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Hora-Melodia M, Tagocon, RA. Clinical Features and Predictors of Post COVID-19 Condition Among Pediatric Patients: A Cross-Sectional Study
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ORIGINAL ARTICLE

CLINICAL FEATURES AND PREDICTORS OF POST COVID-19 CONDITION AMONG PEDIATRIC PATIENTS: A CROSS-SECTIONAL STUDY

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ABSTRACT

Background: Persistent symptoms following SARS-CoV-2 infection have increasingly been reported globally, although currently there are no available local epidemiological data on this. This study aimed to determine the prevalence, common manifestations, and clinical predictors of post COVID-19 condition among the pediatric population.

Methods: A cross-sectional analytical study adapting the ISARIC (International Severe Acute Respiratory and Emerging Infection Consortium) Global COVID 19 – pediatric survey questionnaire was done. There were 356 patients with confirmed SARS-CoV-2 infection (RNA detected by RT-PCR/GeneXpert). Out of the 189 with complete data and who responded, 3 were excluded due to deaths during the acute infection. A total of 186 children aged 0-18 years old were enrolled and children of the same age group having SARS-CoV-2 negative result were included as control in 1:1 ratio. Univariate and multivariate regression analyses were performed to identify variables associated with post COVID-19 symptoms.

Results: The prevalence of post COVID-19 condition was 15%. The most common presenting symptoms during the acute infection were fever and cough, while the common post COVID-19 symptoms included persistent cough (65%), rhinorrhea (55%) and loss of taste (3%). In the univariate analysis, the age group 5-11 years (OR 13.83, p value <0.05) and hospitalization (OR 2.37, p value <0.05) were statistically correlated with persisting symptoms. However, multivariate logistic regression analysis showed that hospitalization (aOR 4.1, p value <0.05) was the only factor significantly associated with the persistence of symptoms.

Conclusion: Children less than 11 years old and male sex have a higher prevalence of persistent symptoms following acute COVID-19 infection. The age group 5-11 years old was identified as a clinical predictor of post COVID-19 condition along with those who were hospitalized.

KEYWORDS: COVID-19, Post COVID-19 condition, long-COVID

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INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified as a novel human pathogen in December 2019 and resulted in a worldwide pandemic. Locally, as of March 31, 2022, the SALVACION Registry, generated by the Pediatric Infectious Disease Society of the Philippines (PIDSP) and the Philippine Pediatric Society (PPS) has recorded 3,221 COVID-19 cases in children with 90.4% of cases that required hospitalization and 36.2% of cases had moderate to critical disease.[1] Research studies of children and adolescents presenting with long-term symptoms after the acute phase of illness have reported a wide range of prevalence estimates from 8-63%.[2-5] With the documented persistent symptoms being diverse and nonspecific.[6-8] Recognizing the limited data and the necessity of a distinct definition, the World Health Organization (WHO) then created a clinical case definition for post COVID-19 condition in children and adolescents (2023, February).[9] The Philippine Academy of Pediatric Pulmonologist also released the first local document on the pulmonary care of children and adolescents with post COVID-19 condition, but local epidemiologic data on children is lacking.

The heightened risk of post COVID-19 condition in children can be a possible basis for strengthening the campaign on immunization. Research studies can assist healthcare professionals in identifying populations at risk and developing evidence-based guidelines for symptom management and further supportive care. This will also enrich the collective knowledge and enable the establishment of surveillance systems to monitor its occurrence and trends in the long run.

It is therefore the objectives of this study to determine the prevalence of post COVID-19 condition among children in Cagayan de Oro City, Philippines and their baseline characteristics and identify the common manifestations and clinico-demographic predictors of post COVID-19 condition.

MATERIALS AND METHODS

Study Design

A cross-sectional analytical study design was employed in this study. The ISARIC (International Severe Acute Respiratory and Emerging Infection Consortium) Global COVID 19 – pediatric survey questionnaire developed by ISARIC COVID-19 follow-up working group (2021, November) was adapted in Visayan dialect and pretested prior to the actual survey. This study was conducted in Cagayan de Oro City, Philippines from May 2023 to July 2023.

Inclusion Criteria

- ***Case Group***: children aged 0-18 years old with confirmed SARS-CoV-2 infection (RNA detected by RT-PCR/GeneXpert) from April 2022-April 2023. All participants were alive at the time of inclusion.
- ***Control Group***: children aged 0-18 years old with SARS-CoV-2 RTPCR negative result (RNA not detected by RT-PCR/GeneXpert) from April 2022-April 2023. All participants were alive at the time of inclusion.

Exclusion Criteria

Those who did not respond to the investigators' calls for a week were excluded. Subjects in the control group who were exposed to a confirmed case of COVID-19 even with a negative RT-PCR/GeneXpert test were also excluded.

Sample size calculation

The total number of identified patients with confirmed SARS-CoV-2 infection from April 2022-April 2023 were 356, sample size was calculated utilizing Danial sample size formula for prevalence with finite population correction:

$$n' = \frac{NZ^2P(1-P)}{d^2(N-1)+Z^2P(1-P)}$$

Where N is the population size, Z is 1.96 for 95% confidence interval, d is the precision at 0.05, P

is the prevalence estimated to be at 66% based on the highest prevalence of post COVID-19 condition reported.[10] From this calculation, the sample size (n) derived was 176 cases.

Data collection

A letter of request was sent to the City Heath Office and Department of Health Region X to access all pertinent data (name, age, sex, birthdate, address, contact numbers, and RT-PCR/GeneXpert result) of children tested with RT-PCR for SARS-CoV2 in Cagayan de Oro City. All the RT-PCR results from both private and government testing centers are reported to CHO and DOH. Upon endorsement for data access, a subsequent data sharing agreement was submitted to the office of the City Mayor. An ordinance was then created which granted access to the data. After the Ethics Board approval, data gathering was then initiated.

A list of pediatric patients who underwent RT-PCR testing was obtained from the City Health Office and Department of Health Region X. Patients were categorized into two groups: SARS-CoV-2 positive (Case group) and SARS-CoV-2 negative (Control group). Patients in each group were assigned a code. An electronic randomizer was used to obtain a recruitment list for the control group (1:1 ratio). The guardian of each patient was contacted and the background of the study was explained. Consent to participate was then obtained. They were contacted between May to July 2023 and the interview was done by the main researcher. Participants aged 12-16 years old were interviewed for assent if parents have already given their consent. Likewise, participants 17-18 years old were interviewed using the questionnaire once consent was secured. A text message was also sent to those who did not respond to the initial call. Those without a message reply within a week were excluded from the study.

The family's monthly income was classified according to Philippine Statistics Authority as follows: poor (less than 12,082 PHP), low-income (12,082-24,154 PHP), lower-middle (24,164-48,328 PHP), middle-middle (48,328-84,574 PHP), upper-middle (84,574-144,984 PHP), upper-income (144,984-241,640 PHP), and rich (above 241,640 PHP). Nutritional status was assessed using World Health Organization's Child Growth Standards (WHO, 2006). Household vaccination status was categorized as complete when all household members were already vaccinated at the time of the index case RT-PCR result date. Incomplete household vaccination status refers to a household with at least 1 member who has not received any COVID-19 vaccine.

Clustering of symptoms refers to any household member having the same signs/symptoms with the index case. In this context, severity of covid infection was categorized as mild for symptomatic patients meeting the case definition for COVID-19 without evidence of pneumonia or hypoxia; moderate COVID infection for symptomatic patients meeting the case definition for COVID-19 with evidence of pneumonia or hypoxia without invasive ventilatory support; and severe COVID infection for symptomatic patients meeting the case definition for COVID-19 with pneumonia or hypoxia given invasive ventilatory support.[11]

The clinical case definition of post COVID-19 condition in children and adolescents include individuals with a history of confirmed or probable SARS-CoV-2 infection, experiencing symptoms lasting at least 2 months which initially occurred within 3 months of acute COVID-19.[9]

Statistical Analysis

Data gathered were processed using a systematized computerization method. Preliminary data tabulation and encoding were done using Microsoft Excel 365. Baseline characteristics with categorical variables were presented in terms of counts and percentages while continuous variables were presented in terms of the mean ± standard deviation. Prevalence was computed using percentages. Chi-square was used to compare categorical variables and t-test for numerical variables. Univariate and multivariate regression analysis were performed using binary stepwise logistic regression with a significance level at 5% to

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identify variables associated with post COVID-19 symptoms.

All valid data were included in the analysis. Missing variables were neither replaced nor estimated. Clinically significant, and variables which give a p-value less than 0.2 in univariable analysis were added to the multivariable model. STATA 15.1 (StataCorp, College Station, Texas, USA) was used for data analysis. Data on co-existing acute and persistent symptoms were presented in UpSet plots.

Ethical Considerations

The study protocol was approved by the Maria Reyna Xavier University Hospital Institutional Review Board prior to the study initiation. Informed and data privacy consent were obtained before enrollment into the study. The respondents were considered eligible to participate only when there was a consent from their parents. Data were obtained through phone interviews and patients were assigned code numbers and names were withheld. Extracted data were treated with utmost confidentiality in accordance with Data Privacy Act. The principal investigator and key personnel have completed the Good Clinical Practice (GCP) training on the responsible conduct of research with human data. The authors have no funding or conflicts of interest to disclose.

RESULTS

A total of 1210 children underwent the SARS-CoV-2 RT-PCR test from April 2022 to April 2023 based on the COVID-19 database of the City Health Office and Department of Health Region X. Of these, 356 patients were confirmed with SARS-CoV-2 infection (RNA detected by RT-PCR/GeneXpert), 39 were excluded due to incomplete data and 128 did not respond to the investigator's call. There were 189 patients who responded but 3 were excluded due to deaths during the acute infection. There were 186 participants included in the analysis (Figure 1).

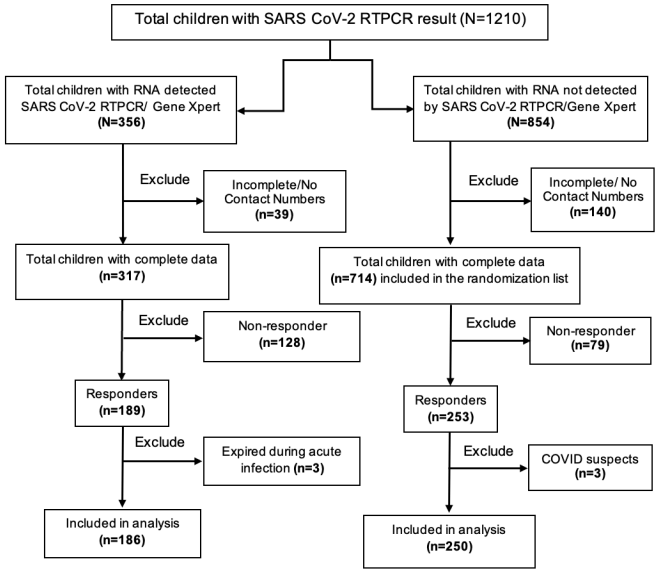

Figure 1: Participant selection process.

On the other hand, there were 854 children with SARS-CoV-2 negative results (RNA not detected by RT-PCR/GeneXpert) from which the control group was assigned. A randomization list was obtained to achieve a 1:1 ratio with the case group. Excluded were 140 children due to incomplete data or with no contact numbers and 79 did not respond to investigator's call. There were 253 patients who responded but 3 were COVID suspects thus were excluded. There were 250 participants included in the analysis (Figure 1).

Sociodemographic variables and health-related information

Among the 186 RT-PCR positive participants, 96 (51.6%) were males and 90 (48.4%) were females with a mean age of 5.9 years old. While in the control group, 131 (52%) were males and with a mean age of 6.3 years old. Nutritional status, vaccination status, and absence of comorbidities were similar for both groups (Table 1).

Significant differences were noted between the groups in terms of the income classification. The control group had a higher percentage of participants belonging to the poor income strata at 52% since inclusive in the study period, government institutions continued requiring routine RT-PCR tests for hospital in-patient care and admittance in correctional and

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child protection agencies. The case group was noted to have significantly higher reported clustering of symptoms within the household which was consistent with COVID-19 infection (Table 1).

Table 1: Sociodemographic data and health characteristics of the participants

Variables	Case (n=186)		Control (n=250)		p-value
Age, mean	5.9		6.3		0.41
	N	%	N	%	
Male	96	51.6	131	52	0.806
Poor-income class	73	39	131	52	<0.001
Clustering of symptoms in the household	108	58	22	8	<0.001
Complete household vaccination status	182	98	237	94.8	0.483
Patient vaccination status					
Unvaccinated	141	75	183	73.2	0.104
1 dose	3	1.6	3	1.2	
2 doses	42	22.5	66	26	
Nutritional status					
Overweight/Obese	5	2.6	3	1.2	0.088
No comorbidities	148	79.6	205	82	0.002

Hospitalization and length of hospital admission were similar for both groups. The case group has a significantly higher reported coryza, fever and sore throat which are consistent with COVID-19 infection (Table 2).

Table 2: Acute Symptoms and Hospitalization Data

Variables	Case (n=186)		Control (n=250)		p-value
	N	%	N	%	
Acute Symptoms					
Asymptomatic	16	8	52	20	0.001
Abdominal pain	2	1	4	1.6	0.099
Diarrhea	10	5	29	11	0.001
Decreased appetite	4	2	9	3	0.001
Vomiting	21	11	36	14	0.001
Cough	92	49	103	41	0.001
Coryza	68	36	63	25	0.001
Fever	126	67	112	44	0.001
Muscle Pain	3	1	0	0	0.089
Rash	3	1	5	2	0.089
Seizure	5	2	6	2	0.001
Headache	8	4	2	0.8	0.099
Loss of taste	7	3	0	0	0.099
Loss of smell	3	1	0	0	0.099
Shortness of breath	21	11	31	12.4	0.001
Sore throat	6	3	2	0.8	0.001
Hospitalization	133	71	190	76	0.24
Length of hospital admission (days) mean, SD	4.1 (±3.5)		4.8 (±4.7)		

Prevalence

The prevalence of post COVID-19 condition was 15% (n=29) out of the 186 participants with RNA detected SARS CoV-2 RT-PCR/GeneXpert. Comparatively, only 1.6% (n=4) of those who had negative SARS CoV-2 RT-PCR/GeneXpert results presented with persistent symptoms (Table 3).

Table 3. Prevalence of Persistent Symptoms

Variables	Case (n=186)		Control (n=250)		p-value
	N	%	N	%	
Persistent Symptoms	29	15	4	1.6	<0.001*
Cough	19	10	2	0.8	
Rhinorrhea	16	8.6	2	0.8	
Loss of Taste	1	0.5		0	

Manifestations

The most predominant post COVID-19 condition was cough (65%), followed by rhinorrhea (55%) and loss of taste (3%). Twenty-four percent had co-existing persistent cough and rhinorrhea. The co-existing acute symptoms are shown in Figure 2a and the co-existing persistent symptoms in Figure 2b.

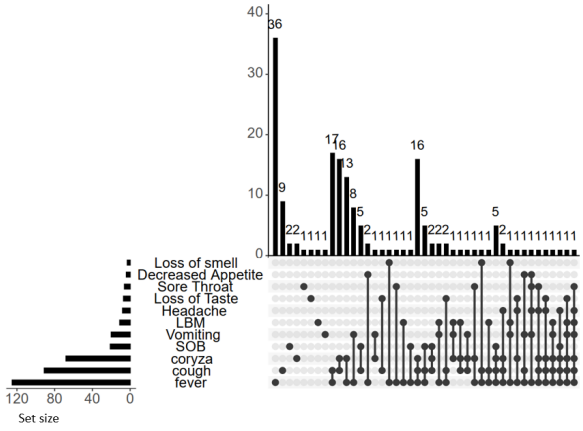

Figure 2a. UpSet plot representing the individual and co-existent acute COVID-19 symptoms

The Y axis represent the number of participants experiencing an individual symptom or combination of symptoms. The X axis represents the specific individual symptom or combination of symptoms. The lines below link multiple reports symptoms, which are indicated by the black circles.

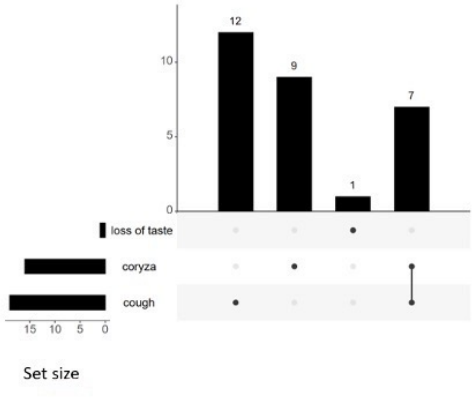

Figure 2b. UpSet plot representing the individual and co-existent persistent symptoms.

The Y axis represent the number of participants experiencing an individual symptom or combination of symptoms. The X axis represents the specific individual symptom or combination of symptoms. The lines below link multiple reports symptoms, which are indicated by the black circles.

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The patients who presented with persisting symptoms (n=29) have a higher male prevalence at 58.6% compared to females at 41.4%. The majority belonged to the age group 2-4 years old (44.8%) and 5-11 years old (34.4%). In terms of severity, 86% had mild acute symptoms. Among the variables included in this study, the univariate analysis showed that the age of 5-11 years old (OR 13.838) and hospitalization (OR 2.37) were associated with post COVID-19 condition. However, multivariate logistic regression analysis revealed that hospitalization (OR 4.104) was the only predictive factor significantly associated with persistent symptoms (Table 4).

Table 4: Clinico-demographic predictors of post-COVID-19 condition

Predictors	With Persistent Symptoms N	%	cOR	Univariate Analysis p-value	aOR	Multivariate Analysis p- value
Age						
0 - 23 months	4	13.8	Reference			
2- 4 years old	13	44.8	7.00	0.071		.824
5-11 years old	10	34.4	13.83	**0.013**	11.9	.053
12-18 years old	2	6.8	2.06	0.62		.145
Sex						
Male	17	58.6	Reference			
Female	12	41.4	0.56	0.412		
Family monthly income						
Poor	10	34.5	Reference			
Low-income class	2	6.9	0.12	0.999		
Lower-middle	1	3.4	0.67	0.999		
Middle-middle	9	31	0.45	0.999		
Upper-middle	5	17.2	0.24	0.999		
Upper income	2	6.9	0.14	0.999		
Vaccination status						
Unvaccinated	25	86.2	Reference			
1 dose	1	3.4	2.7	0.260	1.7	.494
2 doses	3	10.3	4.22	0.116	5.9	.309
Comorbidity						
None	23	80	Reference			
With comorbidity	6	20	0.49	0.961		
Covid Infection Severity						
Mild	25	86.2	Reference			
Moderate	4	13.7	0.07	0.81		
Severe	0	0	0.48	1		
Care Received						
Outpatient	14	48.3	Reference			
Hospitalization	15	51.7	2.37	**0.037**	4.104	**.010**
Oxygen support	4	13.7	0.78	0.644		

DISCUSSION

This study showed that the prevalence rate of post COVID-19 condition was 15% and is similar to the prevalence rates reported in the meta-analyses conducted by Yong-Bo-Zheng et al (ranging from 15% to 26%).[12] Persistent symptoms were only 1.6% (n=4) in the control group and showed statistically significant difference from case group ($p < 0.001$). This finding of higher symptom burden in the case group compared to children in the control group was consistent with the study of Borch et. al.[13] The most common community-acquired infections in the control group were upper respiratory tract infection (19%, n= 48), systemic viral infection (13%, n= 33), dengue fever (10%, n=25), acute gastroenteritis (9%, n=24) and pneumonia (8%, n=20) which corresponded accordingly with the leading causes of morbidity in children.

The two predominant post COVID-19 symptoms seen in this study were cough and rhinorrhea. Similar to the study done by Messiah which reported that congestion or runny nose (41.0%) and cough (35.9%) were the most common persisting symptoms after COVID-19 infection.[14]

All those who presented with persistent symptoms in this study had normal nutritional status and without significant statistical difference in socioeconomic status. These findings were contrary to the findings of Dumont et. al. and Osmanov et. al., that persistent symptoms were associated with older age, lower socioeconomic status, severe acute COVID-19, and obesity.[15,16] The differences in these findings could be attributed to the smaller sample size and a single period assessment used this study. However, a predominance of allergic diseases (n=83%) as comorbid conditions was seen in this study which was congruent to their findings. Five patients had asthma and allergic rhinitis with perceived worsening of previous health conditions.

Furthermore, results showed that 86.2% of patients with persistent symptoms in this study were unvaccinated but there was no noted statistical difference. This finding also contrasts with the results of a meta-analysis by Watanabe et. al. which documented significant lower risks of post COVID-19 condition after vaccination. The differences in results could be due to the small sample size enrolled in this study and the a portion of study population being ineligible for COVID-19 vaccination.

Clinical predictors identified in the univariate analysis showed that post COVID-19 condition was commonly observed between the two age groups 2-4 and 5-11 years old and in those hospitalized participants. However, our results of multivariate logistic regression analysis revealed that hospitalization (OR 4.104) was the only factor significantly associated with the persistence of

symptoms. Hospitalization was also identified as a predictor of post COVID-19 condition in the study of Morello et. al.[18] However, this does not correlate with severity of the acute infection since 86% of those who had persistent symptoms had a mild acute infection.

Although this study utilized a validated questionnaire, it was important to consider the possibility of recall bias given that participants were required to recall symptoms over a 12-month time frame. Furthermore, this study mainly relied on responses coming from participants which may be influenced by their different personal experiences as well as unawareness of certain symptoms of their children who had COVID-19 infection.

CONCLUSION

The prevalence rate of post COVID-19 condition was 15%. Persistent rhinorrhea and cough were the common manifestations. The age group 5-11 years old was identified as a predictor of post COVID-19 condition along with those who required hospital in-patient care.

RECOMMENDATION

We recommend a longitudinal cohort design be done on a larger population to clearly understand the trajectory of the varied symptoms and the clinical predictors of post-COVID condition. A matched cohort is recommended to reduce variance.

CONFLICT OF INTEREST

None declared.

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