Journal of Health and Medical Sciences

Almawazini, A., Alghamdi, A. O., Alnashi, S., Ahmed, M. S. A. S., Alsharkawy, A., Hassan, C. I., Alghamdi, M. A., Alshumrani, K. M., Yahiya, A., Jaman, M., Nakhali, A., Alghamdi, O., Alghamdi, E., Zahrani, M. Almawazini, H., Almawazini, M., Alshumrani, M., Ata, T. Madco, M., PayonGa, A., & Kundoly, T. (2022), Review of COVID-19 in Children Admitted to King Fahad Hospital, Albaha, Saudi Arabia in 2020. *Journal of Health and Medical Sciences*, 5(1), 18-23.

ISSN 2622-7258

DOI: 10.31014/aior.1994.05.01.203

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The Asian Institute of Research
Journal of Health and Medical Sciences
Vol.5, No.1, 2022: 18-23
ISSN 2622-7258

DOI: 10.31014/aior.1994.05.01.203

Review of COVID-19 in Children Admitted to King Fahad Hospital, Albaha, Saudi Arabia in 2020

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Abstract
Background: The coronavirus disease (COVID-19) is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It was first identified at the end of 2019 in Wuhan City, China and then spread worldwide. Objectives: The study aimed to evaluate COVID-19 symptoms, signs, management, and outcomes in admitted children. Methods: This retrospective cohort study was conducted at King Fahad Hospital, Albaha, Saudi Arabia, which is designated as the center for COVID-19 patients. Data were collected retrospectively between Apr 2020 and Mar 2021. The protocols of health authorities in Saudi Arabia were used for the diagnosis and management of all patients. Results: Positive test results were confirmed in 95 patients. Of these, 44 (46%) were males and 51 (54%) were females. Fever, cough, nasal congestion, sore throat, myalgia, and upper respiratory tract infections were the most common symptoms. The common comorbidities in this cohort were respiratory diseases (19%), type1 diabetes mellitus (16%), followed by obesity (11%), chronic kidney disease (4%), congenital heart diseases (2%), while in (48%) pts no comorbidity factors were reported. Fever was the most frequent symptom, reported in 95% of patients. Multisystem inflammatory syndrome (MIS-C) has been reported in one patient. Guillain-Barre syndrome was reported in one female patient and Kawasaki symptoms in one male patient. No mortality was reported. Conclusion: Most children with COVID-19 presented with mild clinical manifestations and good outcomes. No mortality was reported in this study. Obesity is a serious comorbidity and risk factor for severe diseases.

Keywords: COVID-19, SARS-CoV-2

Abbreviations: URT; upper respiratory tract. GIT; gastrointestinal tract. PICU; pediatric intensive care unit. KFH; King Fahad Hospital. BMI; body mass index. IVIG; Intravenous immunoglobulin. CKD; chronic kidney disease. SD; standard deviation. P value; probability of chance. COVID; coronavirus disease.

Introduction

The coronavirus disease (COVID-19) is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [Li Q et al, 2020, Castagnoli R, et al 2020]. It was started and identified at the end of 2019 in Wuhan city, China, and then spread all over the world [Bi Q et al 2020]. World Health Organization (WHO) declared COVID-19 as a pandemic disease in March 2020 [WHO media briefing on COVID-19, 2020, WHO Living guidance,2021]. Prevalence of disease differs among countries [AAP, Post-COVID-19 conditions 2019]. American Academy of Pediatrics provides that children have same risk of infection as the adult but present with mild clinical manifestations [Shekerdemian LS et al, 2019, Zimmermann P et al 2020]. Upper respiratory tract infection, fever, cough, and rhinorrhea are the common presentation signs, while nausea, vomiting, and diarrhea are reported as first symptoms in some cases. Loss of the sense of taste and loss of smell can be seen in children, and its incidence increases with increasing age in children [Dong Y et al, 2019, Timothy G et al 2021]. No significant differences have been reported between male and female children [Timothy G al 2021, De Lusignan S et al 2020]. Children can have COVID-19 through close contact with positive family members and with other students in the school [Sophia T, Ekaterini S 2021, Zhang JJY et al 2020, Li F et al, 2021, Brandon MH et al 2020]. Some laboratory changes reported in some cases include: Lymphocytosis, lymphopenia, neutropenia, high liver and muscle enzymes, increased lactate dehydrogenase, elevated C-reactive protein (CRP) level, elevated erythrocyte sedimentation rate, and elevated D-dimer [Chen W et al 2020, Mehra MR et al 2020]. Supportive care and oxygen supply were the main therapies in children with hypoxia. Remdesivir was the first antiviral gent, approved by FDA for treatment of COVID-19 used in the treatment of hospitalized patients. Remdesivir and hydroxychloroquine, both with and without azithromycin, tocilizumab, and convalescent plasma, were used as therapeutic options in children with severe disease course in a North American study [Mehra M et al 2020, Shen KL et al, 2020]. Corticosteroids and IVIG improve survival in severe cases. Saudi Arabia was among the first countries to implement early and unprecedented precautionary measures to prevent COVID-19 before reporting the first case in the country on March 2nd, 2020 (Algaissi AA et all, WMA Declaration of Helsinki 2013).

Objective

This study aimed to evaluate COVID-19 symptoms, signs, diagnostic tests, management, and outcome in admitted children.

Methodology

This retrospective cohort study was conducted at King Fahad Hospital, Albaha, Saudi Arabia, which is designated as the center for accepting and managing the patients who had positive COVID-19. Data were retrospectively collected between April 2020 and March 2021. The protocols of the health authorities in Saudi Arabia were applied for diagnosis, admission, and management [Algaissi AA et all, WMA Declaration of Helsinki 2013]. A nasopharyngeal swab PCR was performed to confirm the disease (table1). The patient was admitted to the hospital if his score was ≥ 4, isolated, and started on management until his swab result ready. Management was initiated for all admitted patients and modified according to swab results. Positive patients were admitted to isolated COVID words for 14 days and managed by a corona team. Three negative swab results obtained 24 hours apart were requested before discharge. All included children were aged 1–14 years and had a positive corona test. Presence of fever, cough, and shortness of breath, sore throat, rhinorrhea, headache, diarrhea, and vomiting were the important signs checked. Contact with confirmed cases or a history of travel abroad in the last 14 days prior to symptom onset were considered exposure risks for acute respiratory illnesses. Chronic obstructive lung disease, chronic renal failure, coronary artery disease, heart failure, immunocompromised patients, bronchial asthma, diabetes, and obesity were considered comorbidity risk factors. Mild cases received supportive and symptomatic treatment, while corticosteroids, prophylactic dose of

enoxaparin, and antiviral medications were started for ten days when patient developed hypoxia and pneumonia. Statistical significance was calculated by SPSS version 23.0. P-value was considered significant if equal or less than 0.05. The study was approved by the scientific research committee and King Fahad Hospital Albaha Institutional Review Board. Patient privacy was ensured. The principles of the Helsinki Declaration were respected in this cohort [WMA Declaration of Helsinki 2013]. The authors declared that they had no funding and no conflicts of interest.

Table1: Saudi Ministry of health protocol for COVI-19, march 2020.

Risks of acute respiratory illnesses	score	score
1. Exposure risks:	pediatric	adult
• History of travel abroad	3	3
• Contact with confirmed case COVID-19	3	3
• Working in health care facility	3	3
• Exposure to camel's product	3	3
2. clinical symptoms and signs:	score	score
• Fever.	4	4
• Cough.	4	4
• Shortness of breath	4	4
• Headache, sore throat, or rhinorrhea.	1	1
• Nausea, vomiting, or diarrhea.	1	1
• Chronic renal failure.	.	1
• CAD.	.	1
• Heart failure.	.	1
• Immunocompromised.	.	1
Admission if score 4 and more, do nasopharyngeal swab. Isolation 14 days for positive test. Discharge after three negative tests with 24 hours apart.		

Results

Due to strict measures in Saudi Arabia applied on Mar 2020 to limit spread of disease, total of 350 children were admitted with score ≥ 4 and symptoms and signs of suspected COVID-19. The mean age was 7 years (SD 2.57), P = 0.006; positive test confirmed in 95 patients (27%), 44 (46%) were male, and 51(54%) were female. Fever was the most frequent symptom, reported in 95% of patients. Other symptoms frequently reported were cough (58%), rhinorrhea or nasal congestion (67%), myalgias (17%), fatigue (12%), sore throat (32%), and dyspnea (26%). The median duration of cough was 5-7 days. Headache was the common neurological symptom reported in 35% of patients. Diarrhea was observed in 37% of the patients. The presenting vital signs showed a median heart rate of 92 bpm and median temperature of 38.5 °C. The duration of admission was 14 days. Patients were admitted to the pediatric corona ward. Six patients 6% were admitted to the pediatric intensive care unit (PICU). The most common comorbidities in this cohort were respiratory diseases reported in 18 (19%) p=0.16, Type1 diabetes mellitus was reported in 15 (16%) patients p=0.18. Obesity was reported in 10 (11%) patients with high BMI (95% CI [1.3-2.1], (P = 0.21). Chronic kidney disease (CKD) in 4 (4%) patients (P = 0.24). Congenital heart diseases reported in 2 (2%) patients p= 0.33. No comorbidities reported in others 46 (48%) patients (table2). Multisystem inflammatory syndrome in children (MIS-C) was diagnosed in one male patient, who had severe pneumonia associated with liver and kidney impairment. This patient was critically ill and was managed in the PICU. Severe bilateral pneumonia was diagnosed in one obese patient with BMI was (>35). Guillain Barre` Syndrome developed in 4 year old girl. The condition started with cough and fever, and contact to parents positive COVID, in the second day after URTI symptoms, she developed inability to walk and ascending paralysis, COVID test came positive and the patient was diagnosed as GBS, axonal type by nerve conduction velocity, with quadriparesis. Power in the lower limbs was 2–3 and power in the upper limbs was 3–4, with absent reflexes in all limbs, given three courses of IVIG, followed by nine months of oral prednisolone, and extensive physiotherapy with a very good response and minimal residual weakness in the proximal muscles of the lower limbs. Two patients had high levels of pancreatic enzymes. No gastrointestinal bleeding was reported.

Kawasaki-like disease was confirmed in one patient with persistent fever, skin rash, conjunctivitis, and coronary artery ectasia confirmed by echocardiography. Diarrhea**,** vomiting, and abdominal pain without respiratory symptoms were observed in 9 (9%) patients. The overall mortality calculated zero in this cohort. Elevated leukocyte levels (35%), erythrocyte sedimentation rates (25%), and C - reactive protein levels (21%), lactate dehydrogenase levels (19%), neutropenia (2%), lymphopenia (8%), and lymphocytosis (30%) were observed. Kidney dysfunction has been reported in two severely ill children. The highest number of positive patients reported in May, Jun, and Jul 2020, (table3).

Table 2: Common symptoms, signs, and comorbidity in positive test pts

Findings	95 pts	Percent	Male	Female	P value
Fever	90	95%	42	48	0.04
Cough	55	58%	27	28	0.06
Dyspnea	25	26%	11	14	0.15
Rhinorrhea	64	67%	31	33	0.05
Sore throat	30	32%	16	14	0.12
Headache	33	35%	15	18	0.13
Vomiting	15	16%	8	7	0.18
Diarrhea	35	37%	18	17	0.07
No smell	5	5%	2	3	0.22
No taste	3	3%	1	2	0.31
Respiratory	18	19%	10	8	0.16
Type1 DM	15	16%	9	6	0.18
Obese	10	11%	6	4	0.21
CKD	4	4%	1	3	0.24
CHD	2	2%	1	1	0.33

Table 3: Distribution of positive cases per month

Months	**suspected**	**positive**	**%**
Apr 20	30	6	20%
May20	60	24	40%
Jun20	64	26	41%
Jul20	40	11	28%
Aug20	30	8	27%
Sep20	30	5	17%
Oct20	30	4	13%
Nov20	13	1	8%
Dec20	12	3	25%
Jan21	16	4	25%
Feb21	15	2	13%
Mar21	10	1	10%

Discussion

The health authorities in Saudi Arabia immediately applied clear protocols for COVID-19 and implemented strict measures to limit and manage the spread of disease on March 2020 and modified it upon the situation of the disease. Consistent with other published studies, this cohort revealed that history of previous respiratory diseases, diabetes mellitus type1, and obesity were the most common comorbidities associated with severe cases on positive COVI-19 reported in admitted children, and obesity reported more common in male children [Zhang JJY et al 2020, Li F et al, 2021, Brandon MH et al 2020]. Fever, cough, dyspnea, rhinorrhea, chills, upper respiratory tract infection, myalgia, fatigue, and sore throat were the most common symptoms on presentation [Dong Y et al, 2019, Timothy G al 2021]. Gastrointestinal symptoms, myalgia, were reported less common. These results are consistent with WHO findings and other international studies [Li Q et al, 2020, Castagnoli R,

et al 2020, Bi Q et al 2020]. Our cohort reported a zero mortality rate, compared with worldwide COVID-19 mortality was 6.9%, US mortality 3.8%, Spain 10.2%, Italy 12.8% and China 4.0% [7-8-10]. This is the first study in Albaha area focused on the epidemiology, clinical presentation, and management strategies of children with COVID-19. Among the children evaluated for suspected COVID-19, 28% were confirmed to have COVID-19. 98.6% had a history of exposure to infected family members. We observed that most children were asymptomatic or had a mild disease course, and there was no significant difference between affected girls and boys with COVID-19, as reported in other studies (Shekerdemian LS et al, 2019, Zimmermann P, Curtis N 2020, Dong Y et al, 2019). Regarding our protocol, the hospital admission for positive patients was 14 days (Algaissi AA et all, 202, WMA Declaration of Helsinki 2013). In our cohort, 75% of the patients had mild symptoms. The detection of asymptomatic children was important to decrease the transmission process [Bi Q et al 2020, Sophia T, Ekaterini S 2021]. International studies have confirmed that severe illness is far less frequent in children than in adults (Bi Q et al 2020, WHO media briefing on COVID-19, 2020). Only six patients (6%) were admitted to the PICU. Radiological imaging was not routinely performed in children with suspected or confirmed COVID-19 (Chen W et al, 2020, Mehra MR et al 2020). Leukopenia was considered a predictor of a severe disease course in children because it was detected in critically ill children, while normal laboratory workup was reported in asymptomatic and mild cases (Timothy G al 2021, Li F et al, 2021, Brandon MH et all 2020). MIS-c was reported in one critical patient in our study. Favipiravir, intravenous immunoglobulin (IVIG), hydroxychloroquine, and corticosteroid were used as therapeutic options in children with severe disease courses consisting of international studies. We believe that supportive care in pediatric cases remains the main therapeutic option, as reported in the literature (De Lusignan S et al 2020, Mehra M et al 2020, Shen KL et al, 2020].

Limitations

The short follow-up period and retrospective review of affected children were considered limitations of this cohort. More research needs to be done on optimizing the treatment and outcome of COVID-19 in children.

Conclusion

This cohort study reported that the clinical presentation was mild with good outcomes in children admitted with positive COVID-19. Highly negative swab test results have been reported for suspected cases. The overall mortality rate of the admitted children was zero. The study revealed that age, sex, did not affect the occurrence of hospital course of the patients. Obesity is a major comorbidity in critically ill patients. More research is needed to optimize the treatment and outcome of COVID-19, especially after the widespread application of the corona vaccine in Saudi Arabia.

References

Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, et al. Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus-Infected Pneumonia. N Engl J Med, 2020 Mar 26;382(13):1199-1207. doi: 10.1056/ NEJMoa 2001316. Epub 2020 Jan 29.

Riccardo Castagnoli, MD; Martina Votto, MD; Amelia Licari, MD; Ilaria Brambilla, MD, PhD; Raffaele Bruno, MD; Stefano Perlini, MD; Francesca Rovida, PhD; Fausto Baldanti, MD; Gian Luigi Marseglia, MD. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection in Children and Adolescents A Systematic Review.JAMA Pediatr. 2020; 174(9):882-889. Doi: 10.1001/jama pediatrics.2020.1467 published online April 22, 2020].

Bi Q, Wu Y, Mei S, et al. Epidemiology and transmission of COVID-19 in Shenzhen China: analysis of 391 cases and 1,286 of their close contacts. Preprint. Posted online March 27, 2020. medRxiv. doi:10.1101/2020.03.03.20028423].

World Health Organization (WHO). WHO Director-General's opening remarks at the media briefing on COVID-19, 11 March 2020. Available at: https: //www.who.int/ dg/ speeches / detail/ who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19,11-march-2020 (Accessed on May 01, 2020).

World Health Organization. COVID-19 clinical management. Living guidance. World Health Organization 2021. This work is available under the CC BY-NC-SA 3.0 IGO licence. WHO reference number:

WHO/2019-nCoV/clinical/2021.1 Lancet Child Adolesc Health, 2020 Sep;4(9):653-661. doi: 10.1016/S2352 -4642 (20) 30177-2. Epub 2020 Jun 25.

American Academy of Pediatrics. Post-COVID-19 conditions in children and adolescents. AAP. Available at https://services.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/clinical-guidance/post-covid-19-conditions-in-children-and-adolescents/.

R Shekerdemian LS, Mahmood NR, Wolfe KK, Riggs BJ, Ross CE, McKiernan CA, 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,doi:10.1001/jamapediatrics.2020.1948. [PubMed].

Zimmermann P, Curtis N. Coronavirus Infections in Children Including COVID-19. An Overview of the Epidemiology, Clinical Features, Diagnosis, Treatment and Prevention Options in Children. Pediatr Infect DisJ. 2020 May;39(5):355-368. doi: 10.1097/INF.0000000000002660.

Dong Y, Mo X, Hu Y, Qi X, Jiang F, Jiang Z, et al. Epidemiological Characteristics of 2143 Pediatric Patients With 2019 Coronavirus Disease in China. Pediatrics doi: 10.1542/peds.2020-0702. [Internet]

Timothy G.Singer MD, MS. Karen D. Evankovich PhD. Kristen Fisher DO. Gail J.Demmler-Harrison MD. Sarah R. Risen MD. Coronavirus Infections in the Nervous System of Children: A Scoping Review Making the Case for Long-Term Neurodevelopmental Surveillance, https://doi.org/10.1016/j. pediatrneurol. 2021.01.007.

De Lusignan S, Dorward J, Correa A, et al. Risk factors for SARS-CoV-2 among patients in the Oxford Royal College of General Practitioners Research and Surveillance Centre primary care network: a cross-sectional study. Lancet Infect Dis j. 2020 Sep;20(9):1034-1042. doi: 10.1016/S1473-3099(20)30371-6. Epub 2020 May 15

Sophia Tsabouri, MD, PhD. Ekaterini Siomou, MD, PhD. Risk Factors for Severity in Children with Coronavirus Disease 2019, A Comprehensive Literature Review. Published:July 30, 2020 DOI:https:// doi.org/10.1016/j. pcl.2020.07.014. Review article, P321-338, Feb 01, 2021.

Zhang JJY, Lee KS, Ang LW, Leo YS, Young BE. Risk Factors of Severe Disease and Efficacy of Treatment in Patients Infected with COVID-19: A Systematic Review, Meta-Analysis and Meta-Regression Analysis. Clin Infect Dis 2020. doi: 10.1093/cid/ ciaa576 [Epub ahead of print]. [Internet] [PMC free article] [PubMed]

Li F, Li YY, Liu MJ, et al. Household transmission of SARS-CoV-2 and risk factors for susceptibility and infectivity in Wuhan: a retrospective observational study. Lancet Infect Dis 2021 May;21(5):617-628. doi: 10.1016/S1473-3099(20)30981-6. Epub 2021 Jan 18.

Brandon Michael Henry, Giuseppe Lippi and Mario Plebani. Laboratory abnormalities in children with novel coronavirus disease 2019, from the journal Clinical Chemistry and Laboratory Medicine (CCLM). https://doi.org/10.1515/cclm-2020-0272. Published by De Gruyter March 16, 2020.

Chen W, Zheng KI, Liu S, Yan Z, Xu C, Qiao Z. Plasma CRP level is positively associated with the severity of COVID-19. Ann Clin Microbiol Antimicrob, 2020 May 15;19(1):18. doi: 10.1186/s12941-020-00362-2.

Mehra MR, Desai SS, Kuy S, Henry TD, Patel AN. Cardiovascular Disease, Drug Therapy, and Mortality in Covid-19. june 18, N Engl J Med 2020; 382:e102.DOI: 10.1056/NEJMoa2007621

Mehra M, Desai SS, Ruschitzka F, Patel AN. Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis. Lancet 2020 Jun doi: 10.1016/S0140-6736(20)31324-6. [Internet] [PMC free article] [PubMed].

Shen KL, Yang YH, Jiang RM, Wang TY, Zhao DC, Jiang Y, et al. Updated diagnosis, treatment and prevention of COVID-19 in children: experts' consensus statement (condensed version of the second edition). World J Pediatr, 2020 Jun;16(3):232-239. doi: 10.1007/s12519-020-00362-4.

Abdullah A.Algaissi, Naif Khalaf Alharbi, Mazen Hassanain, Anwar M.Hashem. Preparedness and response to COVID-19 in Saudi Arabia: Building on MERS experience. J Infect Public Health, 2020 Jun;13(6):834-838. doi: 10.1016/j. jiph. 2020.04.016. Epub 2020 May 11.

WMA Declaration of Helsinki, ethical principles for medical research involving human subjects. Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and amended by the: 29th WMA General Assembly, Tokyo, Japan, October 1975. 35th WMA General Assembly, Venice, Italy, October 1983. 41st WMA General Assembly, Hong Kong, September 1989. 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996. 52nd WMA General Assembly, Edinburgh, Scotland,October2000, 53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added). 55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added). 59th WMA General Assembly, Seoul, Republic of Korea,October,2008 64th WMA General Assembly, Fortaleza, Brazil, October 2013. https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/