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Predictors and Outcomes of Pediatric COVID 19 Cases in Recent Scenario: Systematic Review & Meta Analysis

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ABSTRACT:

Background – Studies summarizing the clinical findings of COVID 19 in children are lacking. So, we aimed to provide a comprehensive meta-analysis and systematic review of previously published papers related to clinical features and lab findings of COVID -19 in pediatric population.

Methods – a systematic search and meta-analysis of scientific literatures was conducted by using PubMed, Embase, Scopus, Medline, google Scholar databases. Studies were reviewed for methodological quality, and random-effects model was used to conduct the primary meta-analysis. I^2 value and Egger's test was used to estimate heterogeneity and publication bias respectively.

Results – we reviewed 10 eligible studies that included 1215 pediatric population with PCR tested COVID -19 positive. The most frequent symptoms were fever, cough, vomiting, diarrhea, sore throat, and dyspnea. Regarding the combined results of the meta-analysis, fever (60%), cough (78%), dyspnea (74%) and pharyngalgia (59%) were the most widely reported symptom. Besides, positive RT-PCR test results, elevated inflammatory markers including Procal (92 %), D- Dimer (82%) and CRP (73 %) were the most common laboratory findings.

Conclusion - COVID-19 is prevalent across all pediatric age-groups and presents with varying degree of symptomology. However, children have a milder course of the disease with extremely favorable prognosis.Future longitudinal studies are needed to confirm our findings and better

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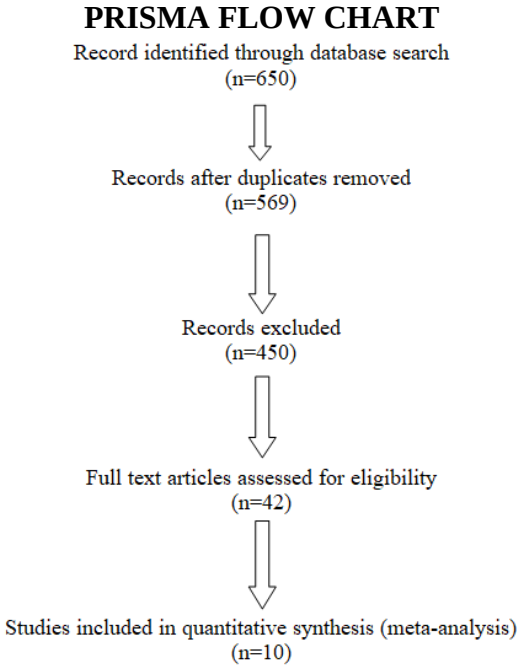
understand which patients are at increased risk for developing severe inflammation and multi organ failure.
Key words: Pediatric, COVID 19, Outcomes, Predictors.

INTRODUCTION

In December 2019, a sudden outbreak of pneumonia cases of unknown origin emerged from Wuhan, China. . Till 3 Jan. 2020 a total of 44 pneumonia cases were detected. On 7 Jan2020, Chinese research authorities were announced that they were isolated new virus from sea food market in Wuhan city; Named as 2019-nCoV. Though the SARS-CoV-2 originated from bats, the intermediary animal through which it crossed over to humans is uncertain.[1] Coronaviruses are enveloped positive sense RNA viruses ranging from 60 nm to 140 nm in diameter with spike like projections on its surface giving it a crown like appearance under the electron microscope; hence the name coronavirus.[2] Differential diagnosis is important in current scenario as it includes all types of respiratory viral infections [influenza, parainfluenza, respiratory syncytial virus (RSV), adenovirus, human metapneumovirus, non COVID-19 coronavirus], atypical organisms (mycoplasma, chlamydia) and bacterial infections. It is not possible to differentiate COVID-19 from these infections clinically or through routine lab tests. Specific diagnosis is by specific molecular tests on respiratory samples (throat swab/ nasopharyngeal swab/ sputum/ endotracheal aspirates and bronchoalveolar lavage).

MATERIAL AND METHODS:



Search strategy and selection criteria

Our systemic review and meta analysis adhere to the guidelines established by preferred reporting items (ie PRISMA).[3]This comprehensive search from 2019 to 2020 was conducted in the following databases – PubMed, Embase, Scopus, Medline, googlescholar using various combinations of keywords – novel coronavirus, COVID – 19, 2019-Ncov, SARS-COV-2,

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Wuhan coronavirus, Wuhan Pneumonia and pediatric or neonate or new born or infant or children or adolescence. Title and abstract screening was conducted by two investigators and results were also reviewed by two authors (conventional double screening). Full texts of selected studies were reviewed and 10 publications were selected for meta analysis. Excluded articles included those that did not contain relevant and adequate data concerning clinical features, lab findings; exclusively neonatal or specific age group studies; comorbidities and non English publications.

Data extraction and quality assessment

Following the full text screening for eligibility all relevant data was collected included author, the type of article (e.g. case series), publication year, country of origin, number of pediatric patients, clinical symptoms (e.g. cough, fever), lab findings (e.g. D-dimer).

RESULTS:

Data analysis

Primary outcomes of study were – clinical symptoms, lab markers. I^2 index was used to assess heterogeneity with values 25%, 50% and 75% representing low, moderate, high heterogenecity.[4] If analysis included more than three studies, egger precision weighted linear regression was used to test potential publication bias, with p-value <0.05 considered significant for publication bias. If publication bias was present, the trim and fill method was performed to evaluate the effect(data not shown). Meta-analysis was performed using metapackages in R (version 3.6.0).

Meta analysis

Meta-analysis was conducted on 9 clinical symptoms and 9 laboratory markers. Overall, 67 % of the patient population were with headache (67 %), fever (60 %), and cough (78%), being the most common symptoms. The remaining clinical symptoms had an overall estimated prevalence of <20 %. Among commonly reported laboratory findings, elevated inflammatory markers including Procal (92 %), D- Dimer (82%) and CRP (73 %) were the most common. Decreased lymphocytes (50 %) and leukocytes (71%) were also more common than elevated counts of these immunological markers.

Table 1: Characteristics of the included studies on COVID – 19/20

Study	Location	N	Age	Gender (male)
Dong, Y. et al [12]	China	728	10 (4-15)	418
Bai K. et al [20]	China	25	11 (6.3 – 14.5)	14
Qiu , H. et al [13]	China	36	8.3 ± 3.5	23
Song, W. et al [21]	China	16	8 (11.5 – 14)	10
Shekerdemian, L.S. [22]	Canada	48	13 (4.2 – 16.6)	25
Feng et al [23]	China	15	4 – 14	5
Tagarro et al [24]	Spain	41	<18	18
Rahimzadeh et al [25]	Iran	9	2 – 10	6
Bialek et al [26]	United States	291	<18	165
Hu et al [27]	China	6	<15	3

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Table 2: Summary of the study characteristics and results of meta-analysis of clinical and laboratory findings in pediatric COVID-19 patients. Abbreviations: GI: Gastrointestinal; LDH: Lactate Dehydrogenase; AST: Aspartate transaminase; ALT: Alanine transaminase; ESR: Erythrocyte Sedimentation Rate; CRP: C reactive protein; Procal:Procalcitonin.

Clinical and lab variables	Number of studies	Total patients	I^2 (%)	Egger's test P - value
Fever	9	388	60 %	0.670
Cough	7	357	78 %	0.353
Dyspnea	7	215	74 %	0.006
Sore throat	6	50	59 %	0.005
Rhinorrhea	9	38	52 %	0.600
Congestion	4	17	75 %	0.125
Headache	5	95	67 %	0.960
Fatigue	6	53	59 %	0.373
GI symptoms	8	21	70 %	0.660
Leukocytosis	5	49	62 %	0.034
Leukopenia	3	30	71 %	0.396
Lymphopenia	4	21	50 %	0.020
Procal	3	60	92 %	0.030
D – Dimer	4	20	82 %	0.045
CRP	5	100	73 %	0.002
LDH	3	45	68 %	0.091
ESR	3	89	76 %	0.784
AST/ALT	4	65	0 %	0.065

DISCUSSION

In the last 6 months, worldwide cases of SARS-COV2 infection & our knowledge of the disease and its epidemiologic and new clinical characteristics continue to evolve. It was first reported in Wuhan city in China in December 2019. Rapidly emerging the new mutants of this novel virus is threat and identification of clinical features and lab findings is essential to guide good clinical care, predict severity and to determine prognosis. COVID-19 is present across all age ranges. Based on current evidence, there does not appear to be any age restriction for COVID-19 susceptibility.[5] However, substantial evidence has established that compared to adults, children only account for a small number of COVID-19 case.[6] In our meta-analysis of COVID-19 prevalence across various pediatric age groups the distribution of cases varied but was highly frequent (21–25 %) in the 8 - 15 year-old age range . Similar observations were made by G¨otzinger et al. in a large European study.[7]Similarly, in regard to common clinical indicators, fever, cough, and headache accounted for the most dominant symptoms while sore throat, rhinorrhea, and GI symptoms were rare. The primary mechanism of SARS-CoV2 pathogenesis is thought to involve its interaction with human ACE-2 receptors leading to T-cell activation and subsequent inflammatory response. In the early stage, viral copy numbers can be high in the lower respiratory tract. Inflammatory signaling molecules are released by infected cells and alveolar macrophages in addition to recruited T lymphocytes, monocytes, and neutrophils. In the late stage, pulmonary edema can fill the alveolar spaces with hyaline membrane formation, compatible with early-phase acute respiratory distress syndrome. This pro-inflammatory state with further vascular and multi-organ injury likely contributes to the variety of laboratory

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abnormalities commonly seen in infected patients. Previous studies including infections caused by other novel coronaviruses have reported typically normal or reduced immunological markers with normal to elevated LDH and D-dimer levels. Our findings were consistent with higher prevalence of leukopenia and lymphopenia as well as elevated levels of D-dimer and LDH. However, the most common laboratory markers seen in our study were elevated Procalcitonin and CRP consistent with a highly inflammatory state.[8,9] These clinical markers alone however are non-specific, thus limiting their clinical utility in absence of a strong clinical correlation to the patient's history and physical symptoms. Overall, these clinical symptoms and laboratory markers are highly non-specific and provide little evidence of COVID-19 infection when assessed individually. Clinicians should not diagnose or rule out COVID-19 infection solely based on any one of these findings, but synthesize information based on prevalence of common features as evidenced in ours and other studies. Although SARS-CoV2 infection was first identified in China, the United States has now amassed the highest number of confirmed cases.[10] Calculations made on June 4th, 2020 from the COVID-19 Dashboard by the Center for Systems Science and Engineering at Johns Hopkins University indicate that China has 45 % of total confirmed COVID-19 cases compared to the United States. [11] As expected, the most common vector for childhood infection is close contact to an affected family member or residing in an area with a high population of cases. Our findings align with the results of an April 2020 report by Dong et al, in which there was a clear trend that the disease spread rapidly from a Chinese province to surrounding provinces and cities in children on December to February.[12]. Furthermore, Qiu and colleague studied 36 pediatric COVID-19 positive patients in which ten patients (28%) were symptomatic latent cases identified secondary to an adult family member who was infected, symptomatic, or traveled to an endemic area.[13]This lends concern that children, who may be asymptomatic, may play a role in community transmission of the virus. Little is known about the perinatal aspects of COVID-19, and there have been several reported cases of neonatal infection, suggesting a possible perinatal or vertical transmission during pregnancy.[14] However, in a report by Chen et al., all nine neonates born to COVID-19 positive mothers tested negative for the virus after cesarean delivery.[15] In another study by Zhang et al., 10 neonates from COVID-19 positive mother all tested negative for the infection.[16] Moreover, this is further supported by analysis of breast milk and placental pathologic specimens from COVID-19 positive mothers, which have returned negative for the virus. Lastly, vertical transmission was not observed with either SARS-CoV-1 or in MERS-CoV[17]therefore, it is unlikely that maternal vertical transmission during third trimester occurs, or is likely very rare. However, from the limited data published, we cannot determine the consequences of SARS-CoV-2 infection in early pregnancy and if it can be transmitted to fetus and hinder organ development, malformations, growth abnormalities, or even lead to premature labor or spontaneous abortions. [18,19]

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