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Systematic Reviews

Clinical and Demographic Characteristics of COVID - 2019 in Asian Pediatric Population – A Systematic Review

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Abstract

Background: Data on demographics, clinical presentation and outcome of COVID-19 in children is increasing day by day. Studies done in Europe states infected children develop less severe disease with a low case fatality rate, no such review is available from Asia.

Methods: Adhering to the PRISMA (Preferred reporting items for systematic reviews and meta-analyses) guidelines a systemic review of the literature was performed looking for clinical characteristics of COVID-19 in the Asian pediatric population searching (PUBMED, SCOPUS, MEDLINE, and WHO -19 databases) from 01 January 2020 to 15 September 2020 to find any relevant article with medical subject headings (MeSH) terms like COVID-19, clinical characteristics, children, Asia, demography, outcome, management were used in different combinations.

Results: We identified 26 case series across Asian countries consisting of 1664 pediatric patients. Asymptomatic children were 14.9 %. Fever 45.65 % and cough 32.62% were the most common symptoms. Contact history with confirmed COVID-19 positive children was 70.21%. Respiratory coinfection and other co morbidities were present in was present at 36.49 % and 14.09 % children respectively. Abnormal x-ray was observed in 52.1% children and ground-glass opacity were seen among 43.71% of abnormal CT scans. Abnormal laboratory data noted were leucocyte and lymphocytes count, C-reactive protein (CRP), Lactate dehydrogenase (LDH) and Procalcitonin. One death from COVID-19 was reported from our review.

Conclusion: Children mostly acquired infection from adults, the course of the disease is usually milder, they have a good prognosis even with associated respiratory infections and co morbidities, and mortality rate is almost nil from Asia due to COVID -19 in our review.

Key words: Asia, Children, COVID-19, SARS-CoV-2

Introduction

After 100 years of the great influenza pandemic, the world is again witnessing an outbreak of unusual respiratory ailment presenting with severe pneumonia since December 2019, originating from the epicenter Wuhan (Hubei province of China) [1]. The virus identified as a novel RNA virus was named as novel coronavirus 2019 (nCov-19) by World Health Organization (WHO) on 7 January 2020, and the disease-associated was labeled as coronavirus disease 2019 (COVID-19). Soon this disease rapidly escalated to other parts of the world resulting in a pandemic. Later on, the International committee taxonomy of viruses renamed it as a severe acute respiratory syndrome coronavirus (SARS-CoV-2) [2]. Till 15th September 2020 a total of 29,119,433 COVID-19 confirmed cases, and 925,965 COVID-19 related deaths worldwide were reported by WHO, whereas by the same date 81, 88,745 cases and 152695 deaths were confirmed by WHO from Asia. [3] Mode of transmission of novel coronavirus -2019 is through respiratory droplets and it potentially uses angiotensin-converting enzyme (ACE) - 2 receptors to cause infection in humans [4]. The incubation period ranges from 0-24 days with a mean around 5 days [5, 6]. Various studies reported the presentation of this infection as fever, dry cough, fatigue, and dyspnea [7, 8]. Children are as vulnerable

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as any other age group to coronavirus infection and they frequently act as carriers to infect other adults [9].

From the onset of the pandemic till now information on the prevalence of COVID-19 infection in children is increasing day by day and various systematic reviews are present in the database now on pediatric COVID-19 population [10,11,12,43,44]. Published data suggests that children with COVID-19 infection have a milder course of the disease compared to adults [11, 12].

Overall the infectivity rate (i.e. number of cases per million population) and case fatality rate are low in Asian countries as compared to other countries [13]. Studies show that a smaller proportion of European COVID-19 infected children develop severe disease with a low case fatality [14].

With extensive search of literature no such review is available from Asian countries. Therefore, the clinical presentation, management and outcomes of COVID-19 in pediatric population has been studied extensively from Asia.

Study Rationale

Data regarding the demography and clinical course of COVID-19 infection in Asian pediatric population and its outcomes e.g. case fatality rate, need of intensive care unit admission, need for non-invasive ventilation or invasive ventilation is scanty. We therefore wish to do the systematic review of the articles containing data of demography & clinical characteristics and to analyze their outcomes with focus on the pediatric population belonging to Asia

Methods

Protocol and Registration

Our study protocol was registered with PROSPERO under registration number CRD42020208284 and conducted according to the guidelines established by Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) and it was used as a basis for reporting our systematic review of clinical characteristics of COVID-19 in the Asian pediatric population

Eligibility Criteria

Eligibility criteria was set to include all articles reporting pediatric cases of confirmed COVID-19 infection published between 1st January 2020 to 15 September 2020 from Asian countries. The pediatric population included neonates, infants and children up to 18 years of age. We excluded experimental studies, case reports, animal studies and case series other than the Asian pediatric population as well as unconfirmed or pending report of COVID-19. Intial search was done without any language restriction. Two independent reviewers' cross checked data retrieved from each article.

Source of Information and Our Search Strategy

An extensive search of literature using PUBMED, SCOPUS, MEDLINE, and WHO -19 databases from 01 January 2020 to 15 September 2020 was done. The medical subject headings (MeSH) terms used included "COVID-19", "coronavirus", "SARS-CoV-2", "children", "pediatric", "neonate", "infant", "Asia", "demography", "outcome", "management", "clinical characteristics". These MeSH terms were used in different combinations. The primary search strategy was ("COVID-19" OR "coronavirus" OR "SARS-CoV-2") AND ("infant" OR "children" OR "pediatrics" OR "neonates") AND "demography" AND "clinical characteristics" AND "outcome" AND "management" AND "Asia". Boolean AND was used as operator in between different names of Asian countries. Reference lists of selected studies were also screened to retrieve relevant data.

Data Extraction and Analysis

The specific variables extracted and analyzed from the publications included: study design, country of study, age of participants, month and year of study, method of data collection, method of diagnosis of COVID-19, clinical presentation, any medical co-morbidity, respiratory co-infections, laboratory results, radiological tests, management, need for pediatric intensive care unit / non-invasive or invasive ventilation, duration of illness and final outcomes. Focus was on data related to confirm COVID-19 pediatric patients only, leaving apart suspected cases. Independent reviewers checked retrieved data and any disagreement resolved by strict inclusion/exclusion criteria and general consensus of all reviewers. Retrieved data was expressed in tabulated form in the spreadsheet of Microsoft excel. Conclusion of data in terms of percentages and actual numbers was separately drawn on a separate conclusion table.

Quality Assessment

The risk of bias assessment was appraised through the quality assessment tool published by National Institute of Health (NIH) [15]. Since development of NIH assessment tool was conducted by researchers in the Agency for Healthcare Research and Quality Evidence - Based Practice Centers, the Cochrane Collaboration, the United States Preventive Service task force, the Scotish Intercollegiate Guideline Network, the National Health Service Center for Review and Dissemination, we decided to utilize this tool for assessing risk of bias. One additional reason for using this tool was that it has been given preference in a systematic review of bias assessment used in PROSPERO registered protocol [16].

Results

At the end of the study analysis, twenty-six case series were eligible for inclusion in the final analysis. [17-42] Of the included studies, all were case series, and these were all published in the year of 2020. The latest one was published in August 2020. There were a total of 1664 pediatric cases of COVID-19 out of which, 939(56.43%) were male and 725(43.35%) were female. All cases, except the cases from a single study were confirmed using nasopharyngeal ± oropharyngeal swab (OPS±NPS) specimens to identify the COVID-19 ribonucleic acid (RNA) by the RT-PCR (reverse transcription-polymerase chain reaction) assay (Table 1). The median age of patients was 7yr [IQR 5.6-8.8] (Table 2).

Data showed that 70.21% (601/856) children had a history of contact with COVID positive persons mainly their family members. Studies reported 17.34% (34/196) patients had a history of travel to the endemic area. Interestingly, one study observed travel history in 71.4 % (10/14) patients while only 28.5% (4/14) had contact history. Asymptomatic cases represented 14.99% (227/1514) of total cases. Detailed data of clinical presentations were available in all of the studies except in one study, of which fever was the most reported symptom, which was present in 45.65% (426/933) of cases. The second most common symptom was cough in 32.62% (291/892) of cases, although the majority of the studies did not specify whether the patients experienced a dry or productive cough. Other symptoms included, rhinorrhea which was reported in 14.66% (67/457), sore throats was reported in 6.22% (50/803) of cases, fatigue was reported in 4.69% (32/ 681) cases, diarrhea in 3.82% (37/837) cases, vomiting in 3.66% (26/710) cases and dyspnea in 2.87% (22/764) cases. Headache, nasal congestion and rashes were rarely reported (Table 3).

Respiratory coinfection was present in 36.49% (77/211) children. Mainly respiratory coinfections were due to mycoplasma, influenza A & B, Respiratory Syncytial Virus, and cytomegalovirus (Table 1).

Finding of chest X-Ray were reported only in 6 articles, among which abnormal x-ray was seen in 52.1 % (62/119) cases. In the study of See et al reported changes of x-rays as perihilar opacity in 2 out 4 patients.[23] A single study reported majority of abnormality as peribronchial infiltration in 58.82 % (30/51) of abnormal x-rays) while 16 of 51 x - rays showed a consolidation pattern i.e. 31.3 % of abnormal x - rays) (Table 4).

Computerized Tomography(CT) reporting was done in 57.69% (15/26) of studies; out of which abnormal CT findings were observed in 63.89 % (200/313) cases. Maximum studies noted that the most common CT abnormality was ground - glass opacity i.e. 43.71% (87/199) which was unilateral or bilateral & patchy or nodular. One of the study reported that most common abnormality in CT was patchy ground - glass shadows with nodules in 64.2% (9/14) cases (Table 4).

Among laboratory data, leucocytes were raised in 10.94% (29/265) cases, whereas leucocytes were decreased by 14.04% (50/356) cases. Interestingly in one of the study none of the patients had raised or low leucocyte counts. (Table 4). Lymphocytes were increased in 16.9 % (32/189) cases, while lymphocytes were decreased by 9.81% (32/326) cases.

C - Reactive Protein (CRP) was raised in 26.12 % (93/356) cases; interestingly in one of the study 66.66 % (4/6) cases were having raised CRP; whereas in another study none of the patients had raised CRP (0/10 cases). Lactate dehydrogenase (LDH) was raised in 31.12 % (61/196) cases. In a single study 82.35 % (28/34) patients were having raised LDH while in other two studies only 6.45% (2/31) and 10.0 % (1/10) patients had raised LDH. Procalcitonin was raised in 17.75 % (30/169) cases. In one study 62.5 % patients (5/8) were having raised procalcitonin levels, whereas, in other two study 3.57 % (1/28) and 3.7 % (3/81) patients were having raised procalcitonin levels. Among other data, serum transaminases were raised in 19.51% (32/164) cases and muscle enzymes were raised in 5.97% (11/184) cases (Table 4).

Fourteen studies revealed previous medical history in children presently infected with COVID-19 infection out of which 14.09 % (52/369) children were reported to be having co-morbidities (Table 1). Comorbidities included asthma, atrial septal defect (ASD) disease or operated ASD, epilepsy, growth retardation, infectious mononucleosis infection, acute leukocytic leukemia, congenital heart diseases and pharyngitis. The average duration from diagnosis to recovery was 11.19±5.08 days.

Antiviral therapy was administered in 32.8 % (137/418), and O2 therapy was needed in 8.45 % (29/343) cases (Table 2). Oxygen through high flow nasal cannula (HFNC) was required only in 2/41 patients in a single study. Non-invasive ventilation (NIV) was not mentioned in any study and invasive ventilation was required in 1.26 % (4/317) patients. Interestingly, one of the studies reported 8 severe or critically ill patients who were treated in the intensive care unit, 6 out of 8 of these patients required high flow oxygen therapy and 2/8 required mechanical ventilation. All of these patients received antivirals and after their study 3 patients remained in the intensive care unit (including two critically ill patients), the others recovered and were discharged home [25]. None of the case series reported mortality except 1 which reported single mortality resulting in case fatality rate of (CFR) (0.0006%) 1/1664 cases.

Table 1: Data regarding study, month & year, design, gender, age range, sampling method, diagnostic technique of COVID-19 , history of contact & travel, previous medical history, respiratory coinfection and diagnosis-recovery duration

No	Study	Month/ year of publication	Country	Study Design	Pediatric Cases	Female	Male	Age range	Method of Sampling	Diagnostic Technique	Contact History	Travel History	Previous Medical History	Respiratory coinfection	Diagnosis - Recovery duration
1	Xia et al	Feb-20	China	Case series	20	7	13	1 day-14.5 yr	OPS	RTPCR	13	0	2-ASD surgery, 1-Epilepsy	8 (Inf,RSV,Myco,CMV)	8-20 days (avg 12.9 days)
2	Feng et al	Feb-20	China	Case series	15	10	5	4 yr-14 yr	OPS	RTPCR	12	3	N/A	N/A	3-5 days; 6 cases recovered
3	Ji et al	Mar-20	China	Case series	2	0	2	9 yr -15 yr	OPS	RTPCR	1	2	No	N/A	2 days
4	Li et al	Mar-20	China	Case series	5	1	4	10 M - 6 yr	OPS	RTPCR	4	1	N/A	N/A	12-14 days; 2 still unrecovered
5	Chen	Mar-20	China	Case series	14	6	8	2 yr-10 yr	NPS,OPS	RTPCR	4	10	N/A	N/A	N/A
6	Liu et al	Mar-20	China	Case series	4	2	2	2 m-9 yr	OPS	RTPCR	N/A	N/A	N/A	3- Pneumonia	N/A
7	See et al	Mar-20	Malaysia	Case series	4	1	3	2 m-11 yr	OPS,NPS	RTPCR	4	1	1 (Asthma)	1 (Inf A)	7-19 days
8	Zhu et al	Mar-20	China	case series	10	5	5	1.7 yr-17 yr	OPS ,Anal	RTPCR	7	0	N/A	4	N/A
9	Sun et al	Mar-20	China	Case series	8	2	6	2 m-15 yr	NPS	RTPCR	5	N/A	1-ALL, 1-Pharyngitis	N/A	9-28 days
10	Duan et al	2020	China	Case series	31	16	15	6 M-17 Yr	OPS	RTPCR	22	9	N/A	N/A	7-23 days
11	Jiehao et al	Apr-20	China	Case series	10	6	4	3M-11 Yr	NPS,OPS	RTPCR	8	0	N/A	N/A	N/A
12	Song et al	Apr-20	China	Case series	16	6	10	11 m-14 yr	Pharyngeal	RTPCR	15	1	No	N/A	8-26 days
13	Wei et al	Apr-20	China	Case series	9	7	2	1m26 day-11m	NPS	RTPCR	4	N/A	N/A	N/A	N/A
14	Tan et al	Apr-20	China	Case series	10	7	3	1yr-12 yr	NPS	RTPCR	10	3	N/A	4 (Myco)	11-25 days
15	Rahimzadeh et al	Apr-20	Iran	Case series	3	0	3	3 yr-5 yr	OPS,NPS	RTPCR	3	N/A	No	N/A	3-13 days
16	Hu et al	May-20	China	Case series	6	3	3	5 yr- 15 yr	OPS	RTPCR	0	3	N/A	N/A	1-14 days; 2 still unrecovered
17	Ma et al	May-20	China	Case series	50	22	28	0-16 yr		RTPCR	N/A	N/A	N/A	Myco-5, RSV-1	7-14 days
18	Peng et al	May-20	China	Case series	75	31	44	6.06yr∓4.78yr	OPS	RTPCR	62	N/A	1-Epilepsy, 2-ASD Surgery, 1-Growth retardation, 1-Fatty liver disease)	Myco-28,Inf A-1,B-3,RSV-1	avg. 6.4 days
19	Kakuya et al	May 20	Japan	Case series	3	0	3	5yr-11yr	OPS,NPS	RTPCR	0	0	0	2(1-inf A, 1-hMPV)	9-14 days
20	Zhang et al	Jun-20	China	Case series	34	14	20	1 m-12 yr	NPS/OPS	RTPCR	18	N/A	6 (Asthma-1,ASD-1,IM-2)	16 (Inf A-3,B-6,RSV-2)	8-14 days
21	Korkmaz et al	Jun-20	Turkey	Case series	81	33	48	0-17.7 yr	OPS,NPS	RTPCR	73	N/A	No	N/A	4-10 days (avg.- 5 days)
22	Dong et al	Jul-20	China	Case series	731	311	420	median 7 yr	OPS,NPS /Blood	RTPCR, gene sequence	N/A	N/A	N/A	N/A	N/A
23	Banerjee et al	Jul 2020	India	Case series	41	17	24	Median 1 yr	OPS/NPS	RTPCR	26	N/A	25 (2-kawasaki disease, 8-malignancy, 4-CHD, 2-CLD, 4-Neurological abnormality	N/A	N/A (40 discharged)
24	Sarangi et al	Jul 2020	India	Case series	50	22	28	Median 6 yr	NPS	RTPCR	29	1	2 (1-febrile seizures, 1-diabetes)	N/A	N/A
25	Guo et al	Aug-20	China	Case series	341	158	183	4 day-14 yr	OPS	RTPCR	220/318	N/A	2-CHD	N/A	13-21 days
26	Han et al	Aug 20	Korea	Case series	91	38	53	Median 11 yr	OPS,NPS	RTPCR	61	N/A	6(3-Asthma, 3-epilepsy)	N/A	N/A

Abbreviations: Feb: February, Mar: March, Apr: April, Jun: June, Jul: July, Aug: August, m: Month, yr: Year, N/A: Not Available, OPS: Oropharyngeal, NPS: Nasopharyngeal, ASD- Atrial septal defect, ALL-Acute lymphocytic leukemia, IM: Infectious Mononucleosis, CHD: Congenital Heart Disease, CLD: Chronic Liver Disease, inf: influenza, myco: mycoplasma, RSV: respiratory syncytial virus, RTPCR: Reverse transcription polymerase chain reaction, hMPV-human metapneumo virus

Table 2: Conclusion of different parameters studied

No.	Parameter	Value	Total cases	percentage
1	Age	Median 7 yr (IQR 5.6-8.7)		
2	Gender	725(F), 939(M)	1664	43.35%(F), 56.43%(M)
3	Contact history	601	856	70.21%
4	Travel history	34	196	17.34%
5	Asymptomatic	227	1514	14.99%
6	Fever	426	933	45.65%
7	Cough	291	892	32.62%
8	Diarrhea	37	837	3.82%
9	Rhinorrhea	67	457	14.66%
10	Dyspnea	22	764	2.87%
11	CXR findings	AB-62	119	52.10%
12	CT findings	AB-200	313	63.89%
13	Leucocyte ↑	29	265	10.94%
14	Leucocyte ↓	50	365	14.04%
15	Lymphocyte↑	32	189	16.90%
16	Lymphocyte↓	32	326	9.81%
17	CRP ↑	93	356	26.12%
18	LDH ↑	61	196	31.12%
19	O2 therapy	29	343	8.45%
20	Antivirals	137	418	32.80%
21	Intubation	4	317	1.26 %
22.	Mortality	1	1664	0.0006%

Table 3: Clinical data of patients in selected studies

No	Study	Pediatric case	Asymptomatic	Fever	Cough	Diarrhea	Fatigue	Rhinorrhea	Dyspnea	Sore Throat	Vomiting
1	Xia et al	20	2	12	13	3	1	3	0	1	2
2	Feng et al	15	8	5	1	0	0	0	0	0	0
3	Ji et al	2	0	1	0	1	0	0	0	0	0
4	Li et al	5	4	1	0	0	0	1	0	0	0
5	Chen et al	14	N/A	6	6	0	3	3	0	0	0
6	Liu et al	4	0	3	3	0	1	N/A	0	0	0
7	See et al	4	1	1	2	1	N/A	1	N/A	N/A	N/A
8	Zhu et al	10	N/A	4	3	0	N/A	N/A	0	0	0
9	Sun et al	8	N/A	6	6	N/A	1	N/A	8	N/A	4
10	Duan et al	31	4	20	14	3	3	2	0	2	2
11	Jiehao et al	10	0	8	6	0	0	2	0	4	0
12	Song et al	16	8	5	6	0	0	N/A	0	N/A	0
13	Wei et al	9	N/A	4	2	0	N/A	1	0	0	0
14	Tan et al	10	2	4	3	N/A	N/A	N/A	N/A	N/A	1
15	Rahimzadeh et al	3	0	3	3	N/A	N/A	N/A	3	N/A	N/A
16	Hu et al	6	5	1	0	0	0	0	0	0	0
17	Ma et al	50	2	32	22	3	2	8	N/A	1	N/A
18	Peng et al	75	N/A	40	46	4	3	5	2	3	N/A
19	Kakuya et al	3	0	3	3	0	0	0	0	0	0
20	Zhang et al	34	N/A	26	21	N/A	N/A	N/A	3	N/A	4
21	Korkmaz et al	81	17	47	42	3	15	3	2	7	3
22	Dong et al	731	94	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
23	Banerjee et al	41	11	9	N/A	N/A	N/A	14	N/A	N/A	N/A
24	Sarangi et al	50	29	17	8	2	N/A	N/A	N/A	7	N/A
25	Guo et al	341	20	106	44	6	3	N/A	3	3	4
26	Han et al	91	20	62	37	11	N/A	24	1/77	22/77	6
	Total	1664	227/ 1514	426/933	291/ 892	37/ 837	32/ 681	67/457	22/764	50/ 803	26/710

Table 4. CT report, x-ray, laboratory data (CRP, LDH, WBC, Lymphocytes, Procalcitonin, sr. transaminase, muscle enzyme), management, need of NIV / IV in selected studies

No.	Study	Pediatric Case	CT REPORT	X RAY	CRP ↑	LDH ↑	WBC ↑	WBC ↓	Lympho↑	Lympho ↓	Procalcitonin↑	Sr.Transaminase↑	Muscle Enzyme↑	Management	NIV / IV
1	Xia et al	20	N-4, AB-16(6-U/L lesions,10-B/L lesions;GGO-12		9	N/A	2	4	3	7	16	5(ALT-5)	5	N/A	N/A
2	Feng et al	15	N-6, AB-9 (7-nodular GGO,2-speckled GGO)		N/A	N/A	N/A	8	N/A	N/A	N/A	N/A	N/A	N/A	N/A
3	Ji et al	2	N-2, AB-0		1	N/A	1	0	N/A	N/A	N/A	N/A	N/A	Only symptomatic	N/A
4	Li et al	5	N-2, AB-3(patchy GGO)		1	N/A	2	N/A	N/A	N/A	N/A	N/A	N/A	Antiviral-N/A, O2 Therapy-N/A	N/A
5	Chen et al	14	N-7, AB-7(GG0-3,GGO with consolidation & nodularity-1)		4	N/A	1	4	0	3	N/A	N/A	N/A	N/A	N/A
6	Liu et al	4	N-1, AB-3 (1-consolidation, 1-GGO, 1-multiple consolidations)		1	N/A	0	1	2	0	N/A	N/A	0	N/A	N/A
7	See et al	4		N-2, AB-2 (perihilar opacity)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	0-Antiviral, O2 Therapy-N/A	N/A
8	Zhu et al	10			0	N/A	1	0	N/A	0	0	3(ALT-3)	N/A	5-Antiviral, 1- O2 Therapy	No
9	Sun et al	8			5	6	1	0	1	1	5	4(ALT-4)	2	8-Antiviral, 8-O2 Therapy (2-IV)	2-IV
10	Duan et al	31	N-17, AB-14(9-patchy ground glass shadows &nodules)		3	2	3	2	4	2	1/28	6/27	4/27	29-Antiviral, O2 Therapy-N/A	N/A
11	Jiehao et al	10		N-6, AB-4(U/L patchy infiltrates)	3	3	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Only symptomatic	
12	Song et al	16	N-5,AB-11 (1 lobe-8,2 lobe-3; GGO-7;nodular-5;patchy-6)		1	3	0	2	0	1	0	N/A	N/A	4-Antiviral, O2 Therapy-N/A	N/A
13	Wei et al	9	N/A		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
14	Tan et al	10	N-5, AB-5 (MULTIPLE GGO-4, bronchopneumonia like changes B/L-1)		1	1	1	0	1	N/A	N/A	2(AST-2, ALT-0)	0	Antiviral-N/A,O2 THERAPY-0	No
15	Rahimzadeh et al	3		Done in 2 pts; N-0, AB-2(air space shadowing-2)	3	N/A	1	0	N/A	N/A	N/A	N/A	N/A	3-Antiviral, 3-O2 Therapy (NIV-0)	No
16	Hu et al	6	N-5, AB-1		4	4	0	4	N/A	4	5	2(ALT-2, AST-0)	N/A	Antiviral-N/A, O2 Therapy-N/A	N/A
17	Ma et al	50	N-7, AB-43 (GGO-29,subpleural lesions-41, lower lung lobe lesion-28		10	N/A	2	19	4	8	N/A	N/A	N/A	N/A	N/A
18	Peng et al	75	N-22, AB-53 (local patchy shadow-22, b/l patchy shadow-26, GGO-5)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	28-Antiviral, O2 Therapy-N/A	N/A
19	Kakuya et al	3	1-AB(consolidation)	N-1, AB-1(linear infiltrations)	2/2	N/A	1/2	1/2	0	2/2	N/A	1/2(AST-1)	N/A	0-Antiviral, 0-O2	No
20	Zhang et al	34	N-6, AB-28 (patchy shadows-28, GGO with patchy shadows-1)		17	28	0	0	17	0	N/A	N/A	0	15-Antiviral, 3- O2 Therapy	No
21	Korkmaz et al	81	30/81 done; N-24, AB-6 (GGO-3, consolidation-3	N-30, AB-51(peribronchial-30, consolidation-16)	13	14	N/A	2	N/A	4	3	9(AST-7,ALT-2)	0	0-Antiviral, 1-O2 Therapy	No
22	Dong et al	731	N/A		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
23	Banerjee et al	41			N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Antiviral-N/A, O2 Therapy-10	2-IV
24	Sarangi et al	50	N/A	N-18/20, AB-2/20	15	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
25	Guo et al	341	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	33/62-Antiviral, 4/62-O2 Therapy	N0
26	Han et al	91	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	12-Antiviral, 2-O2 via prongs	No

Abbreviations: CT: Computed Tomography, N: Normal, AB: Abnormal, U/L: Unilateral, B/L: Bilateral, Pts: Patients, GGO: Ground glass opacity, O2: Oxygen, NIV: Noninvasive ventilation, IV: Invasive ventilation, AST: Aspartate transaminase, ALT: Alanine transaminase, lympho: Lymphocyte.

Discussion

Since December 2019, when the novel Coronavirus infection (COVID-19) was first reported in Wuhan city, 29.11 million cases have been reported worldwide out of which, 8.18 million COVID-19 cases have been confirmed in countries of Asian origin [3]. The knowledge about the clinical and epidemiological characteristics of this rapidly emerging infection continues to evolve at a rapid pace. Various systematic reviews have been published describing clinical, laboratory and radiological characteristics of COVID-19 infected pediatric population [10-12, 43,44].

However, on further searching the database, a systematic review analyzing clinical, laboratory as well as radiological characteristics of the pediatric population in Asian countries have not been conducted yet, therefore we performed this comprehensive systematic review involving COVID-19 infected pediatric population in Asian countries. In this review, we summarized clinical, laboratory and radiological characteristics of COVID-19 in Asian pediatric population.

The analysis of our systematic review was comparable with other authors observing an excellent prognosis in pediatric patients with COVID-19 [43]. Most children and

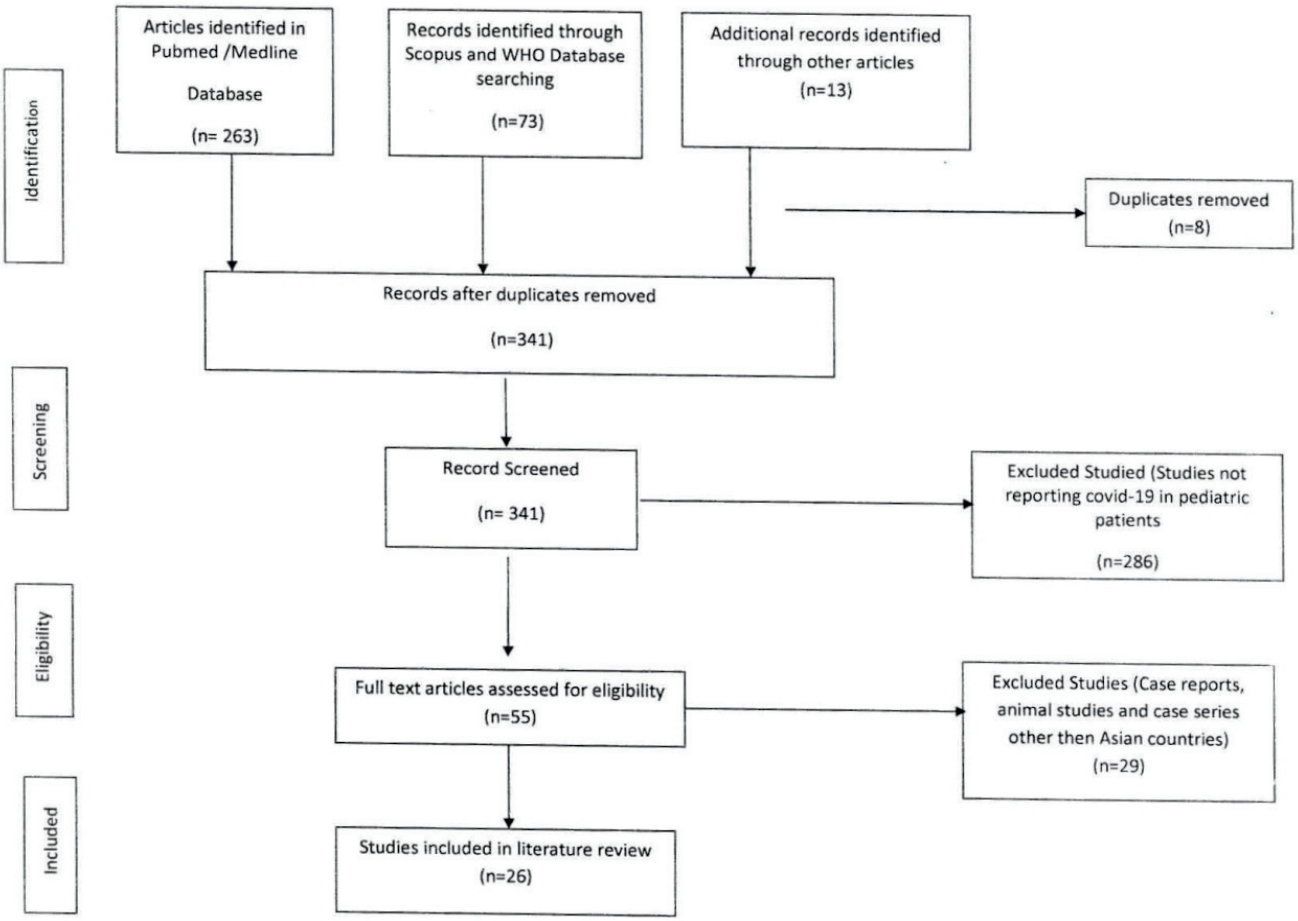

Figure 1 : PRISMA Flow Diagram

adolescents who were infected by SARS-CoV-2 (i .e. tested positive by nasopharyngeal or oropharyngeal swab) presented with mild symptoms. This was in agreement with other systematic reviews which highlighted a milder course and a better prognosis as compared to adults [12,43]. As per our review infectivity was almost equal among males and females whereas European multinational trial reported infectivity 15 times more in females [14]. A total of 70.21% children had contact history with confirmed COVID positive patients, with 17.34% cases showing travel history to endemic areas. This signifies that children may have a pivotal role in infection transmission at community level and underlines the need for rigorous testing for SARS-CoV 2 in children. This might also help in controlling the viral transmission at community level.

The most frequent symptoms were fever (45.65%) and cough (32.62%), along with rhinorrhea, diarrhea and shortness of breath being the lesser common symptoms. Associated comorbidity was present only in 14.09 % of patients in Asian children where as one-fourth of patients were having associated comorbidities in European study [14]. In contrast to COVID-19 presentation in adults, intensive care admission was required in a very small proportion of cases, which were managed by instituting oxygen therapy and assisted ventilation was required rarely. Intubation was required in only 1.26% of Asian children in contrast to European study where requirement was slightly higher (4%) [14]. All these patients were successfully managed with good outcomes. The only one death reported by Banerjee et al was due to type II respiratory failure in a case of post adenoviral bronchiolitis obliterans [39]. Although European multinational study reported low CFR (0.69%) among children but our review reported it to be much lower than there study (0.0006%) [14]. No data could be deduced correlating severity of illness with age or sex in pediatric COVID-19 population, unlike in adults.

The studies analyzed in our systematic reviews demonstrated elevation of systemic inflammation markers like C reactive protein, procalcitonin and lactate dehydrogenase in a smaller proportion of children, in contrast to Covid-19 infected adult population [44-46]. As per our review incidence of lymphocytopenia is low in children infected with Covid-19. Guan et al studied 1099 subjects and found that 83.2% of adults have lymphocytopenia, interestingly in the same study only 3.5%

of pediatric patients had lymphocytopenia [7]. Reduced incidence of lymphocytopenia can be well explained by reduced severity of COVID 19 in the pediatric population.

Regarding radiological findings in Asian pediatric population, chest radiograph findings predominantly revealed peribronchial infiltration and consolidation, while unilateral patchy opacities and perihilar infiltrates were present in few cases [23, 27, 36]. Regarding CT findings, studies involved in our systematic review reported 63.89 % of patients showing positive CT findings. This denotes that the severity of the symptoms did not correlate well with the radiological findings. Most common CT abnormality observed was ground glass opacity presenting as unilateral or bilateral and patchy or nodular. Wang et al in a case series of 14 patients, noted patchy ground glass shadows with nodules to be the most common finding [26]. Our findings align with other meta-analysis, which reported diffuse bilateral ground-glass opacities as the most common CT abnormality defined in COVID-19, at all stages of disease [17, 49]. Long term significance of these radiological changes are currently unavailable.

We also looked for data regarding multisystem inflammatory diseases (MIS-C) in children [50]. MIS-C is described as the presence of fever > 3 days and two of the following : a) Rash or bilateral non-purulent conjunctivitis or mucocutaneous inflammation signs (oral, hands or feet); b) Hypotension or shock; c) Features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including ECHO findings or elevated Troponin/NT-proBNP); d) Evidence of coagulopathy (by PT, PTT, and elevated d-Dimers); e) Acute gastrointestinal problems (diarrhea, vomiting, or abdominal pain) and elevated markers of inflammation such as ESR, C-reactive protein, or procalcitonin in children and adolescents up to 18 years of age. Banerjee et al reported 2 such cases of multisystem involvement having presentation like atypical Kawasaki disease, there are similar case reports from India regarding association ofMIS-C with COVID-19 [39, 51]. Further studies are needed to evaluate whether incidence of MIS-C is same in Asia when compared to Europe and United states.

Limitation

There are a few limitations to our review.

1) All the studies included in our article were case series and few of them had low patient number which doesn't represent the population as a whole.
2) The level of evidence of all our included studies was low.
3) We did not include suspected cases that could act as a control for comparing the severity of various symptoms, laboratory data, and imaging and outcome results.
4) Many studies didn't include comprehensive data of patients resulting in the low denominator of various parameters.
5) Long term consequences of COVID -19 infection could not be ascertained.

Conclusion

This review presents a critical analysis of various demographical and clinical characteristics of COVID-19 infected pediatric Asian population. Children mostly acquired infection from adult contacts. Predominant symptoms include fever and cough. Abnormal findings in CT imaging are quite common with predominant abnormality being ground glass opacity. Only a few patients required oxygen therapy and the requirement of non-invasive or invasive ventilation was rare despite of having abnormal CT imaging and associated co-morbidities and respiratory infections in some patient subgroup. Mortality rate is almost nil as per our review. All these findings depict a mild natural course of the disease, favorable outcome and better prognosis of COVID-19 infected pediatric Asian population.

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References

1. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. The Lancet 2020;395(10223):507-513.
2. Yi Y, Lagniton PNP, Ye S, Li E, Xu RH. COVID-19: what has been learned and to be learned about the novel coronavirus disease. Int J Biol Sci. 2020;16(10):1753-1766
3. WHO coronavirus disease (COVID-19) dashboard. Geneva: World Health Organization, 2020. Available online: https://covid19.who.int/ (last cited: [15 September 2020]).
4. Guo YR, Cao QD, Hong ZS, et al. The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak - an update on the status. Mil Med Res. 2020;7(1):11.
5. Lauer SA, Grantz KH, Bi Q, et al. The Incubation Period of Coronavirus Disease 2019 (COVID-19) From Publicly Reported Confirmed Cases: Estimation and Application. Ann Intern Med. 2020;172(9):577-582.
6. Khalili M, Karamouzian M, Nasiri N, et al. Epidemiological characteristics of COVID-19: a systematic review and meta-analysis. Epidemiol Infect. 2020;148:e130.
7 Guan WJ, Ni ZY, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 2020;382(18):1708-1720.
8. Zhang JJ, Dong X, Cao YY, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. Allergy. 2020;75(7):1730-

1741.
9. Saleem H, Rahman J, Aslam N, Murtazaliev S, Khan S. Coronavirus Disease 2019 (COVID-19) in Children: Vulnerable or Spared? A Systematic Review. Cureus. 2020;12(5):e8207
10. Patel NA. Pediatric COVID-19: Systematic review of the literature. Am J Otolaryngol. 2020;41(5):102573.
11. Cui X, Zhao Z, Zhang T, et al. A systematic review and meta-analysis of children with Coronavirus Disease 2019 (COVID-19). J Med Virol. 2021;93(2):1057-1069.
12. Ludvigsson JF. Systematic review of COVID-19 in children shows milder cases and a better prognosis than adults. Acta Paediatr. 2020;109(6):1088-1095.
13. Max Roser, Hannah Ritchie, Esteban Ortiz-Ospina and Joe Hasell (2020) - "Coronavirus Pandemic (COVID-19)". Published online at OurWorldInData.org. Retrieved from: 'https://ourworldindata.org/coronavirus' [accessed on Sept 20, 2020]
14. Gotzinger F, Santiago-García B, Noguera-Julian A, et al. COVID-19 in children and adolescents in Europe: a multinational, multicentre cohort study. Lancet Child Adolesc Health. 2020;4(9):653-661.
15. National Institutes of Health (2014) National Heart, Lung, and Blood Institute. Quality assessment tool for observational cohort and cross-sectional studies. Nhlbi.nih.gov/health-topics/study-quality-assessment-tools.(accessed on June 3, 2020)
16. Farrah K ,Young K ,Tunis M ,Zhao L. Risk of bias tools in systematic reviews of health interventions: an analysis of PROSPERO-registered protocols. Syst Rev. 2019;1:280
17. Xia W, Shao J, Guo Y, Peng X, Li Z, Hu D. Clinical and CT features in pediatric patients with COVID-19 infection: Different points from adults. Pediatr Pulmonol. 2020;55(5):1169-1174.
18. Feng K, Yun YX, Wang XF, et al. Analysis of CT features of 15 Children with 2019 novel coronavirus infection. Zhonghua Er Ke Za Zhi. 2020;58(0):E007.
19. Ji LN, Chao S, Wang YJ, et al. Clinical features of pediatric patients with COVID-19: a report of two family cluster cases. World J Pediatr. 2020;16(3):267-270.
20. Li W, Cui H, Li K, Fang Y, Li S. Chest computed tomography in children with COVID-19 respiratory infection. Pediatr Radiol. 2020;50(6):796-799.
21. Chen A, Huang J, Liao Y, et al. Differences in Clinical and Imaging Presentation of Pediatric Patients with COVID-19 in Comparison with Adults. Radiology: cardiothoracic imaging.2020;2(2):e200117.
22. Liu H, Liu F, Li J, Zhang T, Wang D, Lan W. Clinical and CT imaging features of the COVID-19 pneumonia: Focus on pregnant women and children. J Infect. 2020;80(5):e7-e13.
23. See KC, Liew SM, Ng DCE, et al. COVID-19: Four Paediatric Cases in Malaysia. Int J Infect Dis. 2020;94:125-127.
24. Zhu L, Wang J, Huang R, et al. Clinical characteristics of a case series of children with coronavirus disease 2019. Pediatr Pulmonol. 2020;55(6):1430-1432.
25. Sun D, Li H, Lu XX, et al. Clinical features of severe pediatric patients with coronavirus disease 2019 in Wuhan: a single center's observational study. World J Pediatr. 2020;16(3):251-259.
26. Wang D, Ju XL, Xie F, et al. Clinical analysis of 31 cases of 2019 novel coronavirus infection in children from six provinces (autonomous region) of northern China. Zhonghua Er Ke Za Zhi. 2020;58(4):269-274.
27. Jiehao C, Jin X, Daojiong L, et al. A Case Series of Children With 2019 Novel Coronavirus Infection: Clinical and Epidemiological Features. Clin Infect Dis. 2020;71(6):1547-1551.
28. Song W, Li J, Zou N, Guan W, Pan J, Xu W. Clinical features of pediatric patients with coronavirus disease (COVID-19). J Clin Virol. 2020;127:104377.
29. Wei M, Yuan J, Liu Y, Fu T, Yu X, Zhang ZJ. Novel Coronavirus Infection in Hospitalized Infants Under 1 Year of Age in China. JAMA. 2020;323(13):1313-1314.
30. Tan YP, Tan BY, Pan J, Wu J, Zeng SZ, Wei HY. Epidemiologic and clinical characteristics of 10 children with coronavirus disease 2019 in Changsha, China. J Clin Virol. 2020;127:104353.
31. Rahimzadeh G, Ekrami Noghabi M, Kadkhodaei Elyaderani F. COVID-19 Infection in Iranian Children: A Case Series of 9 Patients**.** Journal of Pediatrics Review. 2019;8(2):139-144.
32. Hu Z, Song C, Xu C, et al. Clinical characteristics of 24 asymptomatic infections with COVID-19 screened among close contacts in Nanjing, China. Sci China Life Sci. 2020;63(5):706-711.
33. Ma H, Hu J, Tian J, et al. A single-center, retrospective study of COVID-19 features in children: a descriptive investigation. BMC Med. 2020;18(1):123.
34. Peng H, Gao P, Xu Q, et al. Coronavirus disease 2019 in children: Characteristics, antimicrobial treatment, and outcomes. J Clin Virol. 2020;128:104425.
35. Zhang C, Gu J, Chen Q, et al. Clinical and epidemiological characteristics of pediatric SARS-CoV-2 infections in China: A multicenter case series. PLoS Med. 2020;17(6):e1003130.
36. Korkmaz MF, Türe E, Dorum BA, Kýlýç ZB. The Epidemiological and Clinical Characteristics of 81 Children with COVID-19 in a Pandemic Hospital in Turkey: an Observational Cohort Study. J Korean Med Sci. 2020;35(25):e236.
37. Dong Y, Mo X, Hu Y, et al. Epidemiological characteristics of 2143 pediatric patients with 2019 coronavirus disease in China: J.Emerg. Med 2020;58(4):712–713.
38. Guo CX, He L, Yin JY, et al. Epidemiological and clinical features of pediatric COVID-19. BMC Medicine 2020;18:250.
39. Banerjee S, Guha A, Das A, Nandy M, Monda R. A Preliminary Report of COVID-19 in Children in India. Indian Pediatr. 2020:S097475591600217.
40. Sarangi B, Reddy VS, Oswal JS, et al. Epidemiological and Clinical Characteristics of COVID-19 in Indian Children in the Initial Phase of the Pandemic. Indian Pediatr. 2020:S097475591600218.
41. Kakuya F, Okubo H, Fujiyasu H, Wakabayashi I, Syouji M, Kinebuchi T. The First Pediatric Patients with Coronavirus Disease 2019 (COVID-19) in Japan: Risk of Co-Infection with Other Respiratory Viruses. Jpn J Infect Dis. 2020;73(5):377-380.
42. Han MS, Choi EH, Chang SH, et al. Clinical Characteristics and Viral RNA Detection in Children With Coronavirus Disease 2019 in the Republic of Korea.JAMA Pediatr. 2021;175(1):73-80.
43. Castagnoli R, Votto M, Licari A, et al. Severe Acute Respiratory Syndrome CoronaVirus 2(SARS-CoV-2) Infection in Children and Adoloescent: A Systematic Review.JAMA Pediatr. 2020;174(9):882-889.
44. Hoang A, Chorath K, Moreira A, et al. COVID-19 in 7780 pediatric patients: A systematic review. EClinicalMedicine.2020;24:100433.
45. Aziz M, Fatima R, Assaly R. Elevated interleukin-6 and severe COVID-19: A meta-analysis. J Med Virol. 2020:10.1002/jmv.25948.
46. Zhu J, Ji P, Pang J, et al. Clinical characteristics of 3062 COVID-19 patients: A meta-analysis. J Med Virol. 2020:10.1002/jmv.25884.
47. Tan L, Wang Q, Zhang D, et al. Lymphopenia predicts disease severity of COVID-19: a descriptive and predictive study. Signal Transduct Target Ther. 2020;5(1):33.
48. Xia W, Shao J, Guo Y, Peng X, Li Z, Hu D. Clinical and CT features in pediatric patients with COVID-19 infection: Different points from adults. Pediatr Pulmonol. 2020;55(5):1169-1174.
49. Kumar-Venugopal V, Mahajan V, Rajan S, et al. A systematic meta-analysis of CT features of covid-19: lessons from radiology, 2020; April 7.
50. Centers for Disease Control and Prevention Resources for Emergency Health Professionals.Health Alert Netw. 2020; (accessed June 3) https://emergency.cdc.gov/han/2020/han0043
51. Acharyya BC, Acharyya S, Das D. Novel Coronavirus Mimicking Kawasaki Disease in an Infant. Indian Pediatr. 2020;57(8):753-754.