employment status and family structure were significantly comparable with the WHOQOL-BREF scores. There is a positive but weak correlation with parents' educational attainment as compared to QoL scores in the psychological (0.1889) and environmental (0.2958) domain, as is with monthly family income compared to QoL environmental score (0.2977). The scores on the environmental domain was significantly higher when father was employed (59.77 $\pm$ 13.4) as compared with being unemployed (50.58 $\pm$ 9.93). The QoL scores on the psychological and social relationships domain were significantly higher with a 2-parent biologic family structure (70.08 $\pm$ 11.79, 71.6 $\pm$ 13.95 respectively) compared to other family structures (61.4 ± 12.39, 53.7 ± 18.87 respectively.

DISCUSSION

This was one of few local studies that explored the psychosocial and environmental impact that the COVID-19 pandemic may have on the parents of children with neurodevelopmental disorder.

Children with neurodevelopmental disorders are steadily increasing in prevalence. In the United States, from 2009 to 2017, the overall prevalence among children aged 3 to 17 years was 16.93% which increased from 13.87% a decade prior.[23] In the Philippines, based on national health insurance agency estimates in 2017, there are 1 out of 7 Filipino children living with disabilities.[24] This supports the considerable number of patients who are susceptible to the negative effects of a global pandemic and the experience of being quarantined owing to physical and mental limitations, poverty, high likelihood for medical or life-threatening consequences and other social or psychological factors.[25] In the PCMC Neurodevelopmental OPD Clinic, there were 520 patients seen between the months of July to December 2019 who had at least one diagnosis of a neurodevelopmental disorder.

The shutdown of various support services and schools have forced drastic and abrupt changes to the home environment and family dynamic. The parental role in the home environment has become even more crucial in this new normal. Parents who are already the caregiver and house manager are also forced to work from home and take on the role of teachers for those with children who are homeschooling. Previous support systems such as grandparents, friends, leisurely activities and therapy centers are not available. The situation may then result into psychological distress and negative emotions in parents which can cascade into that of their child with special needs.[26]

Parental quality of life, a more comprehensive assessment of parental adaptation and mental health, would also impact the ability of caregivers to notice changes in their child and how to properly respond to their healthcare needs. [11, 12, 27] QoL is a person's changing perception of one's life in relation to various domains relative to one's environment, showing an interplay of their goals, expectations, standards and concerns to their culture and value systems. A study using the WHOQOL-BREF proposed the critical value of 60 as a cut-off point for assessing QoL.[28] As seen in the results, the parental quality of life showed acceptable scores in the physical, psychological and social relationships domains with a lower score (less than 60) for the environmental domain. In WHOQOL-BREF, the environmental domain is composed of items on money to meet needs, availability of information, leisure activity opportunity, conditions of living place, access to health services and means of transportation. These items are most affected by the quarantine measures that have been instituted due to the coronavirus pandemic. The environmental domain is also seen with the most significant comparisons to the child and parent characteristics in this study.

An analytical cross-sectional study done in Pakistan using WHOQOL-BREF during the COVID-19 pandemic compared parents of children with disabilities to those without and revealed statistically significant differences in the physical health and environmental domains.[29] This underscores outcomes in previous studies which highlight the greater caregiver burden of having a child with neurodevelopmental disorders such as difficulty understanding the diagnosis of the child, stressful encounters with health professionals and the time it takes away from pursuing their own healthy habits.

There are previous studies conducted in different Asian countries showing that exposure to natural disasters may impair a person's quality of life.[30, 31] Some risk factors associated with poor QoL include being female, disadvantaged living conditions, lower socio-economic status, less educated and increased dependency on the activities of daily living.[32, 33, 34] In this study, parents had lower environmental QoL score in the environmental domain when their child was female and the father was unemployed. Lower educational attainment and monthly family income would correspond to lower environmental QoL scores. Unemployment and monthly family income factor into the financial resources of a family. A family with a child having a neurodevelopmental disorder are sure to have additional expenses for the specialized interventions that the child may require.

Severity of the neurodevelopmental disorder revealed significant differences. One of those identified was ADHD in the domain of Social Relationships, Parental quality of life studies on ADHD have conflicting results on severity of symptoms. [35, 36] One study specifically identifies the child's academic performance as a predictor for physical, emotional and social domains of QOL.[37] Upon review of the subjects having severe classification in ADHD criteria, all had an associated learning disorder which would be a substantial liability during these times, as parents have to closely monitor and take on an active role in their child's education. The other finding was actually contrary to our expectations wherein the severe classification of Intellectual Disability was associated with a higher parental environmental QoL score. Upon review of the subjects having moderate classification of Intellectual Disability, the majority had at least 3 co-morbid conditions which would further add to the financial and emotional burden of their parents. This may be looked into further with a bigger sampling of subjects.

The outcome of the QoL scores on the psychological and social relationships domain being significantly higher with a 2-parent biologic family structure is also supported by the previous QoL study done in our center on parents of children with autism. Having two parents living together was positively correlated with QoL score on social relationships and was attributed to family-centeredness and close family ties which is deeply ingrained in the Filipino culture.[21] There is a shared burden among family members and the strong social support can also provided by friends and extended family members. Interestingly, in a recent study on the psychosocial and behavioral impact of COVID-19 in ASD, living with a separated or single parent was associated with better outcome in terms of intensity of behavior problems.[38]

A study was done in Liaoning Province in China to investigate the immediate impact of the COVID-19 pandemic on mental health and quality of life among local residents using an online survey distributed through a social media platform done last January and February 2020.[39] The results showed mild stressful impact, with 52.1% of participants reporting that they felt horrified and apprehensive due to the COVID-19 pandemic. However, the majority of participants (53.3%) did not feel helpless due to the pandemic.

Quarantine measures have implemented physical distancing restrictions and local government implemented curfews. Inability to access essential services were further compounded by limited financial resources and public transport. Government response that have been received by most respondents include quarantine pass, food allowance or relief package, disinfection of areas, DSWD SAP and cash distribution.

The online survey on the Situation of Children with Disabilities in the Context of COVID-19 which was fielded last April 2020 through social media platforms by the Sub-committee on Children with Disability of the Council for the Welfare of Children was open to parents and stakeholders and had more than 40,000 respondents in a span of few weeks.[22] When asked how children with disabilities have been affected, pertinent issues to more than 30% of the respondents include inability to access education services, day care centers, health clinic services, rehabilitation services and loss of income or employment. More than 40% of the respondents reported violations of social distancing, unavailability of transportation, effect of enhanced community quarantine on their ability to work/earn and reduced access to education for their children as emerging concerns during the coronavirus pandemic. These were found to be consistent with the results of this study.

These concerns are very critical to the subset of pediatric patients seen in PCMC Neurodevelopmental Pediatrics OPD as limitations in finances, closure of face-to-face and absence of public transport has brought about changes in how medical consults and therapeutic interventions are being implemented. Even the modification to the educational system are very substantial concerns to children who have many academic and cognitive limitations.

The findings of this study should be received discerningly due to its limitations. The study design of a cross-sectional survey may be able to reveal associations among factors but a longitudinal study may be more predictive to define relationships of the parent and child characteristics with the parental quality of life. This may also offer comparison in the results depending on the timing of data collection to the current social and public health milieu. A qualitative study design with focused group discussions or structured interviews may provide more depth regarding the concerns of parents of children with neurodevelopmental disorders. The data may also be enriched with a bigger sample size to improve on representation of the population and more reliable results. As this study provided for different options to accomplish the questionnaire, the phone interview was more prone to response bias as opposed to those that were self-administered. Item analysis of the different options can be done to investigate for the possible biases. The questionnaire on situations and emerging concerns may also be refined to better organize these concepts in the context of the evolving nature of the coronavirus pandemic and the measures being implemented.

In conclusion, this study highlighted how the ongoing COVID-19 pandemic has challenged families of children with neurodevelopmental disorders. Parental quality of life scores showed a lower score in the environmental domain. The child characteristics that are statistically comparable with the QoL scores include sex, severity of ID and ADHD while the parent characteristics that are statistically comparable with the QoL scores include educational attainment, monthly family income, father's employment status and family structure. The quarantine measures have disrupted employment, financial gains and availability of supports that these families need such as medical, rehabilitative and educational services. Inability to access essential services were further compounded by limited financial resources and public transport. Government responses received include quarantine pass, food allowance or relief package, disinfection, DSWD-SAP and cash distribution. Concerns encountered include socio-environmental issues and patient concerns.

Children with a multitude of health, developmental and behavioral concerns are at risk to present with more intense and frequent problems and at present, may not have the infrastructure to address these accordingly. Even with the shift to telemedicine and teletherapy platforms, many of these families are struggling to cover for their basic needs and adjust to the many changes that this public health emergency has brought about. A reframing of current programs and policies need to be taken into account to provide opportunities for the improvement of the quality of life of both the parents and the child with a neurodevelopmental disorder. The government should be able to provide for subsidy and specific interventions that these children and adolescents require which would greatly lift some of the burden from their parents. Hospitals and service providers should organize parent trainings and empower support groups to address specific needs and concerns of parents and patient; these can be made easily accessible through online platforms or face-to-face interactions once restrictions allow for them. Interventions should also take into account the mental health and surveillance of the psychosocial wellbeing of these families.

Parents and pediatric patients with neurodevelopmental disorders have an innate resilence from the situation and experience that they go through but this can be extinguished by the overwhelming burden of their circumstance. Future efforts at designing more inclusive and comprehensive intervention programs will aid in their transition of a post-pandemic society, one that turns challenges into opportunities.

BIBLIOGRAPHY/ REFERENCES

1. World Health Organization. Coronavirus disease (COVID 19) in the Philippines. [Internet]. Representative Office for the Philippines: World Health Organization; 2020 [cited 2020 Apr 27]. Available from: https://www.who.int/philippines/emergencies/covid-19-in-the-philippines
2. World Health Organization. WHO Coronavirus Disease (COVID-19) Dashboard. [Internet]. [cited 2020 October 20]. Available from: https://covid19.who.int
3. Aguilar K. Luzon now under 'enhanced community quarantine' -Palace. Inquirernet [Internet]. Philippine Daily Inquirer; 2020 Mar 16 [cited 2020 Apr 26]. Available from: https://newsinfo.inquirer.net/1243036/luzon-island-now-under-enhanced-community-quarantine-palace
4. Memorandum from the Executive Secretary On Community Quarantine Over the Entire Luzon and Further Guidelines for the Management of the Coronavirus Disease 2019 (COVID-19) Situation. GOVPH [Internet]. Official Gazette of the Republic of the Philippines. 2020 Mar 16. [cited 2020 Apr 26]. Available from: https://www.officialgazette.gov.ph/2020/03/16/memorandum-from-the-executive-secretary-on-community-quarantine-over-the-entire-luzon-and-further-guidelines-for-the-management-of-the-

coronavirus-disease-2019-covid-19-situation/
5. CNN Philippines Staff. LIST: Medical groups, doctors open online consultations to decongest COVID-swamped hospitals. [Internet] CNN Philippines; 2020 Mar 25. [cited 2020 April 26]. Available from: https://www.cnnphilippines.com/lifestyle/2020/3/25/online-consultation-services-coronavirus-COVID-list-Philippines
6. Stevenson E, Barrios L, Cordell R, Delozier D, Gorman S, Koenig LJ, Odom E, Polder J, Randolph J, Shimabukuro T, Singleton C. Pandemic influenza planning: addressing the needs of children. American journal of public health. 2009 Oct;99(S2):S255-60.
7. Thapar A, Cooper M, Rutter M. Neurodevelopmental disorders. The Lancet Psychiatry. 2017 Apr 1;4(4):339-46.
8. Accardo PJ, Capute AJ, editors. Capute & Accardo's Neurodevelopmental Disabilities in Infancy and Childhood: Neurodevelopmental diagnosis and treatment. Brookes Pub; 2008.
9. American Psychiatric Association. Diagnostic and statistical manual of mental disorders (DSM-5®). American Psychiatric Pub; 2013 May 22.
10. Centers for Disease Control and Prevention. Children and youth with special healthcare needs in emergencies. 2018.
11. Leung CY, Li-Tsang CW. Quality of life of parents who have children with disabilities. Hong Kong Journal of Occupational Therapy. 2003 Jan 1;13(1):19-24.
12. Malhotra S, Khan W, Bhatia MS. Quality of life of parents having children with developmental disabilities. Delhi Psychiatry Journal. 2012 Apr;15(1):173-4.
13. Campbell VA, Gilyard JA, Sinclair L, Sternberg T, Kailes JI. Preparing for and responding to pandemic influenza: Implications for people with disabilities. American journal of public health. 2009 Oct;99(S2):S294-300.
14. UNICEF. COVID-19 response: Considerations for Children and Adults with Disabilities. [Internet] Unicef.org; 2020 Apr 8. [cited 2020 Apr 27]. Available from http://www.unicef.org/disabilities/files/COVID-

19_response_considerations_for_people_with_disabilities_190320.pdf

15. Guernsey K, Scherrer V. Disability inclusion in disaster risk management: promising practices and opportunities for enhanced engagement. Washington DC. 2017.
16. Cui K, Han Z. Association between disaster experience and quality of life: The mediating role of disaster risk perception. Quality of life research. 2019 Feb 15;28(2):509-13.
17. Wang Z, Xu J. Association between resilience and quality of life in Wenchuan Earthquake Shidu parents: The mediating role of social support. Community mental health journal. 2017 Oct 1;53(7):859-63.
18. Thurston S, Paul L, Loney P, Wong M, Browne G. The quality of life of a multidiagnosis group of special needs children: associations and costs. International Journal of Pediatrics. 2010 Jan 1;2010.
19. Mugno D, Ruta L, D'Arrigo VG, Mazzone L. Impairment of quality of life in parents of children and adolescents with pervasive developmental disorder. Health and quality of life outcomes. 2007 Dec 1;5(1):22.
20. Gomez IN, Gomez MG. Quality of life of parents of filipino children with special needs. Education Quarterly. 2013 Jul;71(2):42-58.
21. Hulley SB, Cummings SR, Browner WS, Grady D, Newman TB. Designing clinical research An epidemiologic approach. 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2013. Appendix 6A: 79
22. de la Vega SA. Cultural validation of the WHOQOL-BREF in ambulatory community-dwelling Filipino older persons. Philippine Journal of Health Research and Development. 2015 May 22;17:20.
23. Calonge-Torres MVJB, Reyes AL, Avendaño EL, Conducto CC, Bautista MPIL. Quality of life of parents of children with Autism Spectrum Disorder aged 3 to 18 years living in Metro Manila. Abstract published Brain & Development. 2017 Apr; 39 (3 supp): 121-122
24. Sub-committee on Children with Disability of the Council for the welfare of Children. A Survey on the Situation of Children with Disabilties in the Context of COVID-19. [Internet] Docs.google; 2020 Apr 24. [cited 2020 Apr 26].

Available from: https://docs.google.com/forms/d/e/1FAIpQLScMGQRNZAGcctbK5NJEDnPd9GV7cxty9EDUwpcfz_iOI-w6PQ/viewform?fbzx=-1066803621651134783

25. Zablotsky B, Black LI, Maenner MJ, Schieve LA, Danielson ML, Bitsko RH, Blumberg SJ, Kogan MD, Boyle CA. Prevalence and Trends of Developmental Disabilities among Children in the United States: 2009–2017. Pediatrics. 2019 Oct 1;144(4):e20190811
26. Govt. Australia & UNICEF. Philippines Policy Brief No. 6 – Children with disabilities: Finding the way to an inclusive service framework (July 2018) [Internet] Unicef.org; 2018 July 24. [cited 2020 Apr 27]. Available from: https://reliefweb.int/report/philippines/philippines-policy-brief-no-6-children-disabilities-finding-way-inclusive-service
27. Guernsey K, Scherrer V. Disability inclusion in disaster risk management: promising practices and opportunities for enhanced engagement. Washington DC. 2017.
28. Morelli M, Cattelino E, Baiocco R, Trumello C, Babore A, Candelori C, Chirumbolo A. Parents and Children During the COVID-19 Lockdown: The Influence of Parenting Distress and Parenting Self-Efficacy on Children's Emotional Well-Being. Frontiers in Psychology. 2020 Oct 6;11:2584.
29. Ali U, Bharuchi V, Ali NG, Jafri SK. Assessing the Quality of Life of Parents of Children With Disabilities Using WHOQoL BREF During COVID-19 Pandemic. Frontiers in Rehabilitation Sciences. 2021:24
30. Flom-Meland C, Mohr P, Mabey R, Chalmers L, Olson M, Shaeffer P. THE QUALITY OF LIFE OF CAREGIVERS OF CHILDREN WITH SPECIAL NEEDS. Pediatric Physical Therapy. 2005 Apr 1;17(1):66-7.
31. Silva PA, Soares SM, Santos JF, Silva LB. Cut-off point for WHOQOL-bref as a measure of quality of life of older adults. Revista de saude publica. 2014;48:390-7.
32. Cui K, Han Z. Association between disaster experience and quality of life: The mediating role of disaster risk perception. Quality of life research. 2019 Feb 15;28(2):509-13.
33. Wang Z, Xu J. Association between resilience and quality of life in Wenchuan

Earthquake Shidu parents: The mediating role of social support. Community mental health journal. 2017 Oct 1;53(7):859-63.

34. Ardalan A, Mazaheri M, Vanrooyen M, Mowafi H, Nedjat S, Naieni KH, Russel M. Post-disaster quality of life among older survivors five years after the Bam earthquake: implications for recovery policy. Ageing & Society. 2011 Feb;31(2):179-96.
35. Chou FC, Chou P, Lin C, Su TT, Ou-Yang WC, Chien IC, Su CY, Lu MK, Chen MC. The relationship between quality of life and psychiatric impairment for a Taiwanese community post-earthquake. Quality of Life Research. 2004 Aug 1;13(6):1089-97.
36. Cho MS. Factors associated with Quality of Life among Disaster Victims: An Analysis of the 3rd Nationwide Panel Survey of Disaster Victims. Journal of Korean Academy of Community Health Nursing. 2019 Jun 1;30(2):217-25.
37. Azazy S, Nour-Eldein H, Salama H, Ismail M. Quality of life and family function of parents of children with attention deficit hyperactivity disorder. East Mediterr Health J. 2018 Jun 1;24(6):579-87.
38. Xiang YT, Luk ES, Lai KY. Quality of life in parents of children with attention-deficit–hyperactivity disorder in Hong Kong. Australian & New Zealand Journal of Psychiatry. 2009 Aug;43(8):731-8.
39. Lemes P, Soares MC, Hattori WT, Morales NM. Predictors of Quality of Life and Symptom Severity in Attention Deficit/Hyperactivity Disorder. Int Phys Med Rehab J. 2017;1(6):139-45.
40. Colizzi M, Sironi E, Antonini F, Ciceri ML, Bovo C, Zoccante L. Psychosocial and Behavioral Impact of COVID-19 in Autism Spectrum Disorder: An Online Parent Survey. Brain Sciences. 2020 Jun;10(6):341.
41. Zhang Y, Ma ZF. Impact of the COVID-19 pandemic on mental health and quality of life among local residents in Liaoning Province, China: A cross-sectional study. International journal of environmental research and public health. 2020 Jan;17(7):2381

Table 1. Child Characteristics (n=115)

	Frequency (%); *Mean* + *SD*
Age	*5 (3.58 to 7.58)*
Years since diagnosis	*1.92 (0.92 to 3.25)*
Sex	
Male	75 (65.22)
Female	40 (34.78)
Primary neurodevelopmental diagnosis	
ASD	**51 (44.35)**
Level 1	3 (5.88)
Level 2	7 (13.73)
Level 3	41 (80.39)
ADHD	**9 (7.83)**
Mild	0
Moderate	7 (77.78)
Severe	2 (22.22)
CP	**16 (13.91)**
GMFCS level 1	0
GMFCS level 2	3 (18.75)
GMFCS level 3	0
GMFCS level 4	1 (6.25)
GMFCS level 5	12 (75)
Global Developmental Delay	27 (23.47)
ID	**10 (8.70)**
Mild	0
Moderate	7 (70)
Severe	3 (30)
Profound	0
Sensory Impairments	1 (0.87)
Communication Disorder	0
Specific Learning Disorder	1 (0.87)
Number of comorbid conditions	*1.6 (0 to 3)*
Number of medications	
0	74 (64.35)
1	32 (27.83)
2	8 (6.96)
3	1 (0.87)
With ongoing/history of intervention	
Ongoing	37 (32.17)
Discontinued	56 (48.7)
Never	22 (19.13)
Education	
Enrolled in SPED	25 (21.74)
Enrolled in regular school	26 (22.61)
None	64 (55.65)

Table 2. Parents' characteristics (n=115)

	Frequency (%); *Mean* ± *SD*
Age	*36.72 ± 6.71*
Sex	
Female	110 (96.65)
Male	5 (4.35)
Location	
NCR	76 (66.08)
Region III	14 (12.17)
Region IV-A	24 (20.86)
Region IV-B	1 (0.88)
Primary caregiver	
Myself	41 (38.28)
Myself and partner	61 (53.98)
Other family members	8 (7.08)
Friend/Neighbor	1 (0.88)
Yaya/helper	2 (1.177)
Parents' educational attainment	
Elementary undergraduate	1 (0.88)
Elementary graduate	1 (0.88)
High school undergraduate	6 (5.31)
High school graduate	28 (24.78)
Vocational undergraduate	2 (1.77)
Vocational graduate	8 (7.08)
College undergraduate	14 (12.39)
College graduate	51 (45.13)
Post graduate degree	2 (1.77)
Mother's employment status	
Employed	31 (27.19)
Self employed	9 (7.89)
Unemployed	74 (64.91)
Father's employment status	
Employed	75 (67.57)
Self employed	12 (10.81)
Unemployed	24 (21.62)
Monthly family income	
< P5,000	20 (17.39)
P5,000 to P9,999	33 (28.7)
P10,000 to P19,999	40 (34.78)
≥ P20,000	22 (19.13)
Family structure	
Two parent biological	105 (91.3)
Two parent adopted	4 (3.48)
Single mother, no father	5 (4.35)
Others	1 (0.87)
Number of children in the household	*2 (1 to 3)*

Table 3. WHOQOL-BREF Filipino Version domain scores (n=115)

WHOQOL-BREF FV Transformed Scores		Physical	Psychological	Social Relationships	Environmental
	Mean	67.71	69.42	70.04	57.44
	Median	69	69	75	56

Table 4. Situations and Emerging Concerns during the Coronavirus Pandemic (n=115)

	Frequency (%)
Current measures being implemented during the COVID-19 Pandemic	
Social distancing	95 (82.61)
Curfew	93 (80.87)
Mandatory quarantine	35 (30.43)
Other	20 (17.39)
Unsure about the situation in my area	1 (0.87)
Impact of the quarantine measures brought on by COVID-19 pandemic	
• Unable to access habilitation and rehabilitation services (physical therapy, speech therapy, occupational therapy)	86 (74.78)
• Unable to access Child Development Center/ Day Care Centers, Supervised Neighborhood Playgroup, National Child Development Center, Early Learning Center	75 (67.57)
• Loss of income or employment	75 (65.22)
• Unable to access education services / learning resource	52 (45.22)
• Unable to access health clinic services (including public health services, immunization, nutritional screening, medical consultations)	50 (43.48)
• Decline in mental health and well-being (example: fear, anxiety, stress)	37 (32.17)
• Unable to access medicines	25 (21.74)
• Unable to buy essential supplies (food, basic commodities, hygiene products)	25 (21.74)
• Unable to access mental health/psychosocial services and counselling support	24 (20.87)
• Unable to access bank, money remittance services/financial Institutions	15 (13.04)
• Others	13 (11.3)
• Domestic abuse/ violence is now more frequent	5 (4.35)
• *Physical*	*0*
• *Sexual*	*0*
• *Verbal/Emotional*	*5 (4.35)*
• *Online/Cyberspace*	*0*
• *Not applicable*	*110 (95.65*)
• Child abuse is now more frequent	3 (2.61)
• *Physical*	*0*
• *Sexual*	*0*
• *Verbal/Emotional*	*3 (2.61)*
• *Online/Cyberspace*	*0*
• *Not applicable*	*112 (97.39)*
• Limited supply or absence of clean water	3 (2.61)
• None of the above	1 (0.87)
Reasons for limited access to services and neccessities	
• Absence of public transport	69 (60)
• Limited or absence of money to buy	59 (51.30)

• Shops or pharmacies are only opened for a limited time	40 (34.78)
• Physically unable to leave the home and there is no caregiver to provide the support	32 (27.83)
• Other	20 (17.39)
Services or assistances received during the implementation of the quarantine measures	
• Quarantine pass	104 (90.43)
• Food allowance or supply or relief package	99 (86.09)
• Disinfection of areas	70 (60.87)
• Information on COVID-19 prevention and treatment	59 (51.3)
• DSWD Social Amelioration Package	49 (42.61)
• Cash distribution from City/Municipality/ Barangay	48 (41.74)
• Vitamin C / Dietary Supplements	21 (18.26)
• Transportation Services	9 (7.83)
• Testing for COVID-19	17 (14.78)
• Medical and health needs	14 (12.17)
• Other	9 (7.83)
• Training on how to do therapy for my child (physical, occupational, speech therapy)	6 (5.22)
• Provision of medicines	3 (2.61)
• None of the Above	2 (1.74)
• Psychosocial and counselling support	1 (0.87)
Issues or concerns that surfaced during the implementation of the quarantine measures	
• Violations on social distancing	84 (73.04)
• Effect of enhanced community quarantine on our ability to work / earn	81 (70.43)
• No available transportation	63 (54.78)
• Inadequate food and/or medicine ration	58 (50.43)
• Disruption in education and other basic social services	55 (47.83)
• Non-compliance to set curfew time	47 (40.87)
• LGU does not prioritize Persons and Children with Disabilities in relief distribution	43 (37.39)
• No access to test kits	37 (32.17)
• Inaccessible information	29 (25.22)
• No designated area for medical consultation and isolation of patients	24 (20.87)
• Prejudices, stigma, and discrimination toward persons with disability	15 (13.04)
• Non-issuance of quarantine pass	12 (10.43)
• Increased risk of domestic violence	2 (1.74)
• Effect of enhanced community quarantine to our children's access to education.	74 (64.35)
• Medical concerns	51 (44.74)
• Developmental concerns	38 (33.04)
• Behavioral concerns	36 (31.3)
• Sleep concerns	23 (20)
• Nutrition concerns	22 (19.13)
• Others	13 (11.30)

Table 5. Child characteristics data against the QoL scores of parents of children with neurodevelopmental disorders

	Overall QoL	Physical health	Psychological	Social relationships	Environment
	Correlation coefficient; Mean ± SD				
Age	0.0332	0.0206	-0.0886	0.0902	0.0900
Years since diagnosis	0.0453	0.1065	-0.0849	0.1165	0.1165
Sex					
Male	71.77 ± 8.64	68.61 ± 12.67	70.67 ± 12.98	70.15 ± 15.64	59.24 ± 13.78
Female	69.23 ± 6.49	66.53 ± 9.52	66.8 ± 9.71	69.85 ± 14.56	54.08 ± 11.88
P-value	0.106	0.363	0.101	0.921	**0.047**
Primary neurodevelopmental diagnosis					
ASD					
Level 1	75.6 ± 6.42	73.33 ± 13.05	75 ± 6	75	64.67 ± 9.61
Level 2	68.1 ± 7.81	61.57 ± 13.65	67.85 ± 9.21	58.86 ± 11.35	55.43 ± 18.17
Level 3	70.08 ± 7.85	67.20 ± 12.36	68.54 ± 12.27	70.39 ± 14.7	55.73 ± 12.99
P-value	0.383	0.364	0.639	0.110	0.545
ADHD					
Moderate	73.23 ± 5.68	68.71 ± 10.21	68 ± 8.31	80.29 ± 9.14	61.71 ± 12.19
Severe	71.5 ± 9.76	59.5 ± 21.92	78.5 ± 21.92	59.5 ± 13.44	59.5 ± 4.95
P-value	0.747	0.391	0.285	**0.034**	0.816
CP					
GMFCS level 2	68.43 ± 2.66	69 ± 10.39	69	70.67 ± 13.05	48 ± 3.46
GMFCS level 5	72.39 ± 8.43	69.33 ± 9.63	71.33 ± 14.32	74 ± 11.97	58.42 ± 13.32
P-value	0.447	0.959	0.788	0.678	0.213
ID					
Moderate	66.87 ± 5.45	64.43 ± 6.16	66.14 ± 12.36	59 ± 20.94	51.71 ± 6.68
Severe	73.53 ± 5	67 ± 6.93	69 ± 6	73 ± 3.46	66.67 ± 9.71
P-value	0.109	0.574	0.719	0.280	**0.021**
Number of comorbid conditions	0.0290	0.0381	-0.0739	0.0171	0.0607
Number of medications	-0.0138	0.0091	-0.1316	0.0559	-0.0293
With ongoing intervention					
Ongoing	72.11 ± 8.86	69.32 ± 12.24	71.03 ± 13	71.46 ± 16.05	59.56 ± 14.09
	69.53 ± 7.06	66.11 ± 11.32	67.86 ± 11.44	68.29 ± 14.77	55.02 ± 12.39
Discontinued	72.25 ± 8.63	70 ± 11.40	70.18 ± 12	72.14 ± 15.04	60.04 ± 13.84
Never	0.214	0.277	0.435	0.480	0.163
P-value					
Education					
Enrolled in SPED	73.21 ± 7.05	69.56 ± 10.81	71.12 ± 11.04	73.56 ± 14.65	62.6 ± 11.52
Enrolled in regular	70.75 ± 6.87	67 ± 11.36	68.88 ± 11.95	70.12 ± 13.47	58.04 ± 13.11
school	70.03 ± 8.71	67.59 ± 12.21	68.80 ± 12.56	68.64 ± 16.06	55.19 ± 13.67
None	0.245	0.707	0.704	0.394	0.059
P-value					

Table 6. Parents' Socio-demographic data against the QoL scores of parents of children with neurodevelopmental disorders

	Overall quality of life rating	Physical health	Psychological	Social relationships	Environment
	Correlation coefficient; Mean + SD				
Age	0.0675	0.1393	0.0832	0.0445	-0.0691
Sex					
Male	76.26 + 13.5	70.2 + 17.88	79 + 16.75	67.6 + 20.45	67.6 + 18.45
Female	70.64 + 7.7	67.78 + 11.42	68.88 + 11.7	70.15 + 15.04	56.98 + 12.98
P-value	0.126	0.652	0.066	0.715	0.081
Primary care giver					
Myself	71.02 + 7.15	68.85 + 11.77	68.24 + 10.79	69.32 + 16.13	57.73 + 12.74
Myself and partner	70.89 + 8.06	66.08 + 11.68	70.15 + 11.81	71 + 12.79	58.08 + 13.11
Others	70.72 + 11.6	73.54 + 10.74	68.27 + 18.4	67.64 + 24.5	54.73 + 17.18
P-value	0.993	0.119	0.713	0.744	0.746
Parents' educational attainment	0.2248*	0.1640	0.1889*	0.0486	0.2958*
Mother's employment status					
Employed	69.81 + 8.41	67.45 + 11.53	70.45 + 13.77	66.94 + 16.34	54.1 + 13.59
Self employed	75.68 + 8.88	73.56 + 12.83	77.89 + 8.91	76.44 + 17.4	61.22 + 15
Unemployed	70.67 + 7.67	67.36 + 11.65	67.81 + 11.31	70.5 + 14.44	58.15 + 12.87
P-value	0.149	0.320	0.051	0.232	0.237
Father's employment status					
Employed	71.94 + 7.94	68.69 + 11.84	70.16 + 10.96	71.25 + 14.31	59.77 + 13.4
Self employed	71.56 + 8.51	67.83 + 13.97	69.42 + 13.58	72.92 + 11.44	57 + 14.07
Unemployed	67.8 + 7.15	64.71 + 10.63	68.04 + 13.32	69.2 + 15.06	50.58 + 9.93
P-value	0.081	0.360	0.744	0.733	**0.011**
Monthly family income	0.2418*	0.1760	0.1645	-0.0730	0.2977*
Family structure					
Two parent biological	71.3 + 7.92	68.03 + 11.98	70.08 + 11.79	71.6 + 13.95	57.73 + 13.09
Others	66.57 + 8.21	66.4 + 7.96	61.4 + 12.39	53.7 + 18.87	54.4 + 16.09
P-value	0.075	0.675	**0.029**	**<0.001**	0.452
Number of children in the household	-0.0050	-0.0175	-0.0918	0.0112	-0.0700

** - Significant at 5% level of significance*

A DESCRIPTIVE CROSS-SECTIONAL STUDY ON REVERSE TRANSCRIPTASE POLYMERASE CHAIN REACTION (RT-PCR) CYCLE THRESHOLD LEVEL, MORTALITY AND PEDIATRIC ACUTE RESPIRATORY DISTRESS SYNDROME AMONG COVID-19 PATIENTS ADMITTED AT PCMC

IRIS-JANE V. GALIZA-RAVELO, M.D, CRISTAN Q. CABANILLA, MD

ABSTRACT

Severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) is a novel pathogen that has rapidly caused a devastating pandemic of Coronavirus disease 2019 (COVID-19). The real time reverse transcriptase polymerase chain reaction cycle threshold values are inversely related to viral load and believed to have a role in terms of mortality and severity of the disease however, there is limited data in children.

OBJECTIVES: This study aims to determine the RT-PCR cycle threshold level in relation to mortality and pediatric acute respiratory distress syndrome (pARDS) among COVID-19 patients admitted at Philippine Children's Medical Center.

METHODS: A cross sectional study was done on patients with RT-PCR confirmed covid-19 admitted at Philippine Children's Medical Center from September 2020 to June 2021.

RESULTS: 50 nasopharyngeal swab specimens from children admitted for COVID-19 were analyzed. 12 (24%) had acute respiratory distress syndrome. Among the 12 children who had pARDS, six (50%) expired; in those without pARDS, two (5.26%) expired. There was no difference in cycle threshold values between patients who died and who survived, as well as those with or without pARDS.

CONCLUSIONS AND RECOMMENDATIONS: We have no evidence to demonstrate a difference in Ct values alone between children who died or survived, or those who developed pARDS or those who did not. RT-PCR cycle threshold alone cannot predict mortality and development of pARDS, it can only indicate the presence of infection but not its severity. Cycle threshold and its significance may further be explored with a bigger population size in children in future studies.

Keyword/s: *severe acute respiratory syndrome coronavirus 2, RT-PCR cycle threshold, mortality, pediatric acute respiratory distress syndrome*

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) is a novel pathogen that has rapidly caused a devastating pandemic of Coronavirus disease 2019 (COVID-19). It exhibits different disease severity among infected patients, ranging from an absence of symptoms to fatal outcomes.

The gold standard in diagnosing coronavirus disease 2019 is via real-time reverse transcriptase polymerase chain reaction (RT-PCR)[1] from nasopharyngeal and oropharyngeal swab. Given that polymerase chain reaction amplifies a target stretch nucleic acid exponentially, samples which begin the reaction with more abundant target material will produce a detectable signal earlier than samples with lower target abundance. The cycle threshold value (Ct) derived from a sample is essentially a measure of the amplification required for the target viral gene to cross a threshold value and is inversely related to the viral load[2].

The utility of RT-PCR Ct in the management of Covid-19 patients remains controversial. Several published studies on RT-PCR with low Ct in adults showed more serious and greater risk of mortality. A study done by Huang et. al, on RT-PCR Ct value and mortality has been demonstrated the correlation of lower Ct values with high mortality risk. SARS-CoV-2 viral load upon admission among hospitalized patients with COVID-19 independently correlates with the risk of intubation and in- hospital mortality according to Magleby et.al. There are several studies correlating SARS-CoV-2 RT-PCR Ct on mortality and ARDS in adults however, data on mortality and development of pediatric acute respiratory distress syndrome in children with Covid-19 are limited. This study was done to determine the association of RT-PCR Ct with development of pARDS and mortality among admitted patients with

COVID-19 at Philippine Children's Medical Center.

OBJECTIVES OF THE STUDY

Specific Objectives:

To determine whether there is a difference of RT-PCR cycle threshold in terms of:

a. in-hospital mortality
b. pediatric acute respiratory distress syndrome

OPERATIONAL DEFINITIONS OF TERMS AND VARIABLES

All- Cause Mortality: the death rate from all causes of death for a population in a given time period.

ARDS: Acute Respiratory Distress Syndrome.

Base on World Health Organization Clinical Management of COVID -19 Interim Guidance. 2020. Acute Respiratory Distress Syndrome defined as any of the following:

a. Onset: within 1 week of a known clinical insult or new or worsening respiratory symptoms.
b. Chest imaging: (radiograph, CT scan, or lung ultrasound): bilateral opacities, not fully explained by volume overload, lobar or lung collapse, or nodules.
c. Origin of pulmonary infiltrates: respiratory failure not fully explained by cardiac failure or fluid overload.
d. Oxygenation impairment in children:
    1. Bilevel (NIV or CPAP) ≥ 5 cmH_2O via full face mask: $PaO_2/FiO_2 \leq 300$ mmHg or $SpO_2/FiO_2 \leq 264$
    2. Mild ARDS (invasively ventilated): $4 \leq OI < 8$ or $5 \leq OSI < 7.5$.
    3. Moderate ARDS (invasively ventilated): $8 \leq OI < 16$ or $7.5 \leq OSI < 12.3$.
    4. Severe ARDS (invasively ventilated): $OI \geq 16$ or $OSI \geq 12.3$.

COVID 19: Corona Virus Disease 2019, a disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Diagnosed by real time polymerase chain reaction (RT-PCR) and at least one of the following mild clinical symptoms (fever, cough, fatigue, anorexia, shortness of breath, myalgias)

Cycle threshold (Ct) value: specific threshold within a certain number of PCR cycle. Cycle threshold can be defined as the thermal cycle number at which the fluorescent signal exceeds that of the background and passes the threshold for positivity. Typical RT-PCR assay will have a maximum of 40 thermal cycles. The lower the Ct value the higher the quantity of viral genetic material in the sample. Ct values obtained in this way are semi-quantitative and are able to distinguish between high and low viral load. PCR cycle reported as follows based on the machine used at PCMC COVID laboratory.

1. FAM channel (ORF1ab)
   Positive: </= 38
   Negative: > 38 or no Ct value
2. ROX channel (E gene)
   Positive: </=37
   Negative: > 37 or no Ct value
3. Cy5 channel (N gene)
   Positive: </= 38
   Negative: >38 or no Ct value
4. HEX or VIC channel (Internal control)
   Positive: </= 38
   Negative: > 38 or no Ct value

The ORF1ab, N gene, E gene are the tested gene targets for the detection of SARS-Cov-2 at PCMC covid laboratory. The Ct value from each fluorescence channel (ORF1ab, E gene, N gene and Internal control) is labelled positive or negative base on the above cut off Ct value. A test is valid if the internal control result is positive, or the internal control is negative but at least one of the three target channels (ORF1ab, N gene, or E gene) is positive. The test results are interpreted based on the Ct value, a patient sample is labelled as SARS-Cov-2 positive if ORF1ab, N gene, E gene and IC are all (+) or ORF1ab (+), N gene /E gene (any) and Internal control (any).

METHODOLOGY

Study Design

This is a cross sectional study of patients with RT-PCR confirmed covid-19 admitted at Philippine Children's Medical Center from September 2020 to June 2021.

Study Participants

Inclusion/Exclusion Criteria

Subjects included all admitted patients at Philippine Children's Medical Center from September 2020 to June 2021 with a positive RT-PCR SARS- CoV-2 using nasopharyngeal and oropharyngeal swab specimen and presented with mild symptoms of the disease upon admission.

All patients with previous COVID-19 were excluded. Samples collected more than 24 hours upon admission or analyzed outside PCMC were excluded from the study.

Sample Size

No sample size calculation was needed because all RT-PCR confirmed Covid patients were included.

Data Collection and Outcomes

The patient information and data including comorbidities, disease presentation on admission and outcome of patients were collected retrospectively from the medical records. A uniform method of data abstraction was applied which included the following A. Demographic data (1) age (2) biological sex. B. Initial Clinical characteristics upon admission (1) duration of illness (2) presented symptoms such as fever, cough, sore throat, headache, diarrhea. (2) co-morbid conditions – cancer, neurologic, immunodeficient, cardiovascular, chronic lung disease, chronic liver disease and chronic kidney disease. C. Arterial blood gas-Pa02/Fi02 D. ARDS-mild, moderate, severe, died or alive. E. Medications given F. Outcome after 28 days-died, alive.

Nasopharyngeal and oropharyngeal samples collected within 24 hours upon admission was used for this study. Nasopharyngeal and oropharyngeal samples were collected by pediatric residents on duty upon admission. All Specimen collected were submitted to PCMC COVID laboratory for processing. Results of the test released after 24 to 48 hours. Nucleic acid extraction was performed using the machine Alsheng (Hangzhou Allsheng Instruments Co.Ltd). For RT-PCR, MA-6000 machine was used performing the Maccura SARS-CoV-2 RT-PCR kit with 3 primer/probe sets target ORF1ab, N and E gene, respectively. The Ct result value was obtained from the 4 fluorescence channel (ORF1ab, N gene, E gene and Internal Control). Ct value result is positive if ORF1ab less than or equal to 38, N gene less than or equal to 38, E gene less than or equal to 37 and lastly, Internal Control less than or equal to 38.

The cycle threshold value was obtained from the amplification of the

ORF1ab, N gene and E gene. Cycle threshold value from each gene was obtained separately. Median RT-PCR cycle threshold from each gene was determined. The obtained median cycle threshold level from those who died of the disease were determined whether there is difference among those who survived. Among those who survived, median value of RT-PCR cycle threshold who developed acute respiratory distress syndrome were also determined whether there is difference from those who did not.

We used the World Health Organization Clinical Management of COVID -19 Interim Guidance 2020 to diagnosed pediatric acute respiratory distress syndrome as defined in the operational definition section. Patient with pARDS met all the criteria enumerated.

Ethical Considerations

The protocol of this study adheres to the ethical considerations and ethical principles set out in relevant guidelines, including the Declaration of Helsinki, WHO guidelines, International Conference on Harmonization-Good Clinical Practice, Data Privacy Act of 2012, and National Ethics Guidelines for Health Research. The authors report no disclosures.

No potential conflicts of interest have been identified. The principal investigators and co-investigators report no disclosures. This study was fully funded by the author. Subject information was kept in a secure office, with access available only to members of the research team. Computerized study information was stored on a secured network with password access. All identifiable information and data were given a code number. Only members of the research team have access to the list. The research records were stored for at least 6 months following completion of the study. Individually identifiable research data was not shared with others outside of the research and analysis team. The investigator and all key personnel have completed the Good Clinical Practice (GCP) training on the responsible conduct of research with human data.

The study was only commenced upon the approval of the Institutional Review Board. The data were collected through a chart review, precluding informed consent. No adverse events were anticipated, because this is a study conducted retrospectively.

No compensation was given to patients who were part of the research. We recognize that our subjects, patients who tested positive RT-PCR SARS-CoV-2, were particularly vulnerable, and we will take extra care in the confidentiality of their identities. Moreover, this is a retrospective study.

Data Processing and Analysis

Descriptive statistics was used to summarize the general and clinical characteristics of the participants. Frequency and proportion were used for categorical variables. Shapiro-Wilk test was used to determine the normality distribution of continuous variables. Continuous quantitative data that met the normality assumption were summarized using mean and standard deviation (SD), while those that do not were described using median and range.

Continuous variables which were normally distributed were compared using the Independent t-test. Otherwise, the non-parametric Mann-Whitney U test was used. For categorical variables, Chi-square test was used to compare the outcomes. If the expected percentages in the cells are less than 5%, Fisher's Exact test was used instead.

All valid data was included in the analysis. Missing values were neither replaced nor estimated. Null hypothesis was rejected at 0.05α-level of significance. STATA 15.0 (StataCorp SE, College Station, TX, USA) was used for data analysis.

RESULTS

We analyzed a total of 50 nasopharyngeal and oropharyngeal swab specimens from children admitted for COVID-19 from September 2020 to June 2021. Of 50 patients, 12 (24%) had acute respiratory distress syndrome, and 8 died (6 with pARDS, 2 without).

The top three symptoms were fever (50%), cough (24%), and difficulty of breathing (16%). One-fifth of the patients had a neurologic co-morbidity, nine with cancer, and six with chronic kidney disease. Most of the patients are non- oxygen requiring (38%), Arterial blood gases, and treatments received are enumerated on table 2.

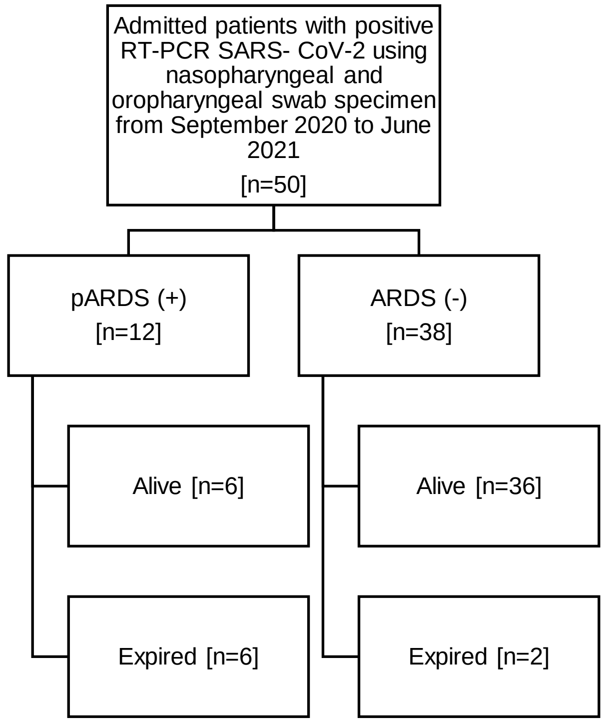


Figure 1. Flowchart of different progression of outcomes

The demographic data is listed in Table 1.

Table 1. Demographic characteristics of patients (n=50)

	Mean (Range); Frequency (%)
Age	
<30 days	1 (2.00)
1 – 11 months	12 (24.00)
1 – 5 years	9 (18.00)
6 – 10 years	16 (32.00)
11 – 15 years	6 (12.00)
16 – 17 years	6 (12.00)
Sex	
Male	34 (68.00)
Female	16 (32.00)

Table 2.Clinical characteristics of patients

	Mean (Range); Frequency (%)
Duration of Illness, days	3 (1-14)
Symptoms	
Fever	25 (50.00)
Cough	12 (24.00)
Sore throat	1 (2.00)
Seizure	7 (14.00)
Chest pain	1 (2.00)
Diarrhea	7 (14.00)
Vomiting	2 (4.00)
Difficulty of breathing	8 (16.00)
Comorbidity	
Cancer	9 (18.00)
CKD	6 (12.00)
Cardiovascular	1 (2.00)
Liver disease	4 (8.00)
Neurologic	10 (20.00)
Hypertension	2 (4.00)
Immunodeficient	1 (2.00)
ABG	
pH	7.36±0.12
PCO2	26.5 (10-80)
PaO2	137.27±65.40
SO2	99 (79-100)
Sodium bicarbonate	16.33±7.14
Base excess	-9.05 (-22.1-3)
O2 requirement	
Room air	19 (38.00)
O2 cannula	6 (12.00)
Face mask	10 (20.00)
NRM	2 (4.00)
BiPAP	3 (6.00)
Nasal CPAP	1 (2.00)
HFNC	4 (8.00)
NIPPV	1 (2.00)
Intubated	4 (8.00)
Medications	
Vitamin D3	43 (86.00)
Zinc	43 (86.00)
Dexamethasone	19 (38.00)
Remdesivir	4 (8.00)
Methylprednisolone	1 (2.00)
Hydrocortisone	1 (2.00)
None	5 (10.00)

RT-PCR Ct for patients with and without pARDS are listed in Table 3. There was no significant difference seen.

RT-PCR Ct for patients who survived and died are listed in Table 4. There was no significant difference seen.

Table 3.SARS-CoV-2 RT-PCR cycle threshold, by pARDS

	pARDS- (n=38)	**pARDS+ (n=12)**	***p***
ORF1ab			
Median (Range)	29.16 (11.70-39.38)	31.07 (12.59-35.77)	.935
Frequency (%)			
≤38	34 (89.47)	10 (83.33)	
>38	4 (10.53)	2 (16.67)	
Internal Control			
Median (Range)	30.18 (26.56-38.10)	29.27 (28.11-35.28)	.448
Frequency (%)			
≤38	37 (97.37)	12 (100)	
>38	1 (2.63)	0	
E gene			
Median(Range)	29.38 (10.13-39.46)	31.15 (12.34-39.63)	.778
Frequency (%)			
≤37	35 (92.11)	10 (83.33)	
>37	3 (7.89)	2 (16.67)	
N gene			
Median(Range)	29.52 (8.75-35.67)	31.59 (13.36-36.04)	.601
Frequency (%)			
≤38	37 (97.37)	12 (100)	
>38	1 (2.63)	0	

Table 4. SARS-CoV-2 RT-PCR cycle threshold, by in-hospital mortality

	Alive (n=42)	Expired (n=8)	*p*
ORF1ab			
Median (Range)	29.17 (11.70-39.38)	30.93 (15.23-36.08)	.900
Frequency (%)			
≤38	37 (88.10)	7 (87.50)	
>38	5 (11.90)	1 (12.50)	
			.751
Internal Control			
Median (Range)	30.05 (26.56-38.10)	30.14 (28.23-34.90)	
Frequency (%)			
≤38	41 (97.62)	8 (100)	
>38	1 (2.38)	0	
E gene			
Median (Range)	29.68 (10.13-39.63)	29.90 (13.90-36.43)	.895
Frequency (%)			
≤37	38 (90.48)	7 (87.50)	
>37	4 (9.52)	1 (12.50)	
N gene			
Median (Range)	29.57 (8.75-35.67)	30.20 (15.43-36.04)	.589
Frequency (%)			
≤38	41 (97.62)	8 (100)	
>38	1 (2.38)	0	

DISCUSSION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has affected the entire world. Clinicians, researcher and scientists are making all efforts to identify ways to diagnose faster, predict outcome and find treatment modalities.

The COVID polymerase chain reaction is the standard test being used for the diagnosis and it gives an additional value known as cycle threshold (Ct), which is the number of PCR cycles required to cross the designated threshold and termed patient as positive for the infection. The Ct value-based estimates of viral load have been used to predict disease progression, infer transmissibility and differentiate active viral replication from prolonged virus shedding.[2]

Several studies on the association of Ct value with mortality and development of respiratory failure has been published. Admission SARS-CoV-2 viral load among hospitalized patients with COVID-19 independently correlates with the risk of intubation and in- hospital mortality.[9-10] Choudhuri et al, SARS-CoV-2 Ct was found to be independent predictor of patient mortality.[11] SARS-Cov-2 Ct value and mortality has been demonstrated the correlation of lower Ct values with high mortality risk.[13]. SARS-CoV-2 viral load, measured by the Ct value of the rRT-PCR in nasopharyngeal swabs on admission, is a viable prognostic marker for the development of respiratory failure.[12]

On the contrary, Cargo et al, studied on Ct values from ORF1ab and S genes and found out that there was no correlation between Ct values for any of these target genes and the oxygen requirements of the patients at the time of sample collection and no difference in the initial nor the nadir Ct values between survivors and non survivors or mild/moderate versus severe/critical illness.[3] Several studies also have shown that nasopharyngeal SARS-CoV-2 Ct values are not associated with COVID- 19 severity and do not support a predictive role for the Ct value in the clinical setting.[4-8] In addition, SARS-CoV-2 Ct values from asymptomatic patients are similar to those in symptomatic patients.[6-8]

In our study, there was no difference in cycle threshold value between patients who died and who survived, and those with and without pARDS. The viral load of SARS-CoV-2 is known to vary during the course of infection.[15] One of the possible reason is the time from onset of symptoms to sampling which is varied between studies and in most of the studies, varied between patients.[16] Furthermore, most literatures correlating Ct value with mortality and pARDS were based on studies with adult subjects. According to Ade et al, age is an important cofactor in SARS-CoV-2 positive patients and may have influence on Ct values in SARS-CoV-2-PCR.[17] Previous studies dealt with older populations and studies on cycle threshold among children are limited and need to investigate more in detail.

CONCLUSION AND RECOMMENDATIONS

Currently , we are not able to demonstrate a difference in Ct values alone between children who died or survived, or those who developed pARDS or those who did not. Reverse transcriptase polymerase chain reaction cycle threshold alone cannot predict mortality and development of pARDS, it can only indicate the presence of infection but not its severity. Our study was limited with small sample size, cycle threshold and its significance may further be explored with a bigger population size in children in future studies.

BIBLIOGRAPHY

1. Tang Y-W, Schmitz JE, Persing DH, Stratton CW. Laboratory diagnosis of COVID-19: current issues and Challenges. J Clin Microbiol. 2020;58 (6):e00512-e520.
2. Infectious Diseases Society of America. IDSA and AMP joint statement on the use of SARS-CoV-2 PCR cycle threshold (Ct) values for clinical decision-making. 2021 March.
3. Camargo JF, Lin RY, Komanduri KV. Lack of correlation between the SARS-CoV-2 cycle threshold (C_t) value and clinical outcomes in patients with COVID-19. J Med Virol. 2021 Oct;93(10):6059-6062.
4. He X, Lau EHY, Wu P, et al. Temporal dynamics in viral shedding and transmissibility of COVID-19. Nat Med. 2020;26(5):672-675.
5. To KK, Tsang OT, Leung WS, et al. Temporal profiles of viral load in posterior oropharyngeal saliva samples and serum antibody responses during infection by SARS-CoV-2: an observational cohort study. Lancet Infect Dis. 2020;20(5):565-574.
6. Lee S, Kim T, Lee E, et al. Clinical course and molecular viral shedding among asymptomatic and symptomatic patients with SARS-CoV-2 in- fection in a Community Treatment Center in the Republic of Korea. JAMA Intern Med. 2020;180(11):1447-1452.
7. Ra SH, Lim JS, Kim GU, Kim MJ, et. al. Upper respiratory viral load in asymptomatic individuals and mildly symptomatic patients with SARS-CoV-2 infection. Thorax. 2021;76(1):61-63.
8. Louie JK, Stoltey JE, Scott HM, et al. Comparison of symptomatic and asymptomatic infections due to severe acute respiratory coronavirus virus 2 (SARS-CoV-2) in San Francisco long-

term care facilities. Infect Control Hosp Epidemiol. 2020:1-3.

9. Magleby R, Westblade LF, Trzebucki A, et al. Impact of SARS-CoV-2 viral load on risk of intubation and mortality among hospitalized patients with coronavirus disease 2019. Clin Infect Dis. 2020.
10. Westblade LF, Brar G, Pinheiro LC, et al. SARS-CoV-2 viral load predicts mortality in patients with and without cancer who are hospitalized with COVID-19. Cancer Cell. 2020;38(5):661-671.
11. Choudhuri J, Carter J et al. SARS-CoV-2 PCR cycle threshold at hospital admission associated with patient mortality. PLOS ONE. December 31, 2020.
12. De la Calle, C., Lalueza, A., Mancheño-Losa, M. *et al.* Impact of viral load at admission on the development of respiratory failure in hospitalized patients with SARS-CoV-2 infection. *Eur J Clin Microbiol Infect Dis* 40**,** 1209–1216 (2021)
13. Huang, J.T.; Ran, R.X.; Lv, Z.H et al. Chronological Changes of Viral Shedding in Adult Inpatients with COVID-19 in Wuhan, China. *Clin. Infect. Dis.* 2020, *71*, 2158–2166.
14. Chu, C.M.; Poon, L.L.M.; Cheng, V.C.C. et al. Initial viral load and the outcomes of SARS. *Cmaj* 2004, *171*, 1349–1352.
15. Pan, Y.; Zhang, D.; Yang, P. et. al. Viral load of SARS-CoV-2 in clinical samples. Lancet Infect. Dis. 2020, 20, 411–412.
16. Rabaan AA, Tirupathi R, Sule AA, et al. Viral Dynamics and Real-Time RT-PCR Ct Values Correlation with Disease Severity in COVID-19. Diagnostics (Basel). 2021 Jun 15;11(6):1091.
17. Ade C, Pum J, Abele I. et. al.. Analysis of cycle threshold values in SARS-CoV-2-PCR in a long-term study. *J Clin Virol*. 2021;138:104791.
18. World Health Organization Clinical Management of COVID -19 Interim Guidance. May 2020.

DIAGNOSTIC ACCURACY OF RAPID ANTIGEN TEST IN DETECTING SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2 (SARS-COV-2) INFECTION.

JILL J. JAIME, MD, RAYMUNDO W. LO, MD, FPSP,
FARRAH KRISTINE F. SANTIAGO, MD, FPSP

ABSTRACT

BACKGROUND: Improving the means to detect SARS-COV-2 infection is important in the ongoing battle against the COVID-19 pandemic. STANDARD™ Q COVID-19 Ag Test offers an easy to use, cheap and rapid way of testing that must be evaluated first to optimize its utility.

OBJECTIVES: This study aims to evaluate the diagnostic accuracy of this test kit compared with Reverse Transcription Polymerase Chain Reaction (RT-PCR) for SARS-COV-2 diagnosis.

METHODS: Using retrospective cross-sectional study, seventy seven (77) nasopharyngeal swabs in viral transport media were used to determine the sensitivity, specificity, positive predictive value and negative predictive value of STANDARD™ Q COVID-19 Ag Test compared with the reference method, RT-PCR.

RESULTS: Among all participants, the rapid antigen test has a sensitivity of 9.86%, specificity of 100%, positive predictive value of 100%, and negative predictive value of 8.57%. The sensitivity increases among symptomatic participants and when Ct value is less than 20 to 25.00% and 31.58%, respectively.

CONCLUSION: Despite the low sensitivity, STANDARD™ Q COVID-19 Ag Test has a high specificity and positive predictive value and could be a cheap and efficient test in the proper clinical context. Its use in conjunction with RT-PCR for those who tested negative initially should be emphasized in the implementation of the existing policies.

Keywords: *SARS-COV-2, COVID-19, Antigen Testing, diagnostic accuracy*

INTRODUCTION

Statement of the Problem

Following its emergence in Wuhan, China in November 2019, the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-COV-2) has infected millions around the globe. The disease it causes known as Coronavirus Disease 2019 (COVID-19) has been declared as a pandemic by the World Health Organization (WHO) in March 2020. Consequently, various methods of testing for the detection of SARS-COV-2 Infection have been developed. The currently accepted gold standard for testing is the Reverse Transcriptase – Polymerase Chain Reaction (RT-PCR)[1]. However, this test requires special equipment, specific and unique infrastructure requirements, and skilled laboratory personnel. Furthermore, this test can be costly, time-consuming and may not be readily available.

Improving the testing capacities of nations is crucial in battling the effects of this pandemic. However, the accuracy in detection of SARS-COV-2 is important in choosing the test as the results do not only support patient care clinically but are also critical for public health management. SARS-COV-2 Antigen Testing was developed for the qualitative determination of the presence of the viral antigen in nasopharyngeal secretions.[2] Theoretically, this test offers the advantage of ease of use, fast turnaround time (TAT) and low-cost. For these reasons, this test may be utilized at point of care (POC).

STANDARD Q COVID-19 Ag Test is a rapid antigen test made by SD Biosensor Inc, a global manufacturer of in vitro diagnostics in South Korea.[3] It is available in the Philippines through its representative importer and distributor, Worldwidelink Trading Corporation. For the purpose of the diagnostic evaluation of the product, Worldwidelink requested for a clinical assessment from the Philippine Children's Medical Center and donated a total of 125 kits to be utilized in this trial.

This rapid antigen test was granted special certification for COVID-19 Diagnostic Test by the Department of Health – Food and Drug Administration in May 27, 2020.[4] The test kit offers results within 30 minutes, ease of use and provision of all the necessary reagents and device needed in one kit. Considering these advantages, the kit must be validated for its diagnostic accuracy to be useful in our setting.

The Philippine Children's Medical Center had setup a molecular laboratory which offers diagnosis of SARS-COV-2 infection via RT-PCR. With the current increase in the number of daily positive SARS-COV-2 cases, an additional way of testing will help the nation's fight in this pandemic.

SIGNIFICANCE OF THE STUDY

With the urgent need to increase the testing capacity to detect SARS-COV-2 infection, this study will help in ensuring that the relatively easy-to-use and available test kits have optimal performance. This study will also add knowledge to the usability of these tests in our setting. Likewise, the results of the study may be used as guidance in the development of clinical protocols in the diagnosis and management of COVID-19.

REVIEW OF RELATED LITERATURE

The diagnostic tests for SARS-COV-2 infection is rapidly evolving as newer methods become readily available and controversially, replace the currently accepted gold standard. As with diagnostic methods for other diseases, there are various issues that must be understood in choosing the right method for SARS-COV-2 infection. Tang et al discussed the various preanalytical, analytical and postanalytical issues regarding laboratory diagnosis of SARS-COV-2 infection[2]. In this paper, nasopharyngeal swab is superior to oropharyngeal swab in the detection of viral particles especially within 5 to 6 days of onset of symptoms when the patient demonstrated high viral loads. This paper also recognized the potential for use of rapid antigen tests, however they warned of poor sensitivity based on the experience with this method for Influenza viruses. This finding is echoed in a review by Loeffelholz[5].

Diagnostic Evaluation of Antigen Tests

Mak et al evaluated the diagnostic performance of commercially available rapid antigen test (BIOCREDIT COVID-19 Ag test) compared with viral culture and RT-PCR[6]. It was found out that the rapid antigen test was 10^3 fold less sensitive than viral culture while the rapid antigen test was 10^5 fold less sensitive than RT-PCR. In this study, a modified procedure was used in utilizing samples already in viral transport media.

Scohy et al did a similar evaluation of rapid antigen test using Coris COVID-19 Ag

Respi-Strip[7]. They found out that amongst the 106 positive RT-qPCR samples, 32 were detected by the rapid antigen test, given an overall sensitivity of 30.2%. Both studies concluded that rapid antigen tests should only be used as an adjunct to RT-PCR because of the potential for false negative results.

Van Honacker et al compared the performance of five (5) SARS-CoV-2 rapid antigen tests in the hospital setting and found out that the sensitivity ranged from 88.9% to 100% for samples with Ct <26, and specificity from 46.2% to 100%[8]. In their evaluation, they adapted the protocol used and tested samples already in viral transport media to avoid additional sampling from the patients. In the implementation phase, about 157 patients were transferred to the COVID-19 ward directly instead of the regular ward due to the rapid turn-around time of the tests.

STANDARD Q COVID-19 Ag Test

STANDARD Q COVID-19 Ag Test is a rapid chromatographic immunoassay for the qualitative detection of specific antigens to SARS-CoV-2 present in human nasopharynx[3]. The principle behind this assay is the lateral flow of the analyte on a porous material from a sample loading zone, to the labeling zone, and ultimately to the detection zone[9]. In general, the proximal end contains labeled antibodies or antigen that mixes with analyte when an aliquot is loaded. Through capillary action, the analyte flow through the membrane and forms a complex with a conjugate in the detection zone resulting to immobilization of the antibody to form a positive-colored line which is interpreted by the reader.

In the clinical evaluation for the STANDARD Q COVID-19 Ag Test conducted at Yeungnam University Medical Center in Korea using 125 specimens, the test kit showed 89.23% sensitivity and 96.67% specificity[10]. A similar study done in Brazil using 21 samples yielded 100% sensitivity and 100% specificity[11].

In the evaluation made by the Foundation for Innovative New Diagnostics (FIND) across Germany and Brazil, the sensitivity of the STANDARD Q COVID-19 Ag Test compared with RT-PCR is 76.6% and 88.7%, respectively, while the specificity is 99.3% and 97.6%, respectively. Factors that increase the sensitivity of the test are symptoms occurring less than or equal to seven days and low Ct values[12]. Further, the ease of usability was rated 86 out of 100.

Since these rapid test kits are designed to be performed without the need for biosafety cabinets, the virus inactivation performance of the extraction kit was evaluated by Jung-Ho et al. In this study, the virus was incubated in one setup with the extraction buffer and with a cell culture media. These are then subsequently inoculated to Vero cells. Cytopathic effects was not seen in the culture mixed with the STANDARD Q COVID-19 Extraction buffer, whereas, all other cell culture media demonstrated cytopathic effects[13].

OBJECTIVES OF THE STUDY

This study aims to evaluate the diagnostic performance of the STANDARD™ Q COVID-19 Ag Test compared with RT-PCR in detecting SARS-COV-2 infection. Specifically, it attempts to answer the following research objectives:

5.1 Determine the sensitivity of STANDARD™ Q COVID-19 Ag Test compared with RT-PCR in detecting SARS-COV-2 infection.

5.2 Determine the specificity of STANDARD™ Q COVID-19 Ag Test compared with RT-PCR in detecting SARS-COV-2 infection.

5.3 Determine the positive predictive value of STANDARD™ Q COVID-19 Ag Test compared with RT-PCR in detecting SARS-COV-2 infection.

5.4 Determine the negative predictive value of STANDARD™ Q COVID-19 Ag Test compared with RT-PCR in detecting SARS-COV-2 infection.

5.5 Determine the overall diagnostic accuracy of STANDARD™ Q COVID-19 Ag Test compared with RT-PCR in detecting SARS-COV-2 infection.

OPERATIONAL DEFINITION OF TERMS AND VARIABLES

- Rapid Antigen Test – a point of care diagnostic test (STANDARDTM Q COVID-19 Ag Test) that detects SARS-COV-2 antigen from the nasopharyngeal swab of a patient.
- RT-PCR – the gold standard for detecting SARS-COV-2 infection in which the rapid antigen test will be compared.
- Confirmed SARS-COV-2 case – a person with detected SARS-COV-2 ribonucleic acid (RNA) based on RT-PCR.

- Negative for SARS-COV-2 – a person who has not detectable SARS-COV-2 RNA based on RT-PCR.
- Sensitivity – the ability of the Rapid Antigen Test to correctly detect a true positive or a confirmed SARS-COV-2 case. [14]
- Specificity – the ability of the Rapid Antigen Test to correctly detect a true negative SARS-COV-2 case.[14]
- Positive Predictive Value – a measure to establish whether the positives in Rapid Antigen Test are actually confirmed SARS-COV-2 cases using RT-PCR.[14]
- Negative Predictive Value – a measure to establish whether the negatives in Rapid Antigen Test are actually negative for SARS-COV-2 using RT-PCR. [14]
- Diagnostic Accuracy - proportion of correctly classified SARS-COV-2 positives and SARS-COV-2 negatives (TP+TN) among all cases (TP+TN+FP+FN). [15]

METHODOLOGY

Research Design

A retrospective cross-sectional study is used to determine the sensitivity, specificity, positive predictive value and negative predictive value of STANDARD™ Q COVID-19 Ag Test compared with the reference method, RT-PCR.

Target Population, Subject Sampling, Sample Size Calculation

The sample population for this study included 81 nasopharyngeal and oropharyngeal swabs confirmed by RT-PCR in the Philippine Children's Medical Center COVID-19 Laboratory, regardless of the exposure, symptom onset, or disease severity. These swabs are collected in the viral transport media routinely used in our laboratory (Kangjian Virus Collection and Preservation system, Jiangsu Kangjian Medical Apparatus CO.,Ltd). Only specimen from patients aged 1 year old and above were included, since only oropharyngeal swab was obtained for patients less than 1 year old. The specimens were selected using non-probability (convenience) sampling from the database of the COVID-19 laboratory based on the Ct values of the RT-PCR and are grouped as Not Detected, $Ct<20$, $20\leq Ct<26$,

$26 \leq Ct < 30$, $30 \leq Ct < 36$. Exclusion criteria for this study were the following: unclear specimen information, contaminated samples, and oropharyngeal swabs only.

The sample size for study was estimated using single population proportion formula with the following assumptions: 95% confidence interval, 10% margin of error, and 10.2% prevalence based on the Philippine SARS-COV-2 positivity rate[16]. The sample size was calculated using Epi Info version 7.2.2.6 and has yielded a minimum sample size of 36.

OUTCOME/S ASSESSMENT, DATA COLLECTION METHOD, INSTRUMENT/S TO BE USED

The Case Investigation Forms (CIF) were retrieved to obtain the demographic profile and presence of symptoms of the patients. These were tabulated in Microsoft Excel.

SARS-COV-2 Testing

The NPS/OPS in viral transport media of the selected participants were retrieved from the storage of the PCMC COVID-19 laboratory. The Case Investigation Forms (CIF) were retrieved to obtain the demographic profile and presence of symptoms of the patients.

As per manufacturer's instruction, direct performance on the nasopharyngeal swab using the Standard Q COVID-19 Ag test kit is recommended. However, the protocol was adapted to validate the antigen test on the swabs already in the transport media to avoid additional direct sampling from the patient. 200µl of the specimen was mixed with 200µl of the extraction buffer included in the kit making a one is to one dilution. Three (3) drops of the extracted specimen was put to the specimen well of the test device. The test was interpreted within 15-30 minutes after specimen collection in a Biosafety Cabinet and using the following guide from the manufacturer[3]:

1. A colored band will appear in the top section of the result window to show that the test is working properly. This band is control line (C).
2. A colored band will appear in the lower section of the result window. This band is test line of SARS-CoV-2 antigen (T).
3. Even if the control line is faint, or the test line isn't uniform, the test should be considered to be performed properly and

the test result should be interpreted as a positive result.
* The presence of any line no matter how faint the result is considered positive.
* Positive results should be considered in conjunction with the clinical history and other data available.

Confirmation of SARS-COV-2 infection is done using Maccura SARS-CoV-2 Fluorescent PCR Kit performed according to manufacturer's instructions.

ETHICAL CONSIDERATIONS

The research is developed in compliance to the Data Privacy Act (2012) and National Ethical Guidelines for Health and Health-Related Research.

To ensure the protection of the study participants, each data is treated with utmost confidentiality. No personal identifiable information is included and each data set is coded with a control number. Only the investigators is allowed to retrieve and have access to the data. The hard copy and excel files used in this research is kept for 5 years from the time the last medical records is retrieved and disposed by shredding the physical copy and deleting the electronic records. Approval is also obtained from the Institutional Review Board prior to the commencement of the study.

The Rapid Antigen Test kits are donated by SD Biosensor for the purpose of diagnostic evaluation. All parts of the study are properties of the PCMC and the authors.

DATA PROCESSING AND ANALYSIS

The data is collated and analyzed using Microsoft Excel. Mean age, percentage of male and female participants, presence of symptoms, percentage of confirmed cases, percentage of invalid PCR results and the Ct value are tabulated to illustrate the characteristics of all patients included and those who tested positive or negative with the Rapid Antigen Test. Table 1 shows an example of the dummy table on the characteristics of the participants.

The individual specimens are grouped per Ct values as follows: Not Detected, $Ct<20$, $20 \leq Ct<26$, $26 \leq Ct<30$, $30 \leq Ct<36$. Diagnostic test evaluation will be done using a 2x2 table (see Table 2) per group and for total number of specimens. The formula for the calculation of sensitivity, specificity, PPV and NPV will be as follows:

Sensitivity = TP/(TP + FN)

Specificity = TN/(TN +FP)

Positive Predictive Value (PPV) = TP/(TP + FP)

Negative Predictive Value (NPV) = TN/(TN + FN)

Diagnostic Accuracy = (TP + TN)/(TN+FP+FN+TN)

Excluded in the computation for sensitivity, specificity, PPV, NPV and diagnostic accuracy are specimens with invalid RT-PCR results.

RESULTS

Eighty-one (81) specimen in viral transport media were obtained for the study; however, four (4) were excluded in the final study sample for containing oropharyngeal swab only. The characteristics of the study sample is illustrated in Table 1. The mean age for the total participants is 34 years old, while those who tested positive in rapid antigen test is 35 years old. 35% of all participants are female. 42% presented with symptoms. 71 out of 77 of the samples in viral transport media had SARS-COV-2 viral RNA detected via RT-PCR, 19 of which have ORF Ct value less than 20, 18 have ORF Ct value greater than or equal to 20 but less than 26, 17 have ORF Ct value greater than or equal to 26 but less than 30, 17 have Ct greater than or equal to 30 but less than 36. Six (6) specimen were not detected to have SARS-COV-2 viral RNA.

Seven (7) out of 77 specimen tested positive using the rapid antigen test device. All of these presented with symptoms. 86% of which have ORF Ct value less than 20, while the remaining 14% have ORF Ct value greater than or equal to 20 but less than 26. All specimen without detected SARS-COV-2 viral RNA via RT-PCR also tested negative using the rapid antigen test device.

Among all participants, the rapid antigen test has a sensitivity of 9.86%, specificity of 100%, positive predictive value of 100%, and negative predictive value of 8.57%. The overall diagnostic accuracy is 16.88%. Table 2 shows the comparison of the rapid antigen test and the gold standard, RT-PCR among all participants.

Table 1. Characteristics of Participants

	Rapid Antigen Test Positive (7)	Rapid Antigen Test Negative (70)	Total Participants (77)
Mean Age (years)	35	34	34
% Female participants	42% (3)	34% (24)	35% (27)
% Male participants	48% (4)	66% (46)	65% (50)
% Symptomatic participants	100% (7)	36% (25)	42% (32)
% Confirmed SARS-COV-2 infection by RT-PCR	100% (7)	91% (64)	92% (71)
Samples with $Ct<20$	86% (6)	19% (13)	25% (19)
Samples with $20\leq Ct<26$	14% (1)	24% (17)	23%(18)
Samples with $26\leq Ct<30$	0	24% (17)	22% (17)
Samples with $30\leq Ct<36$.	0	24% (17)	22% (17)
Samples that are Not Detected on RT-PCR	0	9% (6)	8% (6)

Table 2. Diagnostic accuracy of Rapid Antigen Test compared with RT-PCR among all participants.

Rapid Antigen test	Gold Standard: RT- PCR		Total
	Positive	Negative	
Positive	7	0	7
Negative	64	6	70
Total	71	6	77

Sensitivity: 9.86% (95% CI 2, 17)
Specificity: 100%
Positive Predictive Value: 100%
Negative Predictive Value: 8.57% (95% CI 2, 15)
Diagnostic Accuracy: 16.88%

Among symptomatic participants, the rapid antigen test has a sensitivity of 25.00%, specificity of 100%, positive predictive value of 100%, and negative predictive value of 16.00%. The diagnostic accuracy is 34.37% for symptomatic patients. Table 3 shows the comparison of the rapid antigen test and the gold standard, RT-PCR among symptomatic participants.

Table 3. Diagnostic accuracy of Rapid Antigen Test compared with RT-PCR among participants who presented with symptoms.

Rapid Antigen test	Gold Standard: RT- PCR		Total
	Positive	Negative	
Positive	7	0	7
Negative	21	4	25
Total	28	4	32

Sensitivity: 25.00% (95% CI 9, 41)
Specificity: 100%
Positive Predictive Value: 100%
Negative Predictive Value: 16.00% (1, 30)
Diagnostic Accuracy: 34.37%

When stratified per ORF Ct value, the rapid antigen test has a sensitivity of 31.58%, specificity of 100%, positive predictive value of 100%, and negative predictive value of 31.58% among participants with ORF Ct value less than 20. The diagnostic accuracy is 48.00%. Table 4 shows the comparison of the rapid antigen test and the gold standard, RT-PCR among participants with Ct value less than 20. Specimen with no detected SARS-COV-2 viral RNA were used as true negative for comparison.

Table 4. Diagnostic accuracy of Rapid Antigen Test compared with RT-PCR among participants with ORF Ct value < 20, using specimen with no detected SARS-COV-2 viral RNA as comparison.

Rapid Antigen test	Gold Standard: RT- PCR		Total
	Positive	Negative	
Positive	6	0	6
Negative	13	6	19
Total	19	6	25

Sensitivity: 31.58% (95% CI 11, 53)
Specificity: 100%
Positive Predictive Value: 100%
Negative Predictive Value: 31.58% (95% CI 11, 52)
Diagnostic Accuracy: 48.00%

The rapid antigen test has a sensitivity of 5.55%, specificity of 100%, positive predictive value of 100%, and negative predictive value of 26.09% among participants with ORF Ct value greater than 20 but less than 26. The diagnostic accuracy is 29.17%. Table 5 shows the comparison of the rapid antigen test and the gold standard, RT-PCR among participants with Ct value greater than 20 but less than 26. Specimen with no detected SARS-COV-2 viral RNA were used as true negative for comparison.

Table 5. Diagnostic accuracy of Rapid Antigen Test compared with RT-PCR among participants with ORF Ct value >/= 20 but < 26, using specimen with no detected SARS-COV-2 viral RNA as comparison.

Rapid Antigen test	Gold Standard: RT- PCR		Total
	Positive	Negative	
Positive	1	0	1
Negative	17	6	23
Total	18	6	24

Sensitivity: 5.55% (95% CI -5, 16)
Specificity: 100%
Positive Predictive Value: 100%
Negative Predictive Value: 26.09% (95% CI 8, 44)
Diagnostic Accuracy: 29.17%

DISCUSSION

On October 26, 2020, the DOH Department Memorandum 2020-0468 *Supplemental Guidance on the Use of Rapid Antigen Test* allowed the use of Rapid Antigen Test Kits for diagnostic testing of closed contacts in communities and closed or semi-closed institutions with confirmed outbreaks and in remote settings where RT-PCR is not accessible, provided that the antigen testing can be used as a confirmatory for symptomatic close contacts, and that a confirmation with RT-PCR or a repeat antigen testing within 48 hours after the first negative result should be done for asymptomatic close contacts[17]. The same memorandum also recommends that only rapid antigen tests with a minimum sensitivity of 80% and specificity of 97% be used. After the increase in cases in March 2021 in the National Capital region Plus Bubble, the use of rapid antigen tests as a confirmatory test was operationalized in the DOH Department Memorandum 2021-0169 *Interim Guidelines on Rapid Antigen Test Reporting for the NCR Plus Bubble*, wherein a suspect or a probable COVID-19 case who tested positive with rapid antigen test shall be interpreted as a confirmed COVID-19 case and shall be traced, tested, quarantined/isolated, and managed as per existing DOH guidelines[18].

This decision to use a positive rapid antigen test was backed by the recommendations from the rapid review done by Health Technology Assessment Unit Policy Planning and Evaluation Team and Bayona et al released on September 24, 2020. Based on a meta-analysis conducted for nine studies, the pooled sensitivity of rapid antigen test kits was found to be 49% (95%CI: 28,70; I2=97.33, 95%CI: 96.54, 98.12) while the pooled specificity was found to be 99% (95%CI: 98, 100; I2=0, 95%CI: 0, 87.51)[19]. The same study found out that the sensitivity increases to 50.3% (95%CI: 20, 80.7; I2=99.8) in the presence of symptoms. The evaluation done by the Research Institute for Tropical Medicine (RITM) showed a clinical sensitivity of 71.43% (55.42 to 84.28) and clinical specificity of 100% (91.96 to 100) among symptomatic patients for Standard Q COVID-19 Ag Test between the period of August 11-September 9, 2020[20].

The results of this study show low sensitivity of Standard Q COVID-19 Ag Test compared with the HTAC and RITM findings. Although we use nasopharyngeal swabs as the source of specimen, the dilution with viral transport media which is a deviation from the manufacturer's instruction on the use of Standard Q COVID-19 Ag Test might have affected the overall sensitivity of the assay. The long storage of the specimen, some lasting up to 3 days, from collection to performance of the rapid antigen test might have contributed to the deterioration of the viral particles. However, the study done by Van Honacker et al was able to obtain a sensitivity ranging from 88.9% to 100% for samples with Ct <26, and specificity from 46.2% to 100% using samples already in viral transport media and five (5) different rapid antigen kits.[8]

This study replicates the increase in sensitivity when restricted to symptomatic participants or when the Ct value is less than 20, a potential marker for increased viral load. This, combined with a low-test accuracy in asymptomatic participants poses a question on the utility of a negative rapid antigen test as a single screening method and supports the DOH guidelines of proceeding with an RT-PCR for patients who have negative rapid antigen test result.

While a negative test result should not be used to decrease standard protective measures, the high specificity and high positive predictive value of Standard Q COVID-19 Ag Test implies that there is no cross-reactivity with other antigen that might result to a false positive result. Hence, this helps greatly in clinical decision making in patients who has positive antigen test result and supports the tagging of confirmed COVID-19 case in such instances.

CONCLUSION

The Standard Q COVID-19 Ag Test is less sensitive in detecting SARS-COV-2 infection compared with the current gold standard which is RT-PCR and should not be used as a single screening method. However, rapid antigen test could be a cheap and efficient test in the proper clinical context and in conjunction with RT-PCR for those who tested negative initially, which should be emphasized in the implementation of the existing policies.

REFERENCES

1. WHO. *Laboratory Testing for Coronavirus Disease. Interim Guidance March 2020*.; 2020. https://apps.who.int/iris/bitstream/handle/10665/331329/WHO-COVID-19-laboratory-2020.4-eng.pdf.
2. Tang Y-W, Schmitz JE, Persing DH, Stratton CW. Laboratory Diagnosis of COVID-19: Current Issues and Challenges. McAdam AJ, ed. *J Clin Microbiol*. 2020;58(6). doi:10.1128/JCM.00512-20
3. SD Biosensor. Products - Standard Q COVID 19 Ag. http://sdbiosensor.com/xe/product/7672
4. Administration D of H-F and D. SC-COVID19-2020-314 Special

Certification for Standard Q Rapid Antigen Test.
5. Loeffelholz MJ, Tang Y-W. Laboratory diagnosis of emerging human coronavirus infections – the state of the art. *Emerg Microbes Infect*. 2020;9(1):747-756. doi:10.1080/22221751.2020.1745095
6. Mak GC, Cheng PK, Lau SS, et al. Evaluation of rapid antigen test for detection of SARS-CoV-2 virus. *J Clin Virol*. 2020;129:104500. doi:10.1016/j.jcv.2020.104500
7. Scohy A, Anantharajah A, Bodéus M, Kabamba-Mukadi B, Verroken A, Rodriguez-Villalobos H. Low performance of rapid antigen detection test as frontline testing for COVID-19 diagnosis. *J Clin Virol*. 2020;129:104455. doi:10.1016/j.jcv.2020.104455
8. Van Honacker E, Van Vaerenbergh K, Boel A, De Beenhouwer H, Leroux-Roels I, Cattoir L. Comparison of five SARS-CoV-2 rapid antigen tests in a hospital setting and performance of one antigen assay in routine practice. A useful tool to guide isolation precautions? *J Hosp Infect*. Published online March 2021. doi:10.1016/j.jhin.2021.03.021
9. McPherson, RA; Pincus M. *Henry's Clinical Diagnosis and Management by Laboratory Methods*. 23rd ed. Saunders Elsevier; 2016.
10. Jong HL. In-House Clinical Trial (Unpublished). Published online 2020.
11. Tavora P. Clinical Evaluation Interim Report "Standard Q COVID-19 Antigen Test" (Unpublished). Published online 2020.
12. (FIND) F for IND. FIND Evaluation of SD Biosensor, Inc. STANDARD Q COVID-19 Ag Test External Report Version 1.0, 18 September 2020. Published 2020. https://www.finddx.org/wp-content/uploads/2020/09/SDQ-Ag-Public-Report_20200918.pdf
13. Kim J-H. SARS-CoV-2 in Extraction Buffer Inactivation Report (Unpublished). Published online 2020.
14. Trevethan R. Sensitivity, Specificity, and Predictive Values: Foundations, Pliabilities, and Pitfalls in Research and Practice. *Front Public Heal*. 2017;5. doi:10.3389/fpubh.2017.00307
15. Šimundić A-M. Measures of Diagnostic Accuracy: Basic

Definitions. *EJIFCC*. 2009;19(4):203-211. http://www.ncbi.nlm.nih.gov/pubmed/27683318

16. Department of Health Philippines. Depatment of Health - nCOV tracker. Published 2020. Accessed September 18, 2020. https://ncovtracker.doh.gov.ph/
17. *Deparment Memorandum 2020-0468 Supplemental Guidance on the Use of Rapid Antigen Test Kits*. Department of Health, Philippines
18. *Department Memorandum 2021-0169 Interim Guidelines on Rapid Antigen Test Reporting for the NCR Plus Bubble*. Department of Health, Philippines
19. DOH Health Technology Assessment Unit B et al. (2020). *Rapid Review: Use of Rapid Antigen Test Kits for the Diagnosis of COVID-19*. https://drive.google.com/file/d/1cb5v0PKGIwriGnhibZNIhp9pIzQVeVz9/view
20. Research Institute for Tropical Medicine (RITM). EVALUATION OF RAPID Ag TEST KITS. Published 2021. Accessed August 8, 2021. https://ritm.gov.ph/covid-19-kit-evaluation/completed-evaluations/sars-cov-2-rapid-antigen-ag-test/

APPENDICES

Appendix 1. Data Collection Form

Number	Age	Sex	Symptom	Rapid Antigen Test Result	RT-PCR			
					Ct ORF	Ct E gene	Ct N gene	Result
Ct<20								
1	34	M	Asymptomatic	NEG	**14.16**	**12.39**	**12.53**	Detected
2	81	F	Asymptomatic	NEG	**16.08**	**15.66**	**16.06**	Detected
3	26	M	Asymptomatic	NEG	**15.18**	**13.58**	**13.18**	Detected
4	23	M	Asymptomatic	NEG	**18.42**	**16.42**	**16.17**	Detected
5	29	F	Cough, Fatigue	NEG	**13.96**	**13.21**	**12.47**	Detected
6	30	M	Cough, Fatigue	POS	**17.97**	**15.96**	**18.71**	Detected
7	31	M	Fever	NEG	**17.97**	**17.64**	**19.92**	Detected
8	25	M	Asymptomatic	NEG	**18.11**	**17.78**	**18.36**	Detected
9	22	F	Cough	NEG	**18.25**	**16.5**	**16.08**	Detected
10	60	M	Cough, Fatigue, Sore Throat	NEG	**16.07**	**15.83**	**15.34**	Detected
11	27	M	Cough	POS	**19.23**	**19.36**	**20.97**	Detected
12	29	M	Cough	POS	**18.69**	**19.52**	**22.74**	Detected
13	54	M	Cough, Fatigue, Sore Throat	POS	**16.74**	**16.67**	**16.95**	Detected
14	24	F	Cough, Fatigue	POS	**16.19**	**16.23**	**17.86**	Detected
15	36	F	Fever	POS	**13.38**	**13.38**	**14.91**	Detected
16	15	F	Asymptomatic	NEG	**18.27**	**16.85**	**17.83**	Detected
17	30	M	Fever, Fatigue, Sore throat	NEG	**13.62**	**11.98**	**11.35**	Detected
18	48	M	Fever, Headache	NEG	**17.07**	**17.25**	**19.24**	Detected
19	50	F	Asymptomatic	NEG	**18.03**	**17.88**	**19.95**	Detected
20≤Ct<26								
20	36	F	Asymptomatic	NEG	**23.1**	**21.68**	**20.75**	Detected
21	45	F	Asymptomatic	NEG	**20.51**	**18.39**	**17.23**	Detected
22	45	F	Asymptomatic	NEG	**22.27**	**20.85**	**19.49**	Detected
23	34	F	Asymptomatic	NEG	**23**	**21.16**	**19.78**	Detected
24	38	F	Cough	NEG	**22.06**	**20.76**	**20.18**	Detected
25	31	F	Asymptomatic	NEG	**25.45**	**25.75**	**27.57**	Detected
26	44	M	Asymptomatic	NEG	**21.88**	**22**	**22.48**	Detected
27	29	M	Fever, Headache, Anosmia, Ageusia	NEG	**23.37**	**21.75**	**22.03**	Detected
28	25	M	Asymptomatic	NEG	**25.24**	**24.61**	**24.14**	Detected
29	28	F	Asymptomatic	NEG	**24.65**	**25.14**	**27.04**	Detected
30	32	F	Asymptomatic	NEG	**22.48**	**22.67**	**24.28**	Detected
31	31	F	Asymptomatic	NEG	**21.3**	**22.18**	**23.05**	Detected
32	27	M	Asymptomatic	NEG	**20.98**	**19.12**	**18.58**	Detected
33	41	M	Asymptomatic	NEG	**21.06**	**18.92**	**18.13**	Detected
34	28	M	Asymptomatic	NEG	**24.6**	**22.43**	**22.04**	Detected
35	45	F	Cough	POS	**22.8**	**20.77**	**20.93**	Detected
36	66	M	Fever, Fatigue	NEG	**23.39**	**22.52**	**24.02**	Detected
37	43	M	Asymptomatic	NEG	**21.26**	**20.19**	**19.59**	Detected
26≤Ct<30								
38	32	F	Asymptomatic	NEG	**27.47**	**26.25**	**26.61**	Detected
39	53	F	Asymptomatic	NEG	**27.22**	**26.03**	**26.74**	Detected
40	28	F	Asymptomatic	NEG	**27.52**	**26.51**	**27.3**	Detected
41	21	M	Asymptomatic	NEG	**29.94**	**30.92**	**31.18**	Detected
42	32	M	Asymptomatic	NEG	**29.91**	**28.57**	**29.11**	Detected
43	37	M	Asymptomatic	NEG	**29.06**	**28.93**	**29.39**	Detected
44	24	F	Asymptomatic	NEG	**26.2**	**26.41**	**27.99**	Detected
45	37	M	Asymptomatic	NEG	**27.5**	**27.97**	**29.14**	Detected
46	44	F	Asymptomatic	NEG	**29.77**	**28.95**	**29.97**	Detected
47	36	F	Fever, Anosmia, Ageusia	NEG	**28.81**	**27.25**	**28.36**	Detected

48	45	M	Sore throat	NEG	**29.91**	**29.66**	**29.09**	Detected
49	42	F	Asymptomatic	NEG	**28.3**	**28.16**	**27.9**	Detected
50	41	M	Cough, Sore throat	NEG	**29.19**	**29.4**	**30.52**	Detected
51	27	M	Headache	NEG	**29.02**	**28.95**	**29.96**	Detected
52	23	F	Cough, Headache	NEG	**29.13**	**28.87**	**29.41**	Detected
53	32	F	Asymptomatic	NEG	**29.55**	**28.57**	**27.98**	Detected
54	50	M	Asymptomatic	NEG	**29.32**	**29.46**	**30.56**	Detected
30≤Ct<38								
55	18	F	Asymptomatic	NEG	**33.75**	**32.42**	**32.97**	Detected
56	30	M	Asymptomatic	NEG	**35.41**	**32.76**	**33.62**	Detected
57	43	F	Asymptomatic	NEG	**33.18**	**36.56**	**31.87**	Detected
58	57	F	Asymptomatic	NEG	**30.03**	**29.44**	**29.9**	Detected
59	28	F	Asymptomatic	NEG	**33.2**	**32.61**	**33.36**	Detected
60	27	F	Fever, Cough	NEG	**35.14**	-	**35.8**	Detected
61	28	F	Fever, Headache	NEG	**33.54**	**32.43**	**31.64**	Detected
62	24	M	Cough	NEG	**37.35**	**38.81**	**37.08**	Detected
63	14	M	Asymptomatic	NEG	**36.04**	-	**34.86**	Detected
64	42	M	Asymptomatic	NEG	**33.11**	**31.52**	**32.72**	Detected
65	28	M	Asymptomatic	NEG	**34.1**	**31.66**	**30.61**	Detected
66	26	F	Fever, Sore throat	NEG	**34.52**	**33.01**	**33.8**	Detected
67	33	F	Cough	NEG	**33.71**	**35**	**33.88**	Detected
68	46	F	Asymptomatic	NEG	**33.79**	**30.8**	**31.94**	Detected
69	63	F	Fever, Headache, Sore throat	NEG	**35.98**	**35.53**	**36.99**	Detected
70	49	F	Asymptomatic	NEG	**35.29**	**33.54**	**34.16**	Detected
71	28	F	Fever, Cough	NEG	**32.47**	**34.05**	**33.51**	Detected
Not Detected								
72	8	M	Fever, Cough	NEG				Not Detected
73	16	F	Vomiting	NEG				Not Detected
74	7	M	Fever	NEG				Not Detected
75	15	M	Fever, Headache	NEG				Not Detected
76	22	F	Asymptomatic	NEG				Not Detected
77	18	M	Asymptomatic	NEG				Not Detected

KNOWLEDGE, ATTITUDE, AND PRACTICES (KAP) TOWARDS COVID-19 AMONG MEDICAL RESIDENTS OF A TERTIARY HOSPITAL IN THE PHILIPPINES DURING THE COVID-19 PANDEMIC: A CROSS-SECTIONAL SURVEY

MII ANNE B. TIBUS, M.D., CECILIA O. GAN, M.D.

ABSTRACT

OBJECTIVE. In this study, the KAP were determined among all medical residents in a tertiary hospital in the Philippines during the pandemic.

METHODS. Questionnaires were completed by the medical residents which contained 14 questions on clinical characteristics and prevention of COVID 19. Assessments on attitudes and practices included questions on confidence in winning against COVID19 and wearing masks when going out.

RESULTS. Among the 63 participants, 90.4% were female, 92 % were single and 69.8% younger than 30 years old. The overall correct rate of the knowledge questionnaire was 85.8%. Most did not have confidence (63.5%) on winning the battle against COVID-19 and most had not visited any crowded place (58.7%) and wore masks when going out (95.2%). Logistic regression analysis showed a significant correlation of knowledge scores and practice rates on going to crowded places (OR 1.72, CI (1.02-2.91) $P<0.05$).

CONCLUSION. The medical residents had good knowledge scores on clinical presentation, transmission and prevention control measures on COVID-19. Although attitude rates were poor, practice rates on COVID-19 were good. Furthermore, knowledge on COVID-19 resulted to good practices on not going to crowded places and wearing masks before leaving their houses.

Keywords: COVID-19; medical residents; knowledge, attitudes and practices

INTRODUCTION

An emerging respiratory disease affecting many people worldwide has been declared. Coronavirus disease, famously known as COVID-19, has vastly expanded from Wuhan, China and spread throughout the world [1]. COVID-19 is deemed highly infectious and according to Chen et al (2020) clinical symptoms include fever, dry cough, fatigue, myalgia, dyspnea, and to some extent sore throat and diarrhea. There are cases with COVID-19 patients who developed the severe stage, which is characterized by acute respiratory distress syndrome, septic shock, metabolic acidosis, and bleeding and coagulation dysfunction [2,3] According to the World Health Organization (WHO), the initially declared outbreak of COVID-19 has become a pandemic, which at the time of writing had affected more than 10 million people and caused almost 500, 000 deaths worldwide [4]. In the Philippines while at General Community Quarantine, as of June 2020, COVID-19 has affected 36, 468 people and caused 1255 deaths. Among healthcare workers (HCWs), 2669 tested positive with a death toll of 32 [5]. One of the critical issues during the COVID-19 is the fact that the HCWs are at risk of infection being at the frontline and they have a great role in controlling the spread of disease.

Among these HCWs, COVID-19 transmission may be associated with overcrowding, lack of isolation facilities, environmental contamination and more importantly, inadequate awareness of infection prevention practices [6]. Last January 2020, the WHO and Centers for Disease Control and Prevention (CDC) had published recommendations for the prevention and control of COVID-19 for HCWs [7,8]. Several online training sessions and materials on COVID-19 in various languages were initiated by the WHO to intensify preventive strategies, including raising awareness and training healthcare workers in preparedness activities [9].

Knowledge can influence the perceptions of HCWs due to their past experiences and beliefs, depending also on published information which may cause misinformation [10]. Definitely, there may be delays in recognition and handling of potential COVID-19 patients during the pandemic period due to these differences in perception. However, the level of knowledge and perceptions of HCWs toward COVID-19 remain unclear. Understanding the knowledge, attitude and practice (KAP) and possible risk factors aide to predict the outcomes of planned behavior and help in the creation of relevant training and policies to guide HCWs in prioritizing protection and avoiding occupational exposure. In this regard, the COVID-19 pandemic offers a unique opportunity to investigate the level of knowledge and perceptions of healthcare workers during this global health crisis to facilitate pandemic management and to prevent disease progression.

METHODOLOGY

Research design

The research design used in the study was a cross-sectional, analytical design. In a cross-sectional design, according to Olsen and St. George (2004), either the entire population or a subset thereof was selected, and from these individuals, data were collected to help answer the research questions of interest [11]. This type of design involved the collection of data at one point in time wherein all the phenomena under study were captured over one data collection period [12]. With the use of self-administered questionnaire, data were gathered by the researcher, after which the data was then subjected to statistical analysis to determine the presence of relationship among the different variables being tested –knowledge, attitude and practice towards COVID-19 during a pandemic.

Target population, subject sampling, sample size calculation

Pediatric residents currently employed at the hospital during the COVID-19 pandemic were included in the study. For the exclusion criteria, residents or fellows of other specialties and non-medical professionals were not included in the study. All pediatric medical residents employed in the Administrative year 2020 were included in the sample size. Questionnaires were distributed to every pediatric resident at the Philippine Children's Medical Center.

Intervention, Implementation of Intervention

The primary instrument used was the Knowledge, Attitude and Practice Questionnaire. For this research, the topic was about COVID-19 thus, a KAP survey gathers information about what respondents know about the COVID-19, what they think about how COVID-19 affected their life, and what they actually do with regard to seeking care or taking other actions toward COVID-19. Permission to use the COVID-19 KAP Questionnaire was obtained from Yi Li, one of the authors of the study, "Knowledge, attitudes, and practices towards COVID-19 among Chinese residents during the rapid rise period of the COVID-19 outbreak: a quick online cross-sectional survey." [13] No validation nor translation of the questionnaire was done since it was written in English language. Prior to answering the questionnaire, subjects were asked about their age, marital status, level of education and place of residence. Questionnaires was distributed to subjects after signing the consent and was collected thereafter.

OUTCOME/S ASSESSMENT, DATA COLLECTION METHOD, INSTRUMENT/S

According to guidelines for clinical and community management of COVID-19 by the National Health Commission of the People's Republic of China, a COVID-19 knowledge questionnaire was developed by the authors. The questionnaire had 12 questions: 4 regarding clinical presentations (K1-K4), 3 regarding transmission routes (K5-K7), and 5 regarding prevention and control (K8-K12) of COVID-19. These questions were answered on a true/false basis with an additional "I don't know" option. A correct answer was assigned 1 point and an incorrect/unknown answer was assigned 0 points. The total knowledge score ranged from 0 to 12, with a higher score denoting a better knowledge of COVID-19. Attitudes towards COVID-19 was measured by 2 questions (A1-A2) about the agreement on the final control of COVID-19 and the confidence in winning the battle against COVID-19. The assessment of respondents' practices composed of 2 behaviors (P1-P2, Table 1) : going to a crowded place and wearing a mask when going out in recent days.

Plan for Data Processing and Analysis

Knowledge scores and attitudes and practices of different persons according to demographic characteristics were compared with independent samples t-test, one-way analysis of variance (ANOVA), or Chi-square test as appropriate. Logistic regression analyses were used to identify factors associated with knowledge, attitudes and practices. Odds ratios (ORs) and their 95% confidence intervals (CIs) were used to quantify the associations between variables and KAP. Data analyses were conducted with SPSS version 17.0. The statistical significance level was set at $p < 0.05$ (two-sided).

ETHICAL CONSIDERATION

The purpose and methodology of the study were explained extensively to the participants. Informed consent was obtained from the participants in their own free will and full knowledge of the study. Answering the questionnaires did not cause any harm nor danger to the well-being of the residents. The subjects private details remained confidential and were solely used for the benefit of this study. The results of the study were discussed to the participants during their most available schedule.

RESULTS

A total of 63 participants completed the survey questionnaire. All medical residents were accounted for. Most residents belonged to the 16-29 age group (69.8%), 56 were female (90.4%), 58 were single (92%) and 50 participants reside within Quezon City. Most participants were third year residents at 38% (24), followed by first year residents at 34.9 % (22) and second year residents at 26.7% (17).

On the knowledge questionnaire, the correct answer rates of the 12 questions were 47.62-100% (Table 1). The mean COVID-19 knowledge score was 10.3 (SD 1.6, range 1-12), with an overall 85.8% (10.3/12 *100) correct rate on knowledge test. Knowledge scores did not significantly differ across sex,age group, marital status, education (year level) and place of residence (Table 2).

Table 1. Percentage of correct answer for each knowledge question

Knowledge question	n (%)
K1	40 (63.49)
K2	30 (47.62)
K3	61 (96.83)
K4	55 (87.30)
K5	49 (77.78)
K6	61 (96.83)
K7	63 (100.00)
K8	44 (69.84)
K9	62 (98.41)
K10	62 (98.41)
K11	62 (98.41)
K12	60 (95.24)

The majority of the respondents did not agree that COVID-19 will be successfully controlled (47.6%). Rates of reporting “agree” and “I don’t know” were 33.3% and 19.1%, respectively. The attitude towards the final success in controlling COVID-19 did not significantly differ across sex, age group, marital status, education (year level) and place of residence (Table 3). Many of the respondents (63.5%) did not have confidence that our country can win the battle against COVID-19, only 36.5% had confidence. The attitude towards confidence of winning significantly differed in the education category ($P < 0.05$) (Table 4).

Table 2. Comparison of knowledge score by demographic variables

Variables	Knowledge score (mean, SD)	P value
Overall score	10.30 (1.07)	Nil
Sex		
Male (n=6)	10.67 (1.21)	0.385
Female (n=57)	10.26 (1.06)	
Age group		
16-29 y.o (n=44)	10.18 (1.17)	0.179
30-49 y.o (n=19)	10.58 (0.77)	
Marital status		
Married (n=5)	10.20 (0.45)	0.827
Single (n=58)	10.31 (1.11)	
Education		
First year (n=22)	10.00 (1.11)	0.252
Second year (n=17)	10.53 (0.94)	
Third year (=24)	10.42 (1.10)	
Place of residence		
Within QC (n=50)	10.22 (1.15)	0.239
Outside QC (n=13)	10.62 (0.65)	

Majority of the participants had not visited any crowded place (58.7%) and wore masks when going out (95.2%) in recent days. There were still almost half of the participants who had visited crowded places (41.3%) and few participants had not worn masks when leaving their houses (4.8%) (Table 5). The rates of these two practices did not significantly differ across demographic groups (Tables 6).

There was no significant association between knowledge scores and attitude rates on successfully controlling and confidence on winning against COVID-19 (Table 7). There was significant association of knowledge scores and practice rates on going to crowded places ($P<0.05$) while there was no significant association of knowledge scores and practice rate on wearing masks before leaving their houses (Table 8). No association was noted on attitude rates and practice rates.

Table 3. Comparison of attitude on success in control response by demographic variables

Variables	A1: success in control response options (n, %)			P value
	Agree (n=21)	Disagree (n=30)	Don't know (n=12)	
Sex				
Male	2 (33.3)	2 (33.3)	2 (33.3)	0.608
Female	19 (33.3)	28 (49.1)	10 (17.5)	
Age group				
16-29 y.o	14 (31.8)	21 (47.7)	9 (20.5)	0.881
30-49 y.o	7 (36.8)	9 (47.4)	3 (15.8)	
Marital status				
Married	3 (60.0)	2 (40.0)	0 (0.0)	0.323
Single	18 (31.0)	28 (48.3)	12 (20.7)	
Education				
First year	8 (36.4)	11 (50.0)	3 (13.6)	0.184
Second year	2 (11.8)	11 (64.7)	4 (23.5)	
Third year	11 (45.8)	8 (33.3)	5 (20.8)	
Place of residence				
Within QC	17 (34.0)	24 (48.0)	9 (18.0)	0.914
Outside QC	4 (30.8)	6 (46.2)	3 (23.1)	

Table 4. Comparison of attitude on confidence on winning response by demographic variables

Variables	A2: confidence of winning response options (n, %)		P value
	No (n=40)	Yes (n=23)	
Sex			
Male	4 (66.7)	2 (33.3)	0.865
Female	36 (63.2)	21 (36.8)	
Age group			
16-29 y.o	28 (63.6)	16 (36.4)	0.971
30-49 y.o	12 (63.2)	7 (36.8)	
Marital status			
Married	2 (40.0)	3 (60.0)	0.255
Single	38 (65.5)	20 (34.5)	
Education			
First year	18 (81.8)	4 (18.2)	**0.014**
Second year	12 (70.6)	5 (29.4)	
Third year	10 (41.7)	14 (58.3)	
Place of residence			
Within QC	29 (58.0)	21 (42.0)	0.076
Outside QC	11 (84.6)	2 (15.4)	

Table 5. Attitudes and practices responses

Attitude and practice question	N (%)
A1: success in control	
Agree	21 (33.3)
Disagree	30 (47.6)
Don't know	12 (19.1)
A2: confidence of winning	
Yes	23 (36.5)
No	40 (63.5)
P1: Going to a crowded place	
Yes	26 (41.3)
No	37 (58.7)
P2: wearing mask	
Yes	60 (95.2)
No	3 (4.8)

Table 6. Comparison of practice response by demographic variables

Variables	P1: Going to a crowded place response options (n, %)		P value	P2: wearing mask response options (n, %)		P value
	No (n=37)	Yes (n=26)		No (n=3)	Yes (n=59)	
Sex						
Male	4 (66.7)	2 (33.3)	0.678	0 (0.0)	6 (100.0)	0.565
Female	33 (57.9)	24 (42.1)		3 (5.3)	54 (94.7)	
Age group						
16-29 y.o	23 (52.3)	21 (47.7)	0.113	1 (2.3)	43 (97.7)	0.158
30-49 y.o	14 (73.7)	5 (26.3)		2 (10.5)	17 (89.5)	
Marital status						
Married	4 (80.0)	1 (20.0)	0.314	0 (0.0)	5 (100.0)	0.602
Single	33 (56.9)	25 (43.1)		3 (5.2)	55 (94.8)	
Education						
First year	13 (59.1)	9 (40.9)	0.419	0 (0.0)	22 (100.0)	0.077
Second year	12 (70.6)	5 (29.4)		0 (0.0)	17 (100.0)	
Third year	12 (50.0)	12 (50.0)		3 (12.5)	21 (87.5)	
Place of residence						
Within QC	28 (56.0)	22 (44.0)	0.388	3 (6.0)	47 (94.0)	0.365
Outside QC	9 (69.2)	4 (30.8)		0 (0.0)	13 (100.0)	

Table 7. Association between knowledge score and attitude

	OR (95% CI)	P value
Association between knowledge score and A1 (success in control)	1.11 (0.67-1.84)	0.676
Association between knowledge score and A2 (confidence of winning)	1.21 (0.74-1.99)	0.453

Table 8. Association between knowledge score and practice

	OR (95% CI)	P value
Association between knowledge score and P1 (going to a crowded place)	1.72 (1.02-2.91)	**0.042**
Association between knowledge score and P2 (wearing mask)	0.97 (0.32-2.92)	0.958

Interpretation: Higher knowledge score was significantly associated with not going to any crowded place (OR 1.72, 95% CI 1.02-2.91; p=0.042).

Table 9. Association between attitude and practice

	OR (95% CI)	P value
Association between A1 and P1	0.91 (0.31-2.62)	0.856
Association between A1 and P2	Nil	Nil
Association between A2 and P1	1.53 (0.53-4.43)	0.429
Association between A2 and P2	0.27 (0.02 to 3.15)	0.295

Note: The A1 and P2 analysis cannot be implemented due to small sample size (perfect prediction).

DISCUSSION

To our knowledge, this is the first study in the Philippines that has assessed the KAP of healthcare physicians on COVID-19. In this study, our population comprised of predominantly female, single, age 16 to 29yo, residing within Quezon City. We found an overall correct rate of 85.8% on the knowledge questionnaire, indicating that most respondents had sufficient knowledge about COVID-19. The current finding of good knowledge is in agreement with the findings of Giao et al. (2020) who reported that 88.4% participants, had sufficient knowledge regarding COVID-19 [14] . Another study reported that 89% of respondents had sufficient knowledge regarding transmission, symptoms and treatment of COVID-19 [15]. The current findings provide confidence in terms of the knowledge of medical residents regarding the clinical presentation, transmission routes and preventive measures of COVID-19. This is of particular significance in the current situation when no vaccine exists and research is ongoing, so healthcare workers must be aware of all the updates and take precautions in treating and preventing the infection.

Knowledge is essential for establishing prevention beliefs, forming positive attitudes, and promoting positive practices, and individuals' cognition and attitudes towards disease affect the effectiveness of their coping strategies and behaviors to a certain extent [16]. Compared to the study of Zhong et al (2020) where the questionnaire for this study was adopted and the study of Singh, S and Singh, RK (2020), most of respondents had positive attitude towards control and winning against COVID-19 [17]. On our study, however, majority of the respondents had negative attitude towards the COVID-19 pandemic: 47.6% did not believe that COVID-19 will finally be successfully controlled, and 62.9% did not have confidence that the Philippines can win the battle against COVID-19. This study coincides with a study in Bangladesh wherein respondents had a negative attitude towards COVID-19 situation control and it stated that a plausible reason of this type of attitude can be attributed to the rapid rise in number of cases even in developed countries like Italy and the United States of America [18]. Similarly, the continuous rise in number of COVID-19 cases and deaths, lack of PPEs and medical supplies, and poor implementation of quarantine regulations in the Philippines would have contributed to the negative attitude towards control and winning against COVID-19.

Part of the population, the third year medical residents, however, had an optimistic attitude towards control (45.8%) and winning the battle (58.3%) against COVID-19. Most studies on knowledge, attitude and practices towards COVID-19 in multiple countries such as China and India showed positive association of knowledge and attitude towards control of the disease [13,17]. According to Azlan et al (2020), they attributed the positive attitudes to COVID-19 to the drastic measures taken by the government in mitigating the spread of the virus and swift action to enforce community quarantine in China and Malaysia, respectively [20]. In the Philippines, community quarantine was implemented in March 2020 and COVID-19 facilities were assigned to cater to the COVID-19 cases. Somehow, prompt action of the government and concerted efforts of the people giving donations of PPE and medical needs might have contributed to the positive attitude towards winning and control of COVID-19.

Despite this, the practices of medical residents were cautious: they avoided crowded places (58.7%) and wore masks when leaving the home (95.2%) during the rapid rise period of the COVID-19 pandemic. These strict preventive practices could be due to the very strict prevention and control measures implemented by local governments such as banning public gatherings, closure of establishments and malls and strict home quarantine. Secondly, the adherent practices may be due to the good knowledge of the medical residents on transmission and infectivity of COVID-19 through respiratory droplets. Although the study showed high association of knowledge and practice of not going to any crowded places (Table 8) meaning higher knowledge scores were associated to good practices, unfortunately, the present study still showed that 41.2% of the medical residents went to crowded places and 4.8% did not wear masks when leaving homes recently. These potentially risky behaviors were not related to sex, age group, marital status, education (year level) and place of residence. The practice rates of going to any crowded places might be attributed buying necessities from open establishments and that medical residents are allowed to go out of their houses as long as they possess a valid identification card from the hospital.

We found out that overall higher knowledge score is associated with higher preventive practices toward COVID-19 especially on not going to crowded places, a similar association between the knowledge about the disease and preventive practices were reported in China on COVID-19[13,15], in Bangladesh on COVID-19[18], and in three studies included in a review of KAP on COVID-19[21]. Furthermore, awareness of the diseases other than COVID-19 were generally high, and a positive association between knowledge and preventive practices was consistently demonstrated across all studies [22-25]. No associations were noted on attitude and practice rates which may also be attributed to the small sample.

Our study has some limitations. Firstly, no standardized tool assessing KAPs on COVID-19 has been previously validated. We have, however, adapted a previously published tool for KAP on COVID-19 wherein the questions have been formulated from WHO and CDC guidelines [13]. Secondly, the weakness of this study lies in the small sample of medical residents recruited and most of the participants were female, single and younger than 30 years old. Considering the educational attainment and occupation, we may have overestimated the knowledge scores, attitude rates and preventive practices rates towards COVID-19 due to the small sample and our findings can be generalized to medical residents, particularly women who are single and younger than 30 years old. Therefore, KAP towards COVID-19 on medical residents from other institutions including other healthcare workers deserve special research attention. However, this is the first study to assess KAPs, it can be used to formulate targeted Continuing Medical Education (CME) for HCWs and enrolled in a countrywide survey and training on COVID-19.

CONCLUSION

The participants of the study included mostly female, younger than 30 years old, single and resides within Quezon City. The findings from the current study shows that medical residents had good knowledge scores on clinical presentation, transmission and prevention control measures on COVID-19. Although attitude rates were poor, practice rates on COVID-19 were good. Majority of the respondents did not have confidence that our country can win and control COVID-19. However, most participants maintained appropriate practices on not going to any crowded places and wearing masks before leaving their houses. Furthermore, knowledge on COVID-19 resulted to good practices on not going to crowded places and wearing masks before leaving their houses.

RECOMMENDATION

Continued professional education is advised among medical residents so as improve the knowledge in the prevention of COVID-19 spread and to avert negative attitude and promote preventive and therapeutic practices. We recommend follow up studies involving teaching and non-teaching hospitals across the country to cover for larger sample size.

BIBLIOGRAPHY/ REFERENCES

1. Lipsitch, M., et al. Defining the epidemiology of COVID 19- studies

needed. The New England Journal of Medicine, 2020; 382: 1194-1195.

2. Chen N., et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet, 2020; 395: 507-513.
3. The Novel Coronavirus Pneumonia Emergency Response Epidemiology Team. The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) in China. Chin J Epidemiol, 2020; 41:5, 145-51.
4. World Health Organization. Coronavirus disease (COVID-19) pandemic. https://www.who.int/emergencies/diseases/novel-coronavirus-2019. (last accessed June 2020)
5. Department of Health, Philippines. Updates on novel coronavirus disease (COVID-19). https://www.doh.gov.ph/2019-ncov (last accessed June 2020)
6. Wu, Z. and McGoogan, J. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China. The Journal of American Medical Association Volume, 2020; 323:13, 1239-1242.
7. World Health Organization. Infection prevention and control during health care when novel coronavirus (nCoV) infection is suspected: interim guidance, January 2020. https://tinyurl.com/r7w9key (last accessed May 29, 2020)
8. Centers for Disease Control and Prevention. Update and interim guidelines on outbreak of 2019 Novel coronavirus (2019-nCoV) URL: https://emergency.cdc.gov/han/han00427.asp (last accessed May 30, 2020)
9. World Health Organization. Responding to COVID-19: Real-time training for the coronavirus disease outbreak URL: https://openwho.org/channels/covid-19 (last accessed June 1, 2020)Oppenheim, et al. Knowledge and beliefs about Ebola virus in a conflict-affected area: early evidence

from the North Kivu outbreak. J Glob Health, 2019; 9(2):020311

10. Olsen, C. and St George, D.M. (2004) Cross-Sectional Study Design and Data Analysis. College Entrance Examination Board, New York. http://cdn.physioblasts.org/f/public/1355667773_1_FT0_4297_module_05.pdf (last accessed July 2020)

11. Polit, D. F. and Beck, C. T. Nursing research: Appraising evidence for nursing practice (7th Edition). Philadelphia: Wolters Klower/Lippincott Williams & Wilkins, 2006

12. Zhong, B., et al. Knowledge, attitudes, and practices towards COVID-19 among Chinese residents during the rapid rise period of the COVID-19 outbreak: a quick online cross-sectional survey. International Journal of Biological Sciences, 2020; 16: (1745-1751)

13. Giao, H., et al. Knowledge and attitude toward COVID-19 among healthcare workers at District 2 Hospital, Ho Chi Minh City. Asian Pac J Trop Med, 2020;13:1–6

14. Zhang, M., et al. Knowledge, attitude , and practice regarding COVID-19 among healthcare workers in Henan, China. Journal of Hospital Infection, 2020; 105: 183-187

15. McEachan, R., et al. Meta-analysis of the reasoned action approach (RAA) to understanding health behaviors. Ann Behav Med, 2016; 50: 592-612

16. Singh, S. and Singh, RK. Awareness, attitude and practices towards COVID-19 among people of Bihar during lockdown 1.0: a cross-sectional study. International Journal of Science & Healthcare Research, 2020; 5(2): 432-443.

17. Rahman,A. and Sathi, NJ. Knowledge, attitude, and preventive practices toward COVID-19 among Bangladeshi internet users. Electron J Gen Med, 2020;17(5):em245.

18. Worldometers.info, Dover, Delaware, U.S.A [cited 13 April 2020]. Available at: http://www.worldometers.info/ coronavirus/#countries (last accessed October 2020)
19. Azlan, AA., et al.Public knowledge, attitudes and practices towards COVID-19: A cross-sectional study in Malaysia. PLoS ONE, 2020. 15(5): e0233668.
20. Puspitasari, IM., et al. Knowledge, attitude, and practice during the COVID-19 pandemic: a review. J Multidiscip Healthc, 2020;13:727-733
21. Balogun, MR., et al. Predictors of tuberculosis knowledge, attitudes and practices in urban slums in Nigeria: a cross-sectional study. Pan Afr Med J., 2019;32:60.10.11604/pamj. 2019.32.60.14622
22. Dawaki, S., et al. Is Nigeria winning the battle against malaria? Prevalence, risk factors and KAP assessment among Hausa communities in Kano State. Malar J, 2016;15:351. 10.1186/s12936-016-1394-3
23. Ghani, NA,. et al. Comparison of knowledge, attitude, and practice among communities living in hotspot and non-hotspot areas of dengue in Selangor, Malaysia. Trop Med Infect Dis, 2019;4.
24. Rukmanee, N., et al. Knowledge, attitudes and practices (KAP) regarding influenza A (H1N1) among a population living along Thai-Myanmar border, Ratchaburi Province, Thailand. Southeast Asian J Trop Med Public Health, 2014;45:825-33.

CLINICAL PRESENTATION AND OUTCOME OF PEDIATRIC COVID-19 PATIENTS ADMITTED IN PHILIPPINE CHILDREN'S MEDICAL CENTER (PCMC): THE FIRST 100 CASES

JENNEELYN A. GONZALES-RITONA, MD, CARIDAD M. SANTOS, MD,

MARY ANN C. BUNYI, MD.

ABSTRACT

BACKGROUND: There are numerous studies on adult patients admitted for COVID-19 but there is paucity of local data in children.

OBJECTIVE: This study aims to determine the clinical presentation and outcome of children admitted for COVID-19.

METHODOLOGY: This is a retrospective review of medical records of patients 0 to 18 years old with COVID-19 admitted in Philippine Children's Medical Center (PCMC). Descriptive statistics summarized the clinical profile of the patients. Pearson's Chi Square and Fischer's Exact Test were used for data analysis.

RESULTS: There were 100 confirmed COVID-19 pediatric patients admitted at PCMC from March 2020 to March 2021. Most were within the 0-4 years of age (52%). Fever (63%), respiratory symptoms (31%) and shock (28%) were the predominant clinical manifestations. Most (78%) had no exposure to symptomatic household contacts but all came from communities with known local transmission. Fourteen cases of hospital acquired COVID-19 were also identified. Out of the 100 cases, 53 had critical COVID-19 on admission and 82 had co-morbidities, mostly neurologic, hematologic and infectious diseases. Seventy four patients recovered and 26 patients died.

Fever (p-value=0.014) and shock (p-value=0.000), thrombocytopenia or thrombocytosis (p=0.030) and electrolyte imbalances (p=0.045) were significantly associated with critical COVID-19. There was no significant association between the presence of co-morbid conditions on admission and clinical outcome. O2 support by facemask (p=0.001) or by mechanical ventilator (p=0.001), and inotropic support (p=0.000) were significantly associated with mortality.

CONCLUSION: Children admitted for COVID-19 infection generally recover but those with critical COVID-19 is highly associated with mortality.

Keywords: SARS-CoV-2, COVID-19, children, pediatric patients, clinical profile

LIST OF ABBREVIATIONS:

1. COVID-19- coronavirus diseases 2019
2. RT-PCR - reverse transcriptase polymerase chain reaction
3. ACE 2 receptor- angiotensin-converting enzyme 2 receptor
4. PARDS – pediatric acute respiratory distress syndrome
5. MODS- multiple organ dysfunction syndrome
6. MIS-C – Multisystem Inflammatory Syndrome in Children

INTRODUCTION:

In December 2019, an unprecedented number of pneumonia cases presented in adult individuals from Wuhan, China. The virus was later recognized and named as SARS-CoV-2 causing the Coronavirus disease 2019 (COVID-19). The disease has since spread worldwide, leading to an ongoing pandemic. There are almost 149 million COVID-19 cases in 220 countries and territories worldwide; the US accounted for the majority (about 21.3%) of the cases, followed by India, Brazil and France. Reported COVID-19 deaths reached 3 million (2.1%).[1] In the Philippines, the first recorded, confirmed COVID-19 case was on January 30, 2020.[2]

By April 30, 2021, the number of COVID-19 positive individuals rose to 1 million in the country. The Philippines had the 2nd highest number of confirmed COVID-19 cases in Southeast Asia (after Indonesia) and ranked 7th in Asia, and 26th in the world. Of these cases, 52.4% were males. Most of the cases belonged to the 20-39 age group while children accounted for 95,743 (9.6%) of total cases in the country. There were a total 17,145 (1.7%) recorded deaths, which was mostly noted at 60-74 years of age with the lowest case fatalities among children at 301 (1.8%.)[3]

In a large and comprehensive, systematic review of published studies involving 7,780 pediatric patients with COVID-19, children was noted to have milder symptoms and were less likely to be hospitalized as compared to adults. The most common clinical manifestations found were fever (59.1%), cough (55.9%), rhinorrhea (20%) and myalgia/fatigue (18.7%).[4] However, the clinical presentation and outcome of admitted children with critical COVID-19 is not well known, with limited data on possible associated risk factors.

Due to the lack of local studies, this paper aims to describe the clinical presentation, clinical course, treatment and outcome of admitted COVID-19 pediatric patients in Philippine Children's Medical Center (PCMC), a tertiary, subspecialty, pediatric referral hospital, with the ultimate objective of improving the management of cases of pediatric COVID-19 by identifying individuals who are at risk for severe/critical illness and poor outcomes.

OBJECTIVES

A. General:

To determine common clinical presentation and outcome of children with confirmed COVID-19 admitted at the Philippine Children's Medical Center

B. Specific Objectives:

1. To present demographic characteristics of pediatric patients with COVID-19
2. To describe the association between the clinical presentation and severity of COVID-19

3. To describe the association between the severity of COVID-19 and the clinical outcome
4. To describe the association between the co-morbidities of the pediatric COVID-19 confirmed cases and the clinical outcome
5. To describe the association between the supportive and experimental COVID-19 treatment with clinical outcome

METHODOLOGY

This is a retrospective review of medical records of all COVID-19 confirmed pediatric patients aged 0 to 18 years of age admitted at the Philippine Children's Medical Center (PCMC) from March 2020 to March 2021**.** All COVID-19 suspects consented for review of medical records upon admission to Philippine Children's Medical Center (Appendix A). A separate consent was obtained from those who were transferred to another hospital and those who were discharged prior to the confirmation of COVID-19.

Upon protocol approval from the Institutional Review Board and Institutional Research – Ethics Committee (IR-EC), the study proceeded with the data collection. A registry of all admitted pediatric COVID-19 suspects who underwent SARS CoV-2 RT-PCR was obtained from the hospital's Infection Prevention and Control Committee (IPCC). Those patients whose results showed SARS CoV-2 RNA detected were included. Patients who turned out negative for SARS CoV-2 RT-PCR but positive on COVID-19 serology and satisfied the criteria for MIS-C[5,6] were also included in the study. Given a confidence interval of 95% and a power of 80%, the sample size computed based on a similar study[7] was 50. This was the minimum number of COVID-19 confirmed pediatric cases required for this study.

Using the data collection sheet (Appendix B), the following were collected: demographics, initial clinical presentation and laboratory findings, treatment, outcome, morbidities and adverse events. During data collection, the

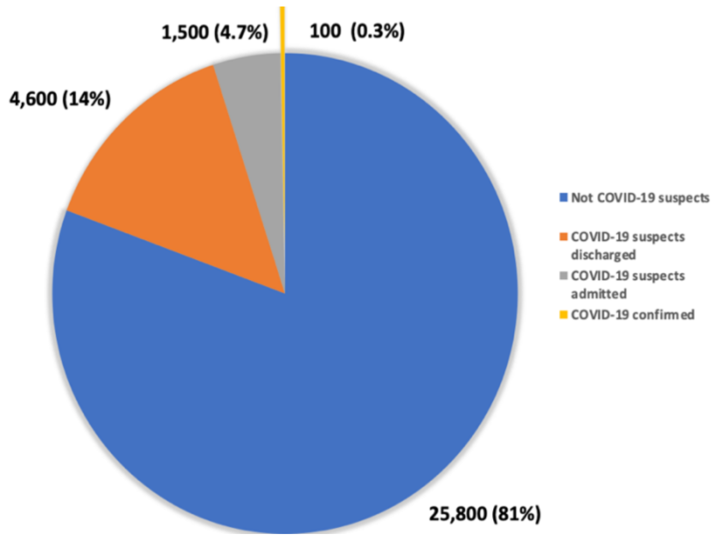
CBC parameters were analyzed according to the normal values for age. The normal range for absolute lymphocyte count (ALC) of patients used was 1,500-4,000 cells/ µg/L.[8] Liver dysfunction was defined as alanine aminotransferase/ aspartate aminotransferase over three times the upper limit of normal, total bilirubin was over two times the upper limit of normal, prolonged bleeding parameters or hypoalbuminemia.[9] Kidney dysfunction was diagnosed according to the KDIGO clinical practice guidelines with serum creatinine 1.5x elevated.[10] Cardiac dysfunction was diagnosed if 2d echo showed ejection fraction of <56%,[11] if serum level of CKMB was 2x elevated, or if abnormalities were shown in electrocardiography.

Severity of COVID-19 was determined through assessment of initial clinical presentation using the Philippine Pediatric Society – Pediatric Infectious Disease Society of the Philippines Classification of COVID-19 Disease Severity (Appendix C).[12] Centers for Disease Control and Prevention (CDC) has defined an **asymptomatic case** as an individual infected with SARS-CoV-2 who does not exhibit symptoms at any time during the course of infection.[13]

Mean and median were computed for numerical data. Descriptive data were reported as frequencies and percentages. Pearson's Chi Square was used to analyze the associations of the following: clinical presentation with the severity of COVID-19, the severity of COVID-19 and the clinical outcome, the presence of co-morbidity and clinical outcome. Both Pearson's Chi Square and Fischer's Exact Test were used to establish the association between the laboratory findings and the severity of COVID-19 and the association between the treatment with clinical outcome.

RESULTS

From March 2020, a total of 32,000 patients were screened at the triage of the Philippine Children's Medical Center based on the algorithm recommended by the Philippine Pediatric Society (PPS) and Pediatric Infectious Disease Society of the



Source: PCMC Triage Census

Figure I. Classification of Patients According to PCMC COVID Triage Screening from March 2020 to March 2021 (N=32,000)

Philippines (PIDSP), with 6,200 patients (19%) tagged as COVID suspects (Appendix D). Four thousand six hundred (14% of the total patients screened) presented with mild symptoms and deemed non-admissible hence discharged and advised on the home intervention for children with mild COVID-19[12] without confirmatory testing.

A total 1600 patients (5% of the total patients screened) were admitted and subjected to SARS CoV-2 RT-PCR. Among these, 98 patients had positive results and were confirmed with COVID-19. Another 2 patients satisfied the criteria for Multisystem Inflammatory Syndrome in Children (MIS-C) [5,6], including a positive serologic test for COVID-19. Thus, a total of 100 subjects were included in the study.

Fifty-two of the 100 subjects were within the 0-4 years of age (52%), and 54% were male. Forty percent of the COVID-19 were residents of Quezon City. Seventy-eight percent apparently had no exposure to a COVID-19 confirmed, probable or suspect case. Most (70%) were admitted within 7 days from the onset of symptoms.

Eighty-two percent had co-morbid conditions upon admission. Most (61%) had no malnutrition. Critical COVID-19 comprised about 53% of the admissions. (Table 1). Majority (33%) were admitted in the hospital for 0-7 days.

Fever was the most common presenting symptom (63%) followed by respiratory symptoms (31%) and shock (28%). The uncommon presenting symptoms of COVID-19 seen in this study were seizure (15%), GI bleeding (5%) two of which had hemorrhagic shock and jaundice (2%). Six percent had no symptoms. (Table 2)

TABLE 1. PHILIPPINE CHILDREN'S MEDICAL CENTER (N=100)

Demographic	Number of Patients	Frequency
Age		
0 to 4 years	52	52%
5 to 9 years	16	16%
10 to 14 years	17	17%
15 to 18 years	15	15%
Sex		
Male	54	54%
Female	46	46%
Geographic Location		
Quezon City	40	40%
NCR (outside Quezon City)	28	28%
Outside NCR	32	32%
COVID Exposure		
No	78	78%
Yes	8	8%
Household Contact	14	14%
Hospital Exposure		
Onset of COVID-19 Symptoms:		
Prior to Hospitalization	70	70%
0 to 7 days	10	10%
8 to 14 days	2	2%
15 to 21 days		
During Hospitalization	3	3%
3rd to 14th hospital day	9	9%
>14th hospital day		
Not applicable (No symptoms)	6	6%
Presenting Symptoms		
Fever	63	63%
Respiratory symptoms	31	31%
GI symptoms	13	13%

Neurologic symptoms	17	17%
Circulatory symptoms (Shock)	28	28%
No symptoms	6	6%
Presence of Co-morbidities		
None	18	18%
Present	82	82%
Nutritional Status		
With malnutrition	39	39%
Without malnutrition	61	61%
Severity of COVID-19		
Asymptomatic	4	4%
Mild	7	7%
Moderate	29	29%
Severe	7	7%
Critical	53	53%
Duration of Hospitalization		
0 to 7 days	33	33%
8 to 14 days	25	25%
15 to 21 days	11	11%
>21 days	31	31%

TABLE 2. PRESENTING SYMPTOMS OF PEDIATRIC COVID-19 CASES ADMITTED AT PHILIPPINE CHILDREN'S MEDICAL CENTER FROM MARCH 2020 TO MARCH 2021

Presenting Symptom	
No symptom	6 (6%)
Fever	63 (63%)
Respiratory	31 (31%)
Cough	9
Difficulty of breathing	22
Gastrointestinal	13 (13%)
Vomiting, abdominal pain, diarrhea	7
Upper GI bleeding	1
Lower GI bleeding	2
Jaundice	2
Abdominal distention	1
Neurologic	17 (17%)
Seizure	15
Headache	1
Decreased sensorium	1
Circulatory (Shock)	28 (28%)
Septic Shock	10
Hemorrhagic Shock	5
Hypovolemic Shock	3
Cardiogenic Shock	1
Dengue Severe	5
MIS-C	4

From the result of Pearson's Chi-Square Test seen on the table below (Table 3), COVID-19 severity is associated with the presenting symptom. Gastrointestinal (p-value = 0.045) and neurologic (p-value = 0.044) symptoms were associated with mild and moderate COVID-19 while fever (p-value=0.014), and shock (p-value=0.000) were associated with critical COVID-19. (Table 3)

As for the laboratory findings, the results of Pearson's Chi-square test and Fischer's exact test showed that the presence of thrombocytopenia or thrombocytosis (p-value=0.030) and electrolyte imbalances (p-value=0.045) in patients were associated with critical COVID-19 as shown on the table below. (Table 4)

Out of 100 COVID-19 patients, 74% recovered and 26% died. Based on the statistical analysis using Pearson's Chi-Square Test, critical COVID-19 was significantly associated with mortality (p value=0.000). (Table 5).

Eighty two percent of COVID-19 patients admitted at PCMC had medical co-morbidities upon admission. The most common co-morbidities were neurologic, followed by hematologic and infectious diseases. However, there was no significant association between co-morbid conditions upon admission and clinical outcome of COVID-19 (p-value=0.775). (Table 6)

TABLE 3. CLINICAL PRESENTATION AND SEVERITY OF COVID-19 INFECTION AT PHILIPPINE CHILDREN'S MEDICAL CENTER FROM MARCH 2020 TO MARCH 2021 (N=100)

Clinical Presentation		Severity of COVID-19					p-value
		Asymptomatic n (%)	Mild n (%)	Moderate n (%)	Severe n (%)	Critical n (%)	
Age	0 to 4 years	1 (1.9)	3 (5.8)	20 (38.5)	3 (5.8)	25 (48.1)	0.655 [a]
	5 to 9 years	0 (0.0)	1 (6.2)	4 (25.0)	1 (6.2)	10 (62.5)	
	10 to 14 years	2 (11.8)	2 (11.8)	2 (11.8)	2 (11.8)	9 (52.9)	
	15 to 18 years	1 (6.7)	1 (6.7)	3 (20.0)	1 (6.7)	9 (60.0)	
Sex	Female	1 (2.2)	4 (8.7)	11 (23.9)	3 (6.5)	27 (58.7)	0.569 [a]
	Male	3 (5.6)	3 (5.6)	18 (33.3)	4 (7.4)	26 (48.1)	
Geographical Location	NCR (Outside Quezon City)	1 (3.6)	2 (7.1)	11 (39.3)	1 (3.6)	13 (46.4)	0.220 [a]
	Outside NCR	2 (6.2)	1 (3.1)	7 (21.9)	4 (12.5)	18 (56.2)	
	Quezon City	1 (2.5)	4 (10.0)	11 (27.5)	2 (5.0)	22 (55.0)	
Covid Exposure	No	3 (3.8)	6 (7.7)	23 (29.5)	4 (5.1)	42 (53.8)	0.384 [a]
	Yes, hospital exposure	1 (7.1)	0 (0.0)	5 (35.7)	1 (7.1)	7 (50.0)	
	Yes, household contact	0 (0.0)	1 (12.5)	1 (12.5)	2 (25.0)	4 (50.0)	
Onset of Illness	None (Asymptomatic)	3 (75.0)	0 (0.0)	1 (25.0)	0 (0.0)	0 (0.0)	0.828 [a]
	0 to 7 days	0 (0.0)	7 (10.1)	19 (27.5)	4 (5.8)	39 (56.5)	
	8 to 14 days	0 (0.0)	0 (0.0)	3 (30.0)	1 (10.0)	6 (60.0)	
	15 to 21 days	0 (0.0)	0 (0.0)	1 (50.0)	0 (0.0)	1 (50.0)	
	3rd to 14th hospital day	0 (0.0)	0 (0.0)	2 (50.0)	1 (25.0)	1 (25.0)	
	>14th hospital day	1 (9.1)	0 (0.0)	3 (27.3)	1 (9.1)	6 (54.5)	
Presenting Symptoms							
	With fever	0 (0.00)	5 (7.9)	14 (22.3)	5 (7.9)	39 (61.9)	0.014* [a]
	Without fever	4 (10.7)	2 (5.4)	15 (40.6)	2 (5.4)	14 (37.9)	
	With GI symptoms	0 (0.0)	1 (7.7)	8 (61.5)	0 (0.0)	4 (30.8)	0.045* [a]
	Without GI symptoms	4 (4.6)	6 (6.9)	21 (24.1)	7 (8.0)	49 (56.4)	
	With neuro symptoms	0 (0.0)	5 (29.4)	6 (35.3)	1 (5.9)	5 (29.4)	0.044* [a]
	Without neuro symptoms	4 (4.8)	2 (2.4)	23 (27.7)	6 (7.2)	48 (57.9)	
	With respiratory symptoms	0 (0.0)	1 (3.2)	8 (25.8)	6 (19.4)	16 (51.6)	0.201 [a]
	Without respiratory symptoms	4 (5.8)	6 (8.6)	21 (30.5)	1 (1.4)	37 (53.7)	
	With shock	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	28 (100.0)	0.000** [a]
	Without shock	4 (5.6)	7(9.7)	29 (40.3)	7 (9.7)	25 (34.7)	
Co-morbidity	With co-morbidity	4 (4.9)	3 (3.7)	27 (32.9)	6 (7.3)	42 (51.2)	0.710 [a]
	Without co-morbidity	0 (0.0)	4 (22.3)	2 (11.1)	1 (5.6)	11 (61.0)	
Nutritional Status	With Malnutrition	1 (2.6)	2 (5.1)	12 (30.8)	3 (7.7)	21 (53.8)	0.802 [a]
	Without Malnutrition	3 (4.9)	5 (8.2)	17 (27.9)	4 (6.6)	32 (52.5)	
Duration of Hospitalization	0 to 7 days	2 (6.0)	2 (6.0)	6 (18.2)	3 (9.2)	20 (60.6)	0.315[a]
	8 to 14 days	0 (0.0)	2 (8.0)	8 (32.0)	2 (8.0)	13 (52.0)	
	15 to 21 days	0 (0.0)	1 (9.0)	5 (45.5)	0 (0.0)	5 (45.5)	
	>21 days	2 (6.5)	2 (6.5)	10 (32.2)	2 (6.5)	15 (48.3)	

* significant at the 0.05 level of significance
** significant at the .01 level of significancE
[a] Using Pearson's Chi-Square Test with row levels and/or column levels merged to satisfy chi-square test criterion.

TABLE 4. DISTRIBUTION OF PEDIATRIC COVID-19 BY SEVERITY AND LABORATORY FINDINGS ADMITTED AT PHILIPPINE CHILDREN'S MEDICAL CENTER FROM MARCH 2020 TO MARCH 2021

Laboratory Findings		Severity of COVID-19					p-value
		Asympto-matic n (%)	Mild n (%)	Moderate n (%)	Severe n (%)	Critical n (%)	
Hgb (n=99)	Anemia	2 (4.5)	1 (2.3)	14 (31.8)	4 (9.1)	23 (52.3)	0.749 [a]
	Normal	2 (3.6)	6 (10.9)	15 (27.3)	3 (5.5)	29 (52.7)	
WBC (n=99)	Leukocytosis	0 (0.0)	2 (6.1)	9 (27.3)	4 (12.1)	18 (54.5)	0.495 [a]
	Leukopenia	1 (5.6)	1 (5.6)	7 (38.9)	0 (0.0)	9 (50.0)	
	Normal	3 (6.2)	4 (8.3)	13 (27.1)	3 (6.2)	25 (52.1)	
Absolute Lymphocyte Count (n=99)	Normal	4 (5.6)	4 (5.6)	21 (29.1)	6 (8.3)	37 (51.4)	0.851[a]
	Low	0 (0.0)	3 (11.1)	8 (29.6)	1 (3.7)	15 (55.6)	
Platelet (n=99)	Normal	4 (8.2)	5 (10.2)	16 (32.7)	4 (8.2)	20 (40.8)	0.030* [a]
	Thrombocytopenia	0 (0.0)	0 (0.0)	8 (22.9)	3 (8.6)	24 (68.6)	
	Thrombocytosis	0 (0.0)	2 (13.3)	5 (33.3)	0 (0.0)	8 (53.3)	
Electrolyte Imbalance (n=93)	None	3 (5.9)	2 (3.9)	20 (39.2)	6 (11.8)	20 (39.2)	0.045* [a]
	Present	0 (0.0)	5 (11.9)	7 (16.7)	1 (2.4)	29 (69.0)	
Deranged Liver Function (n=76)	None	4 (10.8)	4 (10.8)	10 (27.0)	4 (10.8)	15 (40.6)	0.065 [a]
	Present	1 (2.6)	1 (2.6)	8 (20.5)	0 (0.0)	29 (74.3)	
Deranged Kidney Function (n=68)	None	3 (5.0)	5 (8.3)	14 (23.3)	5 (8.3)	33 (55.0)	1.000 [a]
	Present	0 (0.0)	0 (0.0)	3 (37.5)	1 (12.5)	4 (50.0)	
Cardiac Dysfunction (n=10)	None	0 (0.0)	0 (0.0)	0 (0.0)	2 (29.0)	5 (71.0)	Incalculabl e
	Present	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3(100.0)	
Increased Inflammatory Markers (n=68)	None	0 (0.0)	2 (16.7)	4 (33.3)	1 (8.3)	5 (41.7)	0.167 [b]
	Present	1 (1.8)	2 (3.6)	12 (21.4)	5 (8.9)	36 (64.3)	
Sepsis (n=98)	None	4 (4.8)	6 (7.1)	24 (28.6)	7 (8.3)	43 (51.2)	0.397 [a]
	Present	0 (0.0)	1 (7.1)	3 (21.4)	0 (0.0)	10 (71.4)	
Pulmonary Findings (n=99)	None	3 (14.3)	6 (28.6)	1 (4.8)	0 (0.0)	12 (52.3)	0.680 [a]
	Present	1 (1.3)	0 (0.0)	28 (37.4)	7 (9.3)	41 (52.0)	
Positive CNS Findings (n=18)	None	0 (0.0)	3 (37.5)	3 (37.5)	0 (0.0)	2 (25.0)	0.559 [b]
	Present	0 (0.0)	2 (20.0)	2 (20.0)	0 (0.0)	6 (60.0)	

* significant at the 0.05 level of significance
** significant at the .01 level of significance
[a] Using Pearson's Chi-Square Test with row levels and/or column levels merged to satisfy chi-square test criterion.
[b] Using Fisher's Exact Test with row levels and/or column levels merged to satisfy chi-square test criterion.

TABLE 5. DISTRIBUTION OF PEDIATRIC COVID-19 BY SEVERITY AND CLINICAL OUTCOME AT PHILIPPINE CHILDREN'S MEDICAL CENTER FROM MARCH 2020 TO MARCH 2021 (N=100)

		Died n (%)	Recovered n (%)	p-value
Severity of Infection	Asymptomatic	1 (25.0)	5 (75.0)	0.000** [a]
	Mild	1 (14.3)	6 (85.7)	
	Moderate	0 (0.0)	27 (100.0)	
	Severe	0 (0.0)	7 (100.0)	
	Critical	24 (45.3)	29 (54.7)	

** significant at the 0.01 level of significance
[a] Using Pearson's Chi-Square Test with row levels merged whenever possible to satisfy chi-square test criterion

TABLE 6. DISTRIBUTION OF PEDIATRIC COVID-19 BY CO-MORBIDITY AND CLINICAL OUTCOME AT PHILIPPINE CHILDREN'S MEDICAL CENTER FROM MARCH 2020 TO MARCH 2021 (N=100)

	Outcome		
Presence of Comorbidity	Died n (%)	Recovered n (%)	p-value
Without co-morbidity	4 (22.2)	14 (77.8)	0.775 [a]
With co-morbidity	22 (27.0)	60 (73.0)	
Cardiac	0 (0.0)	2 (100.0)	---
Congenital	2 (66.7)	1 (33.3)	
Gastroenterology/ Hepatic	5 (71.0)	2 (29.0)	
Hematologic	3 (15.8)	16 (84.2)	
Infection	1 (7.1)	13 (92.9)	
Metabolic	1 (100.0)	0 (0.0)	
Neurologic	7 (28.6)	14 (71.4)	
Prematurity	1 (25.0)	3 (75.0)	
Renal	2 (28.6)	5 (71.4)	
Surgical	0 (0.0)	4 (100.0)	

** significant at the 0.01 level of significance
[a] Using Pearson's Chi-Square Test with row levels merged whenever possible to satisfy chi-square test criterion.

Mortality was significantly associated with O2 support with facemask or mechanical ventilation (p-value= 0.001) and inotropic support (p-value=0.000). None of the current supportive and experimental treatment for COVID-19 was significantly associated with clinical outcome despite doing sub analysis per indication. (Table 7)

TABLE 7. DISTRIBUTION OF PEDIATRIC COVID-19 BY SUPPORTIVE/EXPERIMENTAL TREATMENTS AND CLINICAL OUTCOME AT PHILIPPINE CHILDREN'S MEDICAL CENTER FROM MARCH 2020 to MARCH 2021

General Supportive Treatment		Clinical Outcome: Died n (%)	Clinical Outcome: Recovered n (%)	p-value
O2 Support n = 100	Cannula	0 (0.0)	10 (100.0)	0.001** [a]
	Facemask	13 (35.1)	24 (64.9)	
	Intubated	12 (47.8)	11 (52.2)	
	Non-invasive ventilation	0 (0.0)	3 (100.0)	
	None	1 (3.7)	26 (96.3)	
Antibiotics n = 100	None	2 (22.2)	7 (77.8)	1.000 [b]
	Yes	24 (25.3)	67 (74.7)	
Inotropic Support n = 100	None	14 (16.7)	70 (83.3)	0.000** [b]
	Present	12 (68.8)	4 (31.2)	
Total Parenteral Nutrition n = 100	None	23 (24.5)	71 (75.5)	0.638 [b]
	Present	3 (33.3)	3 (66.7)	
Other Support n = 100	Dialysis	2 (28.6)	5 (71.4)	0.327 [a]
	None	21 (23.0)	66 (77.0)	
	Surgery	3 (50.0)	3 (50.0)	
COVID-19 Supportive Treatment				
Azithromycin n=78	With Pneumonia			0.128 [a]
	Given	4 (13.3)	26 (86.7)	
	Not given	15 (31.3)	33 (68.8)	
Zinc, Vit D3 n=100	Given	6 (16.7)	30 (83.3)	0.149 [a]
	Not given	20 (29.7)	44 (70.3)	
Dexamethasone n= 53	Critical COVID-19			0.846 [a]
	Given	5 (41.7)	7 (58.3)	
	Not given	18 (43.9)	23 (56.1)	
Dexamethasone n = 56	Elevated inflammatory markers			0.218 [b]
	Given	4 (40.0)	6 (60.0)	
	Not given	9 (20.0)	37(80.0)	
COVID-19 Experimental Treatment				
IVIG n = 5	MIS-C			Incalculable
	Given	1 (20.0)	4(80.0)	
	Not given	0 (0.00)	0 (0.0)	
IVIG n = 14	Sepsis			1.00[b]
	Given	0 (0.00)	1 (100.0)	
	Not given	6 (46.1)	7 (53.2)	
IVIG n = 56	Elevated inflammatory markers			1.00[b]
	Given	2 (22.2)	7 (77.8)	
	Not given	11 (23.4)	36 (76.6)	

* significant at the 0.05 level of significance
** significant at the 0.01 level of significance
[a] Using Pearson's Chi-Square Test with row levels merged whenever possible to satisfy chi-square test criterion
[b] Using Fisher's Exact Test

DISCUSSION

At Philippine Children's Medical Center, among the 1,600 COVID-19 suspects admitted and tested for SARS CoV-2 RT-PCR, 100 turned positive. The case positivity rate (cumulative positive individuals divided by the cumulative individuals tested)[3] was 6.2% as compared to the cumulative positive rate of 10% in the country. This was because only moderate to critical cases were admitted and tested at PCMC. The number of COVID-19 confirmed cases steadily increased from March 2020 with its peak at August 2020. This was followed by a decrease starting from September 2020 until the period of data collection on 1st week of March 2021.

More than half of the examined patients were males (54%) while 46% were females. Fifty two percent were within the 0-4 years of age. This differed from the DOH Data which stated that the highest number of pediatric COVID-19 confirmed cases is concentrated within the 15-19 age range.[3]

Among those within the 0-4 years of age, infants comprised about 71%, signifying that younger children especially those within infancy were more likely to be hospitalized. In fact, this study showed that 47% of the patients with severe and critical COVID were under 5 years of age while 46% of the mortalities belonged to this age group. This was also reported in the nationwide case series of 2,135 pediatric patients with COVID-19 in China wherein the proportions of severe and critical cases were highest among 0-5 years of age, particularly infants.[14] This was compatible with the DOH data that the most number of COVID-19 deaths in children were recorded at 0-4 years of age.[3] According to WHO, this age group has the greatest risk of severity and death from pneumonia and diarrhea which are both COVID-19 manifestations.[15,16]

Forty percent of the COVID-19 were residents of Quezon City. Twenty-eight percent came from other cities of NCR. Since PCMC is a tertiary, subspecialty, pediatric referral hospital, other admissions were from the adjacent provinces. Thirty-two percent reside outside NCR, mostly from CALABARZON region (Bulacan, Cavite, Rizal and Laguna) while the rest were from Central Luzon (Bataan, Nueva Ecija, Pampanga, Zambales) and the Bicol region. According to the DOH, CALABARZON was second to the NCR in terms of the highest number of total COVID-19 cases, followed by the Central Luzon. Majority of the COVID-19 confirmed patients came from Quezon City, City of Manila, Cavite, Rizal, Laguna and Bulacan, all of which belonged to the top cities/provinces with the greatest number of total cases and highest recorded new cases.[3]

In terms of exposure history, 78% apparently had no exposure to a COVID-19 confirmed, probable or suspect case although local transmission in their areas have been confirmed. This finding was in contrast to a study of 582 children positive for COVID-19, where 60% of cases were traced from an infected parent or sibling, and 40% of the cases with the source either outside the family or unknown.[17]

Due to lockdown that limited the exposure of children, the possibility of acquiring COVID-19 from asymptomatic / pre-symptomatic household contacts cannot be excluded in these cases. Researchers from the Center for Disease Control and Prevention used a statistical transmission model to analyze data from more than 27,000 households in Wuhan, stating that 59% of all transmission came from asymptomatic transmission, comprising 35% from pre-symptomatic individuals and 24% from individuals who never develop symptoms.[18]

The European Center for Disease Prevention and Control has defined probable healthcare-associated COVID-19 infection as symptom onset on day 3-7 after admission and a strong suspicion of healthcare transmission or as symptom onset on day 8-14 after admission. On the other hand, the definite hospital acquired COVID-19 infection is described by European CDC as symptom onset on day $\geq$ 14 after admission.[19] In this study, there were 3 probable and 11 definite healthcare associated COVID-19 infection identified. These were the patients admitted at the regular, non-COVID wards or with previous negative COVID-19 swab results. Succeeding SARS CoV-2 RT-PCR (whether initial or repeat) turned out to be positive, with 12 developing new symptoms while the other 2 were just screened prior to a surgical procedure. Only 3 of these hospital-acquired COVID-19 infections had identified sources. Due to limited resources, not all patients and watchers were tested with SARS CoV-2 RT-PCR prior to hospital admission. Patients were cleared to regular wards based on the absence of COVID symptoms and normal Chest X-rays with one accompanying asymptomatic watcher. Therefore, the possibility of asymptomatic transmission cannot be excluded.

Among the infants, there were six neonates with early onset neonatal COVID-19 infection who presented with respiratory distress at birth up to 2nd day of life and were tested ≥ 24th hour of life. Four were critical (intubated and on NIPPV). One died due to multiple organ dysfunction syndrome (MODS); the rest recovered. The possibility of vertical transmission was entertained as ACE2 receptors are expressed in the ovary, uterus, vagina and placenta.[20] However, all mothers were asymptomatic. Three mothers had both negative SARS CoV-2 RT PCR and normal Chest Xray findings. The other 3 mothers only had normal Chest X-rays and did not undergo SARS CoV-2 RT-PCR testing.

There were 4 neonates who had late onset neonatal COVID-19 infection (beyond 2 days of life). One was previously admitted from another hospital, the other one had been staying at the regular newborn ward for a month while the other two had been admitted in NICU for 1-2 weeks in an isolette with the hospital staff observing contact and droplet precautions. Two were swabbed prior to surgical procedures but had positive results. Another two developed healthcare associated pneumonia, sepsis and eventually expired.

In this study, 70% of the patients presented within 0-7 days of illness with a median period of 2 days (range 0-21 days). Among these 70 patients, 33 (47%) belonged to 0-5 years of age and more than half (57%) were critical. This was earlier than the usual deterioration of about one week after illness onset in COVID-19.[21] However, in an investigation made on 14, 618 hospitalized patients with COVID-19 from 114 Belgian hospitals between March 14-June 12, 2020, it was described that age has a major impact on the delay between symptom onset and hospitalization, with the youngest group having the shortest delay (median of day 1up to 2.6 days) as compared to older patients.[22]

Usual reports in children with COVID-19 and their overall symptoms were significantly milder as compared to adults.[23,24] In a systematic review on 7,480 COVID-19 confirmed children, patients showed mainly mild (42.5%) and moderate (39.6%) signs of the infection. About 2% were admitted to pediatric intensive care unit.[25] This study is therefore not a reflection of the general characteristic of children with COVID-19 because as a tertiary, subspecialty referral hospital, most of the admitted COVID-19 confirmed pediatric patients were severely and critically ill. Those with mild clinical manifestations were discharged and not tested with SARS CoV-2 RT-PCR.

In a systematic review of Hoang et al. on 7,780 pediatric patients, the most common presenting symptoms were fever (59.1%), cough (55.9%), rhinorrhea (20%) and myalgia/fatigue (18.7%).[4] In this study, fever and cough were common among the subjects in the present study. However, fever and shock were most commonly observed with critical COVID-19.

Among the 100 COVID-19 confirmed patients, 28% presented with shock. Shock is common in critically ill patients with COVID-19, and is associated with high mortality. All 4 types of shock— distributive, cardiogenic, obstructive, and hypovolemic shock—have been observed in patients with COVID-19.[26]

In this study, ten patients had septic shock which appeared to be the predominant cause of distributive shock in patients with COVID-19, secondary to the virus itself or from bacterial co- infections. Five had hemorrhagic shock secondary to their co-morbidities. There were 3 patients who had hypovolemic shock due to poor oral intake and high grade fever causing insensible losses, along with associated diarrhea or vomiting. One had cardiogenic shock from worsening of underlying cardiovascular disease (RHD). There were also 5 cases of Dengue Severe and 4 cases of MIS-C who all presented with hypotension.

In this study, neurologic and GI symptoms were associated with mild to moderate COVID-19. Seventeen percent of the patients presented with neurologic symptoms such as seizure, decreased sensorium and headache with and without fever. These patients with neurologic symptoms were swabbed due to presence of fever, radiologic pneumonia and clearance prior to a surgical procedure. Among these 17 patients, 5 had known co-morbid neurologic conditions (cerebral palsy, focal/ generalized epilepsy). During admission, three were diagnosed with craniopharyngoma, medulloblastoma, brain abscess by cranial imaging.

Nine patients presented with seizure but had no known underlying neurologic co-morbidity. Among these, two patients were diagnosed with encephalitis. Out of these nine patients, five underwent CSF analysis whose results were normal. Only 3 underwent CSF COVID-19 RT-PCR which all turned out to be negative. One patient with status epilepticus showed background slowing on the EEG.

In the largest cohort of patients with COVID 19 and neurological symptoms who underwent lumbar puncture, RT-PCR for SARS-CoV-2 from CSF were all negative in all 30 cases. CSF analysis findings including WBC, were normal, stating that most neurological symptoms seem to be caused by indirect mechanisms and not due to active CNS invasion of the virus.[27] Although SARS CoV-2 has neurotropic and neuroinvasive capabilities[28], other causes of seizure identified in these patients without underlying neurologic conditions were fever, electrolyte derangement and hypertension. Other neurological problems found in patients with coronavirus infection but not reported in this study were anosmia and ageusia. There are several case series which recognized these symptoms among adolescents.[29, 30]

Thirteen percent manifested with gastrointestinal symptoms such as loose stool, vomiting, and abdominal pain. In a review article of Tian, et al. on 2,023 COVID-19 patients, 79% had gastrointestinal symptoms. Anorexia, diarrhea and vomiting were the most common symptoms while GI bleeding comprised of about 4%.[30] In this present study, there were five patients who presented with GI bleeding, one was due to intussusception with Pneumonia who was screened prior to surgical procedure; four with co-morbid gastrointestinal conditions (1 with biliary atresia, 2 with esophageal varices, 1 with portal vein hypertension secondary to portal vein thrombosis). These patients were screened due to presence of radiologic pneumonia and due to shock. GI bleeding can occur due to direct virus invasion because ACE 2 receptors are also abundant on the gastric, duodenal, and rectum glandular epithelial cell. In these patients with known gastrointestinal co-morbidities, GI bleeding may also be due to secondary reasons such as tissue hypoxia and aggravation of existing coagulopathy.[31]

There were two patients who consulted due to jaundice. There were no history of use of hepatotoxic drugs or food poisoning. None of the family members had hepatic diseases. Both manifested with fever, jaundice, abdominal pain, seizure/ behavioral change. Laboratory findings showed elevated liver enzymes ALT and AST (up to 52-75x), elevated ammonia (6x-9.8x), and elevated total bilirubin with direct hyperbilirubinemia, elevated alkaline phosphatase and prolonged bleeding parameters indicative of an acute liver failure. Both patients died within 3 days from admission. Post mortem SARS COV-2 RT-PCR test turned out positive. Given the higher expression of ACE2 receptors in cholangiocytes (epithelial cells of bile duct), the liver is a potential target for SARS-CoV-2. Hepatic involvement in COVID-19 could be related to the direct cytopathic effect of the virus causing an uncontrolled immune reaction called cytokine storm in severe and critical COVID-19. Moreover, COVID-19 may cause worsening of underlying liver disease leading to hepatic decompensation with higher mortality. [32]

Seven cases of COVID-19 with Dengue co-infection were recorded. Four were already in critical phase while 3 were still in febrile phase. On laboratory examination, they all had hemoconcentration, leukopenia and thrombocytopenia on CBC. All were positive on dengue antibody tests while only two were also positive on dengue NS1. Their clinical courses were compatible with Dengue, however they were co-infected with COVID-19 as evidenced by positive SARS CoV-2 RT-PCR results. Six were later discharged, however, one patient expired because of MODS secondary to severe dengue and COVID-19. Although these illnesses are caused by different viruses, they may share similar clinical and laboratory features[33] hence the consideration for both in the differential diagnosis of acute febrile illness during this pandemic is essential especially in dengue endemic countries like the Philippines. There were several reports on Dengue and COVID-19 co-infection.[34-36] However, there were also case reports like in Singapore which described 2 patients with false positive results from rapid serological testing for dengue, who were later confirmed to have (SARS-CoV-2) infection.[37]

As of March 29, 2021, CDC has reported a total of 3,185 Multisystem Inflammatory Syndrome in Children (MIS-C) cases in the United States with 36 deaths (1.1% mortality rate).[38.] At PCMC, five patients fulfilled the criteria of the WHO and CDC for MIS-C. Four of these patients were beyond 5 years of age. They presented with a 5-to-9-day history of fever with associated gastrointestinal symptoms, Kawasaki-like features and hypotension. CBC showed neutrophilia with low to normal platelet count. The inflammatory markers were elevated with Ferritin as high as 89,390 ng/ml in the patient who expired. 2d echo findings were coronary arteritis, minimal pericardial effusion, mitral and tricuspid regurgitation with decreased ejection fraction. Three patients were positive for SARS-CoV2 RT-PCR. Since the other 2 patients fulfilled the clinical and laboratory criteria for MIS-C despite a negative SARS CoV-2 RT-PCR, further investigation with serology was done which showed reactive COVID IgM and/or IgG results. All were managed with IVIG and two were given Aspirin. One patient was given an additional Methylprednisolone but remained hemodynamically unstable and expired on the 17th day of illness. The management was in accordance with the clinical guidance later released by American College of Rheumatology for MIS-C. [39]

In adults, co-morbidities were associated with significantly increased risk of mortality such as kidney, cerebrovascular, cardiovascular, respiratory diseases including diabetes, hypertension and cancer.[40] While the co-morbidities in adults are often acquired and may be associated with lifestyle, those of the children were mostly congenital conditions. There were several reports which stated that children with comorbidities, just like in adults, have higher risk of critical COVID-19 and associated mortality than children without underlying disease.[41,42] In fact, in a cross-sectional study done in children with COVID-19 admitted to 46 North American pediatric ICUs between March 14 and April 3, 2020, out of the 48 children, forty (83%) had significant pre-existing co-morbidities.[43] In the present study, 82% of the COVID-19 confirmed patients had comorbidities. The most common identified were neurologic, followed by hematologic and infectious. Other co-morbidities recognized were renal, gastric, surgical, cardiac, metabolic (MSUD), prematurity, congenital anomalies and trisomy 21. Although 85% of the mortalities in this study had co-morbidities, there was no significant association noted between these underlying co-morbidities and the clinical outcome. This data may be skewed because majority (82%) of the subjects in this study had co-morbidities.

Most (61%) of the COVID-19 confirmed subjects in this study had good nutritional status, with 39 (39%) classified as malnourished, mostly wasted (22%). Three of the patients were obese for which only one became critical and was intubated but all recovered. This was in contrast to a retrospective review by Zachariah, et al. that among 50 pediatric COVID-19 confirmed patients admitted in a children's hospital in New York City, obesity was the most prevalent co-morbidity and that it was significantly associated mechanical ventilation in children 2 years or older.[43] The high visceral adiposity present in obese individuals is known to induce higher levels of local and systemic inflammatory cytokines. These cytokines have been positively correlated with COVID-19 severity.[44] Obesity also decreases lung capacity and reserve, making ventilation more difficult.[45]

The duration of hospitalization was mostly 0-7 days in 33% of the patients with a median period of 12 days (range 0-268 days). This was similar to the median length of hospitalization of 10-13 days among survivors of COVID-19 according to CDC.[46]

In the present study, laboratory findings associated with severity of COVID-19 were the presence of thrombocytopenia/thrombocytosis and electrolyte imbalances. In adult patients, thrombocytopenia has been associated with increased severity or worse outcomes similar to this study. Other laboratory findings associated with COVID-19 severity in adults were lymphocytopenia (specifically CD4+ and CD8+ T lymphocytes), elevated liver enzymes, LDH, and inflammatory markers (e.g., CRP, ferritin), elevated inflammatory cytokines (IL-6 and TNF-∝), elevated D-dimer, prothrombin time, troponin, creatinine phosphokinase and acute kidney injury [47-50] In observational studies, elevated inflammatory markers like CRP, procalcitonin, interleukin 6, Ferritin and D-dimer at admission have been associated with severe disease in children.[7, 51-52] In this study, only a limited panel of inflammatory markers (procalcitonin, ESR, CRP, Ferritin, LDH) were determined in 68 patients. Based on currently available data, it is not possible to document a pattern of laboratory values in pediatric COVID-19 according to the severity of the disease.

For the imaging, 72% of the patients had findings of Pneumonia on Chest Xray while 25% had normal results. Due to a limited sensitivity of 69%, a negative chest radiograph does not exclude COVID-19.[54] These readings of Pneumonia were clinically compatible in 47 (65%) patients while 25 (35%) were just radiologic.

Chest Xray findings of pediatric COVID-19 patients were nonspecific in this study. The most common Chest Xray reports were hazy or reticulonodular densities on both inner lungs. Four had findings of ground glass opacities while only 3 had reading of PARDS on Chest X-rays. This was in contrast to the International Expert Consensus Statement on Chest Imaging in Pediatric COVID-19, that the typical chest Xray finding in children is bilateral distribution of peripheral and/or subpleural ground glass opacities and/or consolidations.[55] Despite milder CXR findings were present in these patients as compared to common Chest Xray findings in COVID-19, almost ¼ of the patients (23%) had respiratory distress as the presenting symptom. The reason for the difficulty of breathing might be multifactorial in these patients.

Due to increased radiation dose, a chest CT scan may be considered in pediatric patients who are not responding appropriately to management and demonstrate clinical deterioration.[55]

In this study, the need for O2 support via facemask/ mechanical ventilation and inotropic support were associated with mortality, as these were provided to the critical patients.

Zinc (for 2 months to < 5 years of age: 15 mg elemental zinc BID, for $\geq$ 5 years: 20 mg elemental zinc BID) and Vitamin D3 (<2 years: 1,000 IU/day while for those $\geq$ 2 years: 2,000 IU/day) were given to 36 patients as supportive treatment. Zinc is an essential micronutrient supporting the normal function of immune system. It plays a role in the early cure of pneumonia, and can reduce the duration of diarrhea and limiting its complications.[58] Vitamin D, on the other hand, has multiple immunomodulating actions. It favors the ability of macrophages to mature and prevents macrophages from releasing inflammatory cytokines and chemokines.[57]

Thirty two patients with pneumonia were given Azithromycin 10 mg/kg/day once a day (max of 500 mg/day) for 5 days. Azithromycin is a macrolide with activity against gram-positive cocci and atypical pathogens causing pneumonia though it may also act as an immunomodulator.[58] In the earlier studies, Azithromycin is to be given in combination with Hydroxychloroquine/ Chloroquine to promote more efficient viral reduction.[59] However, recent meta-analysis on hydroxychloroquine or chloroquine did not show reduction in mortality or mechanical ventilation, and may cause cardiac toxicity and arrhythmias, therefore these are not recommended for the treatment of COVID-19 based on Infectious Disease Society of America (IDSA)Guidelines.[60] The use of Azithromycin in the present study had no significant association with the clinical outcome.

Thirteen patients who were critical, in shock, on mechanical ventilator and with elevated inflammatory markers were given Dexamethasone 0.15 mg/kg IV once daily up to 10 days. The anti-inflammatory effect of corticosteroids may prevent the systemic inflammatory response and multisystem organ dysfunction in COVID-19.[57] In a Recovery trial in adult patients hospitalized with COVID-19, the use of dexamethasone resulted in lower 28-day mortality among those who were receiving either invasive mechanical ventilation or oxygen alone at randomization but not among those receiving no respiratory support.[61] In this study, there was no significant association between the use of Dexamethasone and the clinical outcome although this was inconclusive because of the limited number of patients treated with Dexamethasone.

IVIG was administered to 10 patients (5 cases of MIS-C, to 1 neonatal sepsis, three with severe pneumonia with elevated inflammatory markers and one patient with MODS, PARDS also with elevated inflammatory markers). Out of the 5 MIS-C patients, 4 improved. In this study, there was no significant association between the use of IVIG and the clinical outcome although this was again inconclusive because of the limited number of patients treated with IVIG. In the latest recommendation of PPS-PIDSP, IVIG should not routinely be given for pediatric COVID-19, only to those with multisystem inflammatory syndrome in children (MIS-C).[12]

During the hospital admission, 29 patients experienced different morbidities such as healthcare associated pneumonia (9), healthcare associated infections(12), multiple organ dysfunction syndrome (5), pneumothorax (1), osteomyelitis(1) on the patient with empyema thoracis (MSSA) and fracture on the patient with osteomyelitis (1). No adverse event happened.

Of all the 100 patients, majority (74%) recovered while 26% died. This 26% all-cause mortality rate among the admitted pediatric patients was higher than the 1.8% mortality rate of COVID-19 confirmed children in the country.[3] This was because as a tertiary, subspecialty referral hospital, most of the admitted COVID-19 confirmed pediatric patients were severely and critically ill.

Among these 26 mortalities, 12 (46%) belonged to 0-4 years of age. Fifteen (58%) were females. Twenty four (92%) were critical whose presentation were mostly shock (46%) and difficulty of breathing (33%). An asymptomatic patient with Acute Myelogenous Leukemia turned positive on SARS CoV-2 RT PCR prior to a surgical procedure. She was discharged but rushed back to PCMC triage for possible intracranial bleeding and expired. One COVID-19 confirmed patient with Medulloblastoma presented with mild symptoms of fever and headache who expired secondary to brain herniation. Majority (42%) of the mortalities had shorter length of stay for 0-7 days.

Twenty two (85%) of the mortalities had underlying co-morbidities and 10 (38%) had co-infection as evidenced by the positive growth on the cultures, both of which may have had contributed to the demise of these patients.

CONCLUSION

Majority (53%) of the COVID-19 confirmed pediatric cases admitted at PCMC had critical COVID-19. Fever, respiratory (cough, DOB) and shock were the predominant presenting symptoms. Eighty-two percent of the patients had co-morbidities, mostly neurologic, hematologic and infectious however, in this study there was no significant association between the presence of co-morbidity and the mortality. A large percentage (76%) of the admitted cases recovered while 24% died.

The presence of fever and shock, thrombocytosis/thrombocytopenia or electrolyte imbalances were significantly associated with severity of COVID-19. Patients under critical condition who received O2 (via facemask and mechanical ventilation) or cardiac support were associated with poor clinical outcome.

LIMITATION AND RECOMMENDATION

This study has several limitations. Since this is a retrospective, chart review, the authors dealt only with the data available in the medical chart, which some were lacking or missing. Majority of the population consists of patients with co-morbidities. Some parameters/clinical and laboratory findings may not be directly associated with COVID-19 and the underlying illness may be the contributing factor of the outcome. The detailed information on the causality and mechanism of death, as to whether directly or indirectly caused by COVID-19, were not explored. No autopsy was done to any of the subjects included in this study.

The COVID-19 data was presented on pediatric patients from a single center, observational study. It is not a representation of the general population of COVID-19 pediatric patients. Therefore, a recommendation of a larger, multicenter study on the clinical presentation and outcome of all outpatient and inpatient COVID-19 pediatric patients be done in the country.

More focused study is recommended on the different subset of patients like the maternal-neonatal dyads, dengue and COVID-19 co-infected patients, MIS-C, patients with co-morbidities as to further understand COVID-19 in these patients. A scoring system for prediction of disease severity in COVID-19 may also be done.

Due to the possibility of asymptomatic or pre-symptomatic transmission to children, this study also recommends active contact tracing of household contacts of COVID-19 confirmed pediatric patients.

REFERENCES

1. World Health Organization. WHO COVID-19 Dashboard. 2021 Apr 30. Available from: https://covid19.who.int/
2. World Health Organization. COVID-19 in the Philippines. 2021 Feb 21. Available from: https://www.who.int/philippines/emergencies/covid-19-in-the-philippines
3. Department of Health (PH). COVID-19 Tracker. 2021 Apr 30. Available from: https://doh.gov.ph/covid19tracker
4. Hoang A, Chorath K, Moreira A et al. COVID-19 in 7780 pediatric patients: A Systematic review. EClinicalMedicine [Internet]. 2020 June 26 [cited 2020 Jul 01];24:100433. Available from: https://doi.org/10.1016/j.eclinm.2020.100433
5. Centers for Disease Control and Prevention Health Alert Network (US). Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with Coronavirus Disease 2019 (COVID-19) [Internet]. 2020 May 14. Available from: https://emergency.cdc.gov/han/2020/han00432.asp
6. World Health Organization. Multisystem inflammatory syndrome in children and adolescents with COVID-19: Scientific Brief [Internet]. 2020 May 15. Available from:
7. Chao J, Derespina K, Herold B, et al. Clinical Characteristics and Outcomes of

Hospitalized and Critically Ill Children and Adolescents with Coronavirus Disease 2019 at a Tertiary Care Medical Center in New York City. J Peds [Internet]. 2020 May 11 [cited 2020 Aug 01];223:14-19. Available from: https://dx.doi.org/10.1016%2Fj.jpeds.2020.05.006

8. Coates T. Approach to the child with lymphocytosis or lymphocytopenia. UptoDate. 2020 Apr 14.

9. Cai Q, Huang D, Yu H, et al. COVID-19: Abnormal liver function tests. J Hep [Internet]. 2020 April 13 [cited 2020 Sep 01];73(3);566-574. Available from: https://doi.org/10.1016/j.jhep.2020.04.006

10. Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. Nephron Clin Pract [Internet]. 2012 August 07;120:c179–c184. Available from: https://doi.org/10.1159/000339789

11. Jayaprasad N. Heart Failure in Children. Heart Views [Internet]. 2016 Oct 19;17(3):92-99. Available from: https://dx.doi.org/10.4103%2F1995-705X.192556

12. Philippine Pediatric Society; Pediatric Infectious Disease Society of the Philippines (PH). Interim Guidelines on the Screening, Assessment and Clinical Management of Pediatric Patients with Suspected or Confirmed Coronavirus Disease (COVID-19) Version 4 [Internet]. 2021 Feb 06.

13. Centers for Disease Control and Prevention (US). Pandemic Planning and Scenarios [Internet]. 2021 Mar 19. Available from: https://www.cdc.gov/coronavirus/2019-ncov/hcp/planning-scenarios.html

14. Yuanyuan D, Mo X, Hu Y, et al. Epidemiology of COVID-19 among Children in China. Peds [Internet]. 2021 Jun 01;145(6):e20200702. Available from: https://doi.org/10.1542/peds.2020-0702

15. World Health Organization. Diarrheal Diseases [Internet]. 2017 May 02. Available from: https://www.who.int/news-room/fact-sheets/detail/diarrhoeal-disease

16. World Health Organization. Pneumonia [Internet].2020 November 11. Available from: https://www.who.int/news-room/fact-sheets/detail/pneumonia
17. Götzinger F, Santiago-García B, Noguera-Julián A, et al. COVID-19 in children and adolescents in Europe: a multinational, multicentre cohort study. Lancet Child Adolesc Heal [Internet]. 2020 Jun 05 [cited 2020 Sep 01];4(9):653–661. Available from: https://doi.org/10.1016/S2352-4642(20)30177-2
18. Johansson MA, et al. SARS-CoV-2 Transmission From People Without COVID-19 Symptoms. *JAMA Netw Open* [Internet]. 2021 Jan 07;4(1):e2035057. Available from: https://doi.org/10.1001/jamanetworkopen.2020.35057
19. Abbas M, Nunes T, Martischang R, et al. Nosocomial Transmission and Outbreaks of Coronavirus Disease 2019: the need to protect both patients and healthcare workers. Antimicrob Resist Infect Control [Internet]. 2021 Jan 06;10:7. Available from: https://doi.org/10.1186/s13756-020-00875-7
20. Jing Y, Run-Qian L, Hao-Ran W, et al. Potential influence of COVID-19/ACE2 on the female reproductive system. Mol Hum Reprod [Internet]. 2020 May 04;26:367–73. Available from: https://dx.doi.org/10.1093%2Fmolehr%2Fgaaa030
21. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* [Internet]. 2020 Jan 24 [cited by 2020 Feb 15]; 395(10223):497-506.
Available from: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30183-5/fulltext
22. Faes C, Abrams S, Van Beckhoven D, et al. Time between Symptom Onset, Hospitalisation and Recovery or Death: Statistical Analysis of Belgian COVID-19 Patients. Int J Environ Res Public Health [Internet]. 2020 Oct 17;17(20):7560. Available from:

https://doi.org/10.3390/ijerph17207560

23. Harman K, Verma A, Cook J, et al. Ethnicity and COVID-19 in children with comorbidities. Lancet [Internet]. 2020 May 28 [cited by 2020 Jul 01];4(7):E24-E25. Available from: https://doi.org/10.1016/S2352-4642(20)30167-X
24. Tsankov B, Allaire M, Irvine M, et al. Severe COVID-19 Infection and Pediatric Comorbidities: A Systematic Review and Meta-Analysis. Int J Infect Dis [Internet]. 2020 Nov 20 [cited by 2021 Feb 01].103:246-256. Available from: https://dx.doi.org/10.1016%2Fj.ijid.2020.11.163
25. Liguoro I, Pilotto C, Bonanni M, et al. SARS-CoV-2 infection in children and newborns: a systematic review. Eur J Pediatr [Internet].2020 May 18;179(7):1029. Available from: https://dx.doi.org/10.1007%2Fs00431-020-03684-7
26. Fox S, Vashisht R, Siuba M, et al. Evaluation and management of shock in patients with COVID-19. CCJM [Internet]. 2020 Jul. Available from: https://www.ccjm.org/content/early/2020/07/10/ccjm.87a.ccc052
27. Neumann B, Schmidbauer M, Dimitriadis K, et al. Cerebrospinal fluid findings in COVID-19 patients with neurological symptoms. J Neurol Sci [Internet]. 10 Aug 2020 [cited by 2020 Nov 15].2020;418:117090. Available from: https://dx.doi.org/10.1016%2Fj.jns.2020.117090
28. Asadi-Pooya A. Seizures associated with coronavirus infection. European Journal of Epilepsy [Internet]. 2020 May 11 [cited by 2020 Jul 01].79: 49-52. Available from: https://dx.doi.org/10.1016%2Fj.seizure.2020.05.005
29. Mak P, Chung K, Wong J, et al. Anosmia and Ageusia: Not an Uncommon Presentation of COVID-19 Infection in Children and Adolescents. J Pediatr Infect Dis [Internet]. 2020 Aug 08;39(8):e199-e200. Available from: doi: 10.1097/INF.0000000000002718

30. Dagli H, Ackan O, Peckan S, et al. Uncommon Presentation of COVID-19 in Pediatric Patients: Anosmia. J Pediatr Infect Dis [Internet]. 2021 Feb 18;16(2):80-84. Available from: http://dx.doi.org/10.1055/s-0041-1723974
31. Tian Y, Rong L, Nian W, et al. Review article: gastrointestinal features in COVID-19 and the possibility of fecal transmission. Aliment Pharmacol Ther [Internet]. 2020 Mar 29;51:843–851. Available from: https://doi.org/10.1111/apt.15731
32. Luglio M, Tannuri U, de Carvalho W, et al. COVID-19 and Liver Damage: Narrative Review and Proposed Clinical Protocol for Critically Ill Pediatric Patients. Clinics [Internet]. 2020 Nov 02;75:e2250. Available from: https://doi.org/10.6061/clinics/2020/e2250
33. Verduyn M, Allou N, Gazaille V, et al. Co-infection of dengue and COVID-19: A case report. PLoS Negl Trop Dis [Internet]. 2020 Aug 3;314(8):e0008476. Available from: https://doi.org/10.1371/journal.pntd.0008476
34. Centers for Disease Control and Prevention (US). Is it Dengue or is it COVID-19? 2020 June 24. Available from: https://www.cdc.gov/dengue/healthcare-providers/dengue-or-covid.html
35. Figueredo M, Amancio T, Salvatierra J, et al. COVID-19 and dengue coinfection in Brazil. World J Clin Infect Dis [Internet]. 2020 Oct 28;10(4):51-54. Available from: http://dx.doi.org/10.5495/wjcid.v10.i4.51
36. Bicudo N, Bicudo E, Costa J, et al. Co-infection of SARS-CoV-2 and dengue virus: a clinical challenge. Braz J Infect Dis [Internet].2020 Aug 26;24(5):452-4. Available from: https://doi.org/ 10.1016/j.bjid.2020.07.008
37. Yan G, Lee C, Lam L, et al. Covert COVID-19 and false-positive dengue serology in Singapore. Lancet Infect Dis[Internet]. 2020 March 04 [cited by 01 May 2020];20(5):536. Available

from: https://doi.org/10.1016/S1473-3099(20)30158-4

38. Centers for Disease Control and Prevention (US). Multisystem Inflammatory Syndrome in Children [Internet]. Available from: https://www.cdc.gov/mis-c/cases/index.html
39. Henderson L, Canna S, Friedman K, et al., American College of Rheumatology Clinical Guidance for Multisystem Inflammatory Syndrome in Children Associated with SARS-CoV-2 and Hyperinflammation in Pediatric COVID-19 (Version 2). Arthritis and Rheumatology [Internet]. 2020 Dec 05;73(4):e13-e-29. Available from: https://doi.org/10.1002/art.41616
40. Biswas M, Rahaman S, Biswas T, et al. Association of Sex, Age, and Comorbidities with Mortality in COVID-19 Patients: A Systematic Review and Meta-Analysis. Intervirology [Internet]. 2020 Dec 09;64:36-47. Available from: https://doi.org/10.1159/000512592
41. Harman K, Verma A, Cook J, et al. Ethnicity and COVID-19 in children with comorbidities. Lancet [Internet]. 2020 May 28 [cited by 2020 Jul 01];4(7):E24-E25. Available from: https://doi.org/10.1016/S2352-4642(20)30167-X
42. Tsankov B, Allaire J, Irvine M, et al. Severe COVID-19 Infection and Pediatric Comorbidities: A Systematic Review and Meta-Analysis. Int J Infect Dis [Internet]. 2020 Nov 20 [cited by 2021 Feb];103:246-256. Available from: http://doi.org/10.1016/j.ijid.2020.11.163
43. Shekerdemian L, Mahmood N, Wolfe K, et al. Characteristics and Outcomes of Children with Coronavirus Disease 2019 (COVID-19) Infection Admitted to US and Canadian Pediatric Intensive Care Units. JAMA Pediatr [Internet]. 2020 May 11;174(9):868–873. Available from: https://doi.org/10.1001/jamapediatrics.2020.1948
44. Simonnet A, Chetboun M, Poissy J, et al. High Prevalence of Obesity in

Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) Requiring Invasive Mechanical Ventilation. Obesity [Internet]. 2020 Apr 09;28(7):1195-9. Available from: https://doi.org/10.1002/oby.22831

45. CDC COVID-19 Response Team (US). Coronavirus Disease 2019 in Children — United States, February 12–April 2, 2020. MMWR [Internet]. 2020 Apr 10. 69(14). Available from: https://www.cdc.gov/mmwr/volumes/69/wr/mm6914e4.htm
46. Centers for Disease Control and Prevention (US). Clinical Care Guidance [Internet]. 2021 Feb 16. Available from: https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html
47. Liang Su, Xiang M, Yu H, et al. The different clinical characteristics of corona virus disease cases between children and their families in China – the character of children with COVID-19. Emerging Microbes & Infections [Internet]. 2020 Mar 25;9(1):707-713. Available from: https://dx.doi.org/10.1080%2F22221751.2020.1744483
48. Wu C, Chen X, Cai Y, et al. Risk Factors Associated with Acute Respiratory Distress Syndrome and Death in Patients with Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA Intern Med [Internet]. 2020 Mar 13; 180(7):934. Available from: https://doi.org/10.1001/jamainternmed.2020.0994
49. Shi S, Qin M, Shen B, et al. Association of Cardiac Injury with Mortality in Hospitalized Patients With COVID-19 in Wuhan, China. JAMA Cardiol [Internet]. 2020 Mar 25;5(7):802. Available from: https://doi.org/10.1001/jamacardio.2020.0950
50. Liao D, Zhou F, Luo L, et al. Haematological characteristics and risk factors in the classification and prognosis evaluation of COVID-19: a retrospective cohort study. Lancet Haematol [Internet]. 2020 Jul 10;7(9):e671. Available from:

https://doi.org/10.1016/S2352-3026(20)30217-9

51. Zachariah P, Johnson C, Halabi K, et al. Epidemiology, Clinical Features, and Disease Severity in Patients with Coronavirus Disease 2019 (COVID-19) in a Children's Hospital in New York City, New York. JAMA Pediatr [Internet]. 2020 Jul 10 [cited by 2020 Sep 01];174(10): e202430. Available from: https://doi.org/10.1001/jamapediatrics.2020.2430
52. Kainth M, Goenka P, Williamson K, et al. Early Experience of COVID-19 in a US Children's Hospital. Pediatrics [Internet].2020 Jul 13 [cited by 20 Oct 01];146(4):e2020003186.Available from: https://doi.org/10.1542/peds.2020-003186
53. Del Valle D, Kim-Schulze S, Huang H, et al. An inflammatory cytokine signature predicts COVID-19 severity and survival. Nat Med [Internet]. 2020 Aug 24.;26(10):1636. Available from: https://doi.org/10.1038/s41591-020-1051-9
54. Aljondi R, Alghamdi S. Diagnostic Value of Imaging Modalities for COVID-19: Scoping Review. J Med Internet Res [Internet]. 2020 April 28;22(8):e19673. Available from: https://doi.org/10.2196/19673
55. Foust A, Philipps G, Chu W, et al. International Expert Consensus Statement on Chest Imaging in Pediatric COVID-19 Patient Management: Imaging Findings, Imaging Study Reporting and Imaging Study Recommendations. Radiology: Cardiothoracic Imaging [Internet]. 2020 Apr 23;2(2):e200214. Available from: https://doi.org/10.1148/ryct.2020200214
56. Kumar A, Kubota Y, Chernov M, et al. Potential role of zinc supplementation in prophylaxis and treatment of COVID-19. Med Hypotheses [Internet]. 2020 May 25;144:109848. Available from: https://doi.org/10.1016/j.mehy.2020.109848
57. Murdaca G, Pioggia G. Negrini S. Vitamin D and Covid-19: an update on

evidence and potential therapeutic implications. Clin Mol Allergy [Internet].19 Nov 2020;18:23 Available from: https://doi.org/10.1186/s12948-020-00139-0

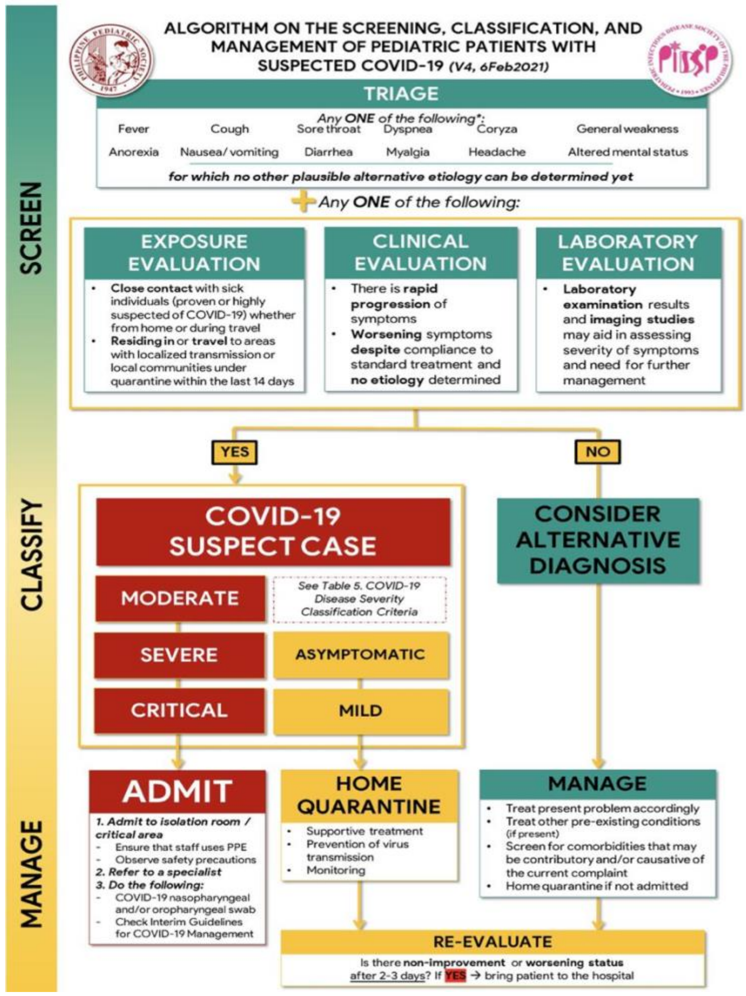
58. Recto M, Tan F, Cuajunco E, et al. A Review of Immunomodulators as Therapeutic Interventions for Moderate to Severe COVID-19 Infection version 3. Philippine Society of Allergy, Asthma and Immunology. 2020 Sep 20.
59. Gautret P, Lagier J, Parola P, et al. Hydroxychloroquine and Azithromycin as a treatment of COVID-19: Results of an Open-Label Non-Randomized Trial. Int Journal Antimicrob Agents [Internet]. 2020 Jul;56(1):1-6 Available from: https://doi.org/10.1016/j.ijantimicag.2020.105949
60. Infectious Disease Society of America (US). Treatment and Management of Patients with COVID-19 [Internet]. 2020 Apr 11. Last updated March 18, 2021. Available from: https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/
61. RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with COVID-19. NEJM [Internet] . 2021 Feb 21;384:693-704. Available from: https://doi.org/10.1056/NEJMoa2021436

PPS PIDSP Classification of COVID-19 Severity[12]

Mild Disease		Symptomatic patients meeting the case definition for COVID-19 without evidence of viral pneumonia or hypoxia
Moderate Disease	**Pneumonia**	Child with clinical signs of non-severe pneumonia (cough or difficulty of breathing + fast breathing and/or chest indrawing) and no signs of severe pneumonia. Fast breathing (in breaths/min): • <2 months: ≥ 60 • 2-11 months: ≥ 50 • 1-5 years: ≥ 40 Adolescent or adult with clinical signs of pneumonia (fever, cough, dyspnea, fast breathing) but no signs of severe pneumonia, including SpO2 ≥ 90% on room air While the diagnosis can be made on clinical grounds, chest imaging (radiograph, CT scan, ultrasound) may assist in diagnosis and identify or exclude pulmonary complications.
Severe disease	**Severe Pneumonia**	Child with clinical signs of pneumonia (cough or difficulty in breathing) + at least one of the following: • Central cyanosis or SpO2 <90%; severe respiratory distress (e.g. Fast breathing, grunting, very severe chest indrawing); general danger sign; inability to breastfeed or drink, lethargy or unconsciousness, or convulsions Fast breathing (in breaths/min): • <2 months: ≥ 60 • 2-11 months: ≥ 50 • 1-5 years: ≥ 40 Adolescent or adult with clinical signs of pneumonia (fever, cough, dyspnea, fast breathing) plus one of the following: respiratory rate >30 breaths/min; severe respiratory distress or SpO2 <90% on room air While the diagnosis can be made on clinical grounds, chest imaging (radiograph, CT scan, ultrasound) may assist in diagnosis and identify or exclude pulmonary complications.
Critical Disease	**Acute Respiratory Distress Syndrome (ARDS)**	**Onset**: within 1 week of a known clinical insult (i.e. pneumonia) or new or worsening respiratory symptoms **Chest imaging:** (radiograph, CT scan, or lung ultrasound): bilateral opacities, not fully explained by volume overload, lobar or lung collapse, or nodules. **Origin of pulmonary infiltrates**: respiratory failure nit fully explained by cardiac failure or fluid overload. Need objective assessment (e.g. ECG) to exclude hydrostatic cause of infiltrate/ edema if no risk factor present **Oxygenation impairment in adolescents/ adults:** a) Mild ARDS: 200 mmHg < PaO2/FiO2 ≤ 300 mmHg (with PEEP or CPAP ≥ 5 cm H2O) b) Moderate ARDS: 100 mmHg < PaO2/FiO2 ≤ 200 mmHg (with PEEP ≥ 5 cm H2O) c) Severe ARDS: PaO2/FiO2 ≤ 100 mmHg (with PEEP ≥ 5 cm H2O)

		Oxygenation impairment in children: note OI and OSI, use OI when available. If PaO2 not available, wean FiO2 to maintain SpO2 $\leq$ 97% to calculate OSI or SpO2/FiO2 ratio: • Bilevel (NIV or CPAP) $\geq$ 5 cm H2O via full face mask: PaO2/FiO2 $\leq$ 300 mmHg or SpO2/FiO2 $\leq$ 264 • Mild ARDS (invasively ventilated) 4 $\leq$ OI < 8 or 5 $\leq$ OSI < 7.5 • Moderate ARDS (invasively ventilated) 8 $\leq$ OI < 16 or 7.5 $\leq$ OSI < 712.3 • Severe ARDS (invasively ventilated): OI $\geq$ 16 or OSI $\geq$ 12.3
Critical Disease	**Sepsis**	**Adolescents/adults:** acute life-threatening organ dysfunction caused by a dysregulated host response to suspected or proven infection. Signs of organ dysfunction include: altered mental status, difficult or fast breathing, low oxygen saturation, reduced urine output, fast heart rate, weak pulse, cold extremities or low blood pressure, skin mottling, laboratory evidence of coagulopathy, thrombocytopenia, acidosis, high lactate or hyperbilirubinemia **Children:** suspected or proven infection and $\geq$ 2 age-based systemic inflammatory response (SIRS) criteria, of which one must be abnormal temperature or white blood cell count
	Septic Shock	**Adolescents/adults:** persistent hypotension despite volume resuscitation, requiring vasopressors to maintain MAP $\geq$ 65 mmHg and serum lactate level > 2 mmol/L **Children:** any hypotension (SBP < 5th percentile or > 2 SD below normal for age) or two or three of the following: altered mental status; bradycardia or tachycardia (HR<90 bpm or >160 bpm in infants and heart rate < 70 bpm or > 150 bpm in children); prolonged capillary refill (2 sec) or weak pulse; fast breathing; mottled or cool skin or petechial or purpuric rash; high lactate; reduced urine output; hyperthermia or hypothermia
	Acute thrombosis	Acute venous thromboembolism (i.e. pulmonary embolism), acute coronary syndrome, acute stroke
	MIS-C	Preliminary case definition: children and adolescents 0-19 years of age with fever > 3 days **AND** two of the following: rash or bilateral non-purulent conjunctivitis or mucocutaneous inflammation signs (oral, hands or feet); hypotension or shock; features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including ECHO findings or elevated troponin/NT-pro BNP); evidence of coagulopathy (by PT, PTT, elevated D-dimers), acute gastrointestinal problems (diarrhea, vomiting or abdominal pain); **AND** elevated markers of inflammation such as ESR, C-reactive protein, or procalcitonin **AND** no other obvious microbial cause of inflammation, including bacterial sepsis, staphylococcal or streptococcal shock syndromes **AND** evidence of COVID-19 (RT-PCR, antigen test or serology positive), or likely contact with patients with COVID-19

Algorithm on the Screening, Classification and Management of Pediatric Patients with Suspected COVID-19[12]



NEUROLOGIC MANIFESTATION OF COVID-19 PEDIATRIC PATIENTS ADMITTED AT THE PHILIPPINE CHILDREN'S MEDICAL CENTER IN THE YEAR 2020: A CASE SERIES[1]

JEMIMA GRACE D. FRONDA, MD, DPPS, TRACY ANNE P. VICTORINO-RIVERA, M.D, DPPS, MELADY D. IMPERIAL-GILBUENA, M.D, DPPS,

MARTHA LU-BOLAÑOS, M.D, FPNA, FCNSP

ABSTRACT

COVID-19 which was first documented in the Philippines in January 2020 had spread alarmingly. Severe acute respiratory symptoms were the most common presentation of this novel coronavirus infection. Reports have described neurologic manifestations of this disease involving the central nervous system as well as the peripheral nervous system. However, studies among the pediatric population are limited. In this paper, we present three pediatric patients who were diagnosed with COVID-19, via RT-PCR, presenting with seizures and behavioral changes. Two of these patients have no concomitant respiratory symptoms while the other one also had Pediatric Community Acquired Pneumonia. These patients were managed as cases of acute viral meningoencephalitis and were given supportive care.

KEYWORDS: Covid-19, Neurologic Manifestations of COVID-19 in children, viral meningoencephalitis

Abbreviations
ACE-2 - *Angiotensin-converting enzyme-2,* COVID-19 - *Coronavirus Disease 19,* CNS - *Central Nervous System,* CSF - *Cerebrospinal fluid,* CT Scan - *Computerized tomography scan,* RT-PCR - *Reverse Transcription-Polymerase Chain Reaction,* SARS-CoV2 - *Severe Acute Respiratory Syndrome-Corona Virus 2,* ER – Emergency Room

INTRODUCTION

Coronavirus disease 2019 (COVID-19) has been declared a worldwide pandemic since March 2020. Also known as the SARS-CoV2, this infectious disease, had been more commonly associated with severe acute respiratory syndrome. Utilizing its mechanisms of entry via the angiotensin-converting enzyme-2 and later, activation of the inflammatory cascade, other non-specific symptoms have also been reported and documented which includes cough, shortness of breath, fatigue and diarrhea. A number of reports have described neurologic manifestations associated with COVID-19 specifically involving the central and peripheral nervous system. Neurologic symptoms most commonly reported were dizziness, headache, impaired consciousness, ataxia, seizures and acute cerebrovascular disease, owing to the neurotropism of the virus[2,4]. Most studies on the neurologic manifestations have primarily included adult subjects with limited reports for the pediatric age group. There is also no published report to date in this institution.

OBJECTIVE

To present the neurologic manifestations of three confirmed COVID-19 cases in the pediatric age group admitted in this institution in the year 2020.

Case 1

This is a 1 year and 7-month-old female, previously at par with age who had intermittent fever 2 days prior to admission with no associated respiratory or gastrointestinal symptoms. She developed generalized tonic-clonic seizures on the second day, with a temperature of 38.8^o. Seizures were recurrent hence was brought for consult at the ER, where she was noted to be irritable with inconsistent regard and stable vital signs. Neurologic examination showed nuchal rigidity and a bilateral Babinski reflex. Initial laboratory results including a complete blood count, electrolyte determination, urinalysis and chest radiograph. While admitted, she remained febrile until the 3rd hospital day with seizure recurrences until the 5th hospital day. Nasopharyngeal RT-PCR swab results came out positive for SARS-CoV2 on the fifth hospital day. Levetiracetam was started and doses were increased to a total of 50mg/kg/day which offered seizure control.

Lumbar puncture with CSF analysis was performed and showed normal results (Table 1). She was noted to have lost previously met developmental milestones, and was discharged with poor head control and no visual tracking. Improvement was noted at two weeks post discharge follow up, and on the 4th week post discharge, she was again able to walk, talk in phrases and feed self with a spoon. Levetiracetam was continued. An EEG was requested as outpatient basis.

Case 2

This is a 10-year-old male, at par with age, who presented with a sudden onset of high grade fever of 40ºC 2 days prior to consult, associated with frontal headache and behavioral changes described as difficulty initiating sleep and disorientation. This was followed by an episode of generalized tonic-clonic seizure, which lasted for less than a minute, after which, he was noted to have no verbal output, regard and no response to name calling, with purposeless fidgeting of clothes. Seizure recurrence of the same semiology prompted consult and subsequent admission at our institution. Examination at the ER showed an agitated patient with stable vital signs, who cannot follow commands with incomprehensible word and eventually needing restraints. Pertinent neurologic findings included a nuchal rigidity, hyperreflexia on bilateral lower extremities with unsustained clonus and positive Babinski. Initial diagnostic tests showed leukocytosis with segmenter predominance, with normal serum electrolyte, urinalysis and chest radiograph. During the course of admission, he remained highly febrile with temperature reaching 41ºC and seizure recurrences. He was started on Levetiracetam at a dose of 20mg/kg which offered seizure control. CSF analysis via lumbar puncture done on the third hospital day showed pleocytosis, all lymphocytes with a slightly low CSF:serum glucose ratio of 49.6% (table 1) and negative cultures. Nasopharyngeal swab of SARS-CoV2 showed a positive result. Neurologic status showed minimal improvement on the 4th hospital day, being able to have spontaneous eye opening but still without regard or verbal output. No seizure recurrences were noted during the rest of admission and he was transferred to a COVID referral institution where a cranial MRI was done, which showed abnormal thalamic intensities and subtle T2/FLAIR hyperintensities in the cortex of the left temporoparietal lobe with gyral enhancement. As of this writing and last follow up, the patient was noted to be discharged from the said institution ambulatory with good regard, but only had minimal verbal output.

Case 3

The only patient in our series with respiratory symptoms, is a 6 month-old male who presented with a 3-day history of cough and fever reaching up to 38ºC associated with recurrent episodes of generalized tonic-clonic seizures, lasting for less than a minute, occurring twice daily at home. This prompted consult at the ER where he was eventually intubated for respiratory distress. A chest radiograph showed bilateral pneumonia. A seizure episode of the same semiology was noted at the ER which lasted for 3 minutes. Intravenous Diazepam at a dose of 0.3mg;kg was given, and he was started on Levetiracetam 20mg/kg/day. Complete blood count and electrolytes determination were all normal but Nasopharyngeal swab for SARS-CoV2 showed a positive result on the 3rd hospital day. While admitted, the patient remained highly febrile and had recurrent episodes of generalized tonic clonic seizures which was poorly controlled despite increased doses of Levetiracetam to 60mg/kg/day. Phenobarbital was then started orally at a dose of 20mg/kg loading dose and maintained at 5mg/kg/day which offered seizure control. However, maculopapular rashes were noted on the subsequent days, leading to discontinuation of Phenobarbital, while maintaining Levetiracetam. Seizures were still controlled. A Cranial CT Scan was done on the 5th hospital day which showed normal results. CSF analysis on the 7th hospital day did not show CSF pleocytosis but had a low CSF:serum ratio of 48% (table 1). CSF Culture studies were all negative, but blood culture results showed growth of *Acinetobacter baumanii*. Appropriate antibiotics were given and he was extubated on the 9th hospital day. He was discharged with a number of neurologic deficits including poor head control, no visual threat, a left central facial palsy and referential movement of the right extremities. He is still due for follow up and diagnostic workup as of this writing.

DISCUSSION

Coronaviruses are large enveloped single- stranded RNA viruses which causes common colds in humans. There are 7 human pathogenic coronaviruses to date, and this SARS-COV2 is the third strain to have caused a global pandemic. The virus has

79.5% similarity with the previous SARS-CoV, which was already proven to cause central nervous system invasion.[2]

COVID-19 infection had its peak in the year 2020 when this series was done. In 2020, during the time of this data collection, there were 395 confirmed pediatric patients with the highest percentages found in the 15-18 years age group (DOH, 2020)[1] and as of June 2021, a total of 37 patients were documented to have presented with neurologic manifestations.

Neurologic manifestations

A number of studies have already postulated how neuronal invasion of SARS-COV2 infection occurs. The virus's spike proteins contain a variable receptor-binding domain (RBD) which allows binding to ACE-2 inhibitors in epithelial cells (Wu et al, 2020) and subsequent entry into the host cells[2] and subsequent neuronal invasion. Entry to the CNS entry occurs retrograde and anterograde neuronal transport from the peripheral nerves or via the olfactory bulb in the nasal cavity [2,3] Pathogenesis of the disease may occur from direct injury to the brain, from hypoxic injury secondary to respiratory symptoms and from ACE-2 immunologic and inflammatory responses, which may lead to infectious encephalopathy, viral encephalitis and cerebrovascular diseases.[2]

Most neurologic manifestations appear early in the disease within 1-2 days.[2,4] The most common neurologic symptoms reported in adult patients were impaired consciousness and acute cardiovascular disease. Infections in children have been observed to have a milder clinical course than adults and asymptomatic infections are more common.[5] Our patients all presented with early onset seizures and impaired consciousness, occurring on the first to second day of illness, prior to the release of a positive COVID PCR result. Only one of our patients also had severe respiratory distress on presentation. Table 1 summarizes the clinical characteristic of these patients.

CSF findings

In patients with SARS-COV-2 CNS infections, complete blood count findings may show leukocytosis with neutrophilic predominance, lower lymphocyte count and thrombocytopenia.[4] This was not consistently observed in our cases. Previous studies have reported patients with neurologic symptoms and a positive CSF RT-PCR SARS-COV-2 but had negative nasopharyngeal swabs which may describe the neuro-invasive potential of the virus in the absence of pulmonary infection.[6] In our series, however, no CSF RT-PCR was done as this was not yet available in our setting at the time of the study. However, all of them revealed positive nasopharyngeal swabs. This is one of the limitations of this study.

Neuroimaging studies

Cranial MRI findings in patients with SARS-COV-2 infection and meningoencephalitis showed diverse findings but hyperintensities along the wall of the inferior horn of the right lateral ventricle in DWI studies, and hyperintense signal changes in the right mesial temporal lobe and hippocampus in FLAIR studies was noted by a study by Murogoshi in 2020.[6] Cranial CT scan may show symmetric hypoattenuation of the bilateral median thalami with normal basilar and proximal posterior cerebral arteries on CT angiogram. 6,8 Only Case 2 had an abnormal MRI finding similar to those previously reported cases. Table 2 summarizes our neuroimaging findings

Management

In COVID positive patients who developed seizures, it is reasonable and necessary to start an antiepileptic drug.[9] According to this study, Levetiracetam is an optimal AED for these patients. Tapering after 6 weeks, then discontinuing after 1-2 weeks is also recommended. Our patients were given appropriate antibiotics as well as Azithromycin and zinc sulfate during their admission. All of our patients were started on Levetiracetam and were maintained on this AED until discharge.

LIMITATIONS OF THE STUDY

Neurodiagnostic procedures were not completed for our patients due to the lack of facilities during the early part of this pandemic. CSF RT-PCR was also not documented for our patients as this test is not available in our institution.

RECOMMENDATIONS

As of this writing, there are no established guidelines for the identification and treatment of COVID-19 CNS infections. Further studies on the neurologic presentation and clinical manifestations of this infection is recommended. A test for CSF

COVID (RT-PCR) which is now readily available will also be beneficial.[11]

REFERENCES:

1. Yan-Chao L, Wan-Zhu Bai, Tsutomu Hashikawa, the neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients
2. Yeshun Wu, Xiaolin Xu, Zijun Chen, Jiahao Duan, et al. Nervous System Involvement after infection with COVID-19 and Other Coronaviruses. (March 2020) Brain, Behavior and Immunity, https://doi.org/10.1016/j.bbi.2020.03.031
3. Xiaoxia Lu et al. SARS-CoV-2 Infection in Children. (April 2020) The New England Journal of Medicine, Volume 382;17; Accessed May 8, 2020
4. Ling M. Huijuan J. Mengdie W. et al. Neurologic Manifestations of Hospitalized Patients with Coronavirus Disease 2019 in Wuhan, China, JAMA Neurology, 2020 Published online: April 10, 2020
5. Li et al. Neuroinvasive potential of SARS-CoV-2 plays a role in the respiratory failure of COVID19 patients. Journal of Medical Virology (Feb 2020)
6. MorugoshiT. HariiN. GotoJ. et al. A first case of meningitis and encephalitis associated with SARS-Coronavirus-2. 2020. International Journal of Infectious Disease. Published online: March 25, 2020
7. Asadi-Pooya AA., Leila Simani, Seizures associated with coronavirus infections. Seizure. 2020 Jul; 79:49-52.
8. Pojadji N. MD, Gassan Shashin MD, Noujaim D., MD et. al. COVID-19-associated Acute Hemorrhagic Necrotizing Encephalopathy: CTand MRI Features. Radiology. https://pubs.rsna.org/doi/10.1148/radiol.2020201187 March 31, 2020
9. Oxley et al. Large Vessel Strokes in the young as a Presenting Feature of COVID-19. The New England Journal of Medicine, 2020 Published online: April 29, 2020
10. Dugue R. Cay-Martinez K. Thakur K et al. Neurologic Manifestions in an Infant with COVID-19 . (2020) Neurology Accessed April 24, 2020
11. 2020. McIntosh K. Coronavirus disease 2019 (COVID-19).. Available at https://www.uptodate.com/contents/coronavirus-disease-2019-covid-19

Table 1. CSF Findings of cases

	CASE 1	CASE 2	CASE 3
Color	Colorless	Colorless	Colorless
Transparency	Clear	Clear	Clear
RBC	3 (100% crenated)	3 (70% crenated)	None
WBC	0	7 (100% lymphocytes)	None
Protein (g/L)	0.1	0.1	0.3
Sugar (mmol/L)	3.87	3.5	2.77
Ratio	57%	49.6%	48%
Culture	Negative	Negative	Negative
HSV 1 and 2	Not done	Negative	Negative
Jap B	Not done	Negative	Negative

Table 2. Neuroimaging Findings of Patients

	Case 1	Case 2	Case 3
Cranial CT scan			Normal
Cranial MRI		Abnormal thalamic intensities and subtle T2/FLAIR hyperintensities in the cortex of the left temporoparietal lobe with gyral enhancement	