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REVIEW

Clinical Profile of Covid-19 in Children, Review of Existing Literatures

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Firew Tiyare Tiruneh

Department of Midwifery, College of Health Science, Mizan Tepi University, Mizan Teferi, Ethiopia

Abstract: WHO has confirmed that COVID-19 disease is a pandemic on March 11, 2020. The disease is caused by a new virus called SARS-CoV-2. Since, the pandemic was announced around 18,854,287 cases and 708,639 deaths were reported as of August 7, 2020. This review aimed to explore the etiology, pathogenesis, manifestation and complication. The phylogenetic study showed that SARS-CoV-2 is a single-stranded RNA virus. The virus is very contagious and has rapidly spread globally. Its unique structure called S glycoproteins help the virus enters in and cause infection in the body. Children's body reacts against SARS-CoV-2 infections through the involvement of innate and adaptive immune system. The clinical manifestation in children is not specific and not determined. However, fever and cough have mostly been profiled. Though the severe condition is rarely reported in children compared with adults, life-threatening complications, and death associated with COVID-19 disease have been documented. Underlying chronic pulmonary disease, cardiovascular disease, immunosuppression, and obesity significantly contribute to the complications.

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

Background

In the history of Human beings, there have been different pandemics, such as Cholera, bubonic plague, smallpox, and influenza.[1] In the 21st century, most of the pandemics were caused by either coronavirus or influenza virus.[2] The cause for the current COVID-19 pandemic is also coronavirus. The pandemic is causing a global health and socio-economic crisis and is the major problem encountered after the second global war that lasted from 1939 to 1945. Following its first report in December 2019, SARS-CoV-2 almost reached all over the world.[3] It was at the beginning identified as an outbreak of cases of pneumonia with an unexplained cause in China. It was first informed to the World Health Organization (WHO) in December 2019.[4]

The World Health Organization (WHO) stated Coronavirus disease 2019 as a pandemic on March 11, 2020. The etiology for Coronavirus disease 2019 is a newly identified virus called SARS-CoV-2.[5] Individuals infected with the virus can transmit to a healthy person mainly through droplets discharged from the nose and mouth.[6] So far, no one has identified specific vaccination or medicine for the disease.[7] According to the latest data, around 18,854,287 COVID-19 confirmed cases and 708,639 associated deaths of all ages have been reported from 215 countries as of August 7,2020.[8]

Correspondence: Firew Tiyare Tiruneh
Department of Midwifery, College of Health Science, Mizan Tepi University, PO Box- 260, Mizan Teferi, Ethiopia
Tel +251-917-83-0101
Email mtu2012x@gmail.com

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At the earlier outsets of Covid-19 pandemics, children were believed to have mild COVID-19.[9] However, at later time children seriously affected with COVID-19 have appeared to be seen.[10] One study in USA reported nearly 5.7% of pediatric patients have been admitted in hospitals.[11] Another study conducted among children admitted in ICU in USA showed that nearly 69% of children were critically ill and 38% who were in ICU required ventilation.[12] Infants appeared to be affected more seriously than older children. Nearly 11% of infants had serious cases compared to 3% of ages 16 and older.[13]

In contrast to adults, fewer children were reported to encounter critical illness and admission. Earlier data from china reported nearly 2.4% children with COVID-19 were aged 19 or younger. Besides, only 0.2% pediatrics encountered life threatening complication in contrast with 6.1% overall.[11] Similarly, other studies from the USA supported the risk of life threatening complication in children is lower than adults. Hospitalization rate appeared to rise as the age increases. Among children less than 19 years old, only 2–3% of them were hospitalized when more than 31% of patients older than 85 years were hospitalized.[14] Furthermore, about 6% of children have been reported to have a critical illness, compared to 18.5% of adults.[15] The age-specific fatality ratio appeared to rise from 0.1% in children aged ≤19 years to approximately 80% in adults aged ≥60 years.[16] Following treatment children typically recovered within 3 to 4 days.[11]

Different studies have attempted to characterize the manifestation of COVID-19 disease in children.[17] However, the clinical presentation of COVID-19 exclusively in children has not yet been extensively studied. Even the available study showed contradicting findings. For instance, a study from China suggests that children with COVID-19 might have different symptoms than adults.[13] On the contrary, another study reported that COVID-19 has similar manifestation both in children and adults.[18] This contradicting finding showed how far extensive research is required to enrich the body of knowledge regarding COVID-19 characteristics in children. Thus, this review of existing literature was conducted with the hope to provide an insight into the disease in children. Hence, readers can refer to this review to increase their awareness.

Basics of Etiology

There have been seven corona virus species infecting human being. In 1965s the first coronavirus that infect human being was recognized. The seventh type of newly identified coronavirus is known as SARS-CoV-2.[19] Coronaviruses are single-stranded, positive-sense, enveloped, RNA viruses with a crown-like appearance. Genera of corona viruses have been categorized into four: Deltacoronavirus (deltaCoV), Gammacoronavirus (gammaCoV), Alphacoronavirus (alphaCoV), and Betacoronavirus (betaCoV).[20] Coronaviruses are involved in human. They can infect, gastrointestinal, respiratory, central nervous system, and hepatic of human and vertebrate's diseases.[21]

SARS-CoV-2 goes to βCoVs, however SARS-CoV-2 is different from other viruses belonging to βCoVs.[22] Bats and rodents have been suspected as the source of βCoVs . The virus has four main structural proteins, namely core nucleocapsid (N) protein, envelope (E), membrane (M) glycoprotein, and spike (S) glycoprotein.[23] (see Figure 1). Among them, S proteins (S1 and S2 subunits) has the most important function in viral attachment, fusion, and entry into cells.[24]

Pathogenesis

Mucous membranes of the respiratory tract are the way through which SARS-CoV-2 might get to the lung. From the lung, the virus enters into the blood circulation and reach different organs.[25] SARS-CoV-2 may use angiotensin-converting enzyme 2 (ACE2) as a host cell receptor to get in and cause infection in humans. This receptor is found widely in various organs, such as the gastrointestinal tract, the lung, heart, and kidney. These organs are targets of SARS-CoV-2.[26] Pathophysiology mechanisms of SARS-CoV-2 have been linked to the function of the nonstructural proteins and structural proteins.

The replication process of SARS-CoV-2 follows five steps: (i) binding to receptor, (ii) fusion in to host cell, (iii) RNA translation, (iv) viral maturation, and (v) bud out.[27] The spike protein of coronavirus, S1 substructure facilitates the virus attachment with receptors whereas S2 substructure help cell membrane integration.[28] After the virus binds with the host cell, S protein will undergo conformational change by a host cell serine protease called TMPRSS2 which leads to viral entry through the process of endocytosis.[29] Following the viral entry into the cells, the viral RNA genome is released into the cytoplasm. Then from the released RNA structural proteins and polyproteins will be synthesized, finally the reproduced virus will be released out.[30]

Viral entry and cell infection stimulate the body's immune reaction. In response to the antigen, the inflammatory process is initiated by antigen-presenting cells. After the antigen (virus) is presented, T cells will identify the virus.[31] In reaction to antigen presentation, both cell mediated and antibody mediated immune responses will be stimulated. The

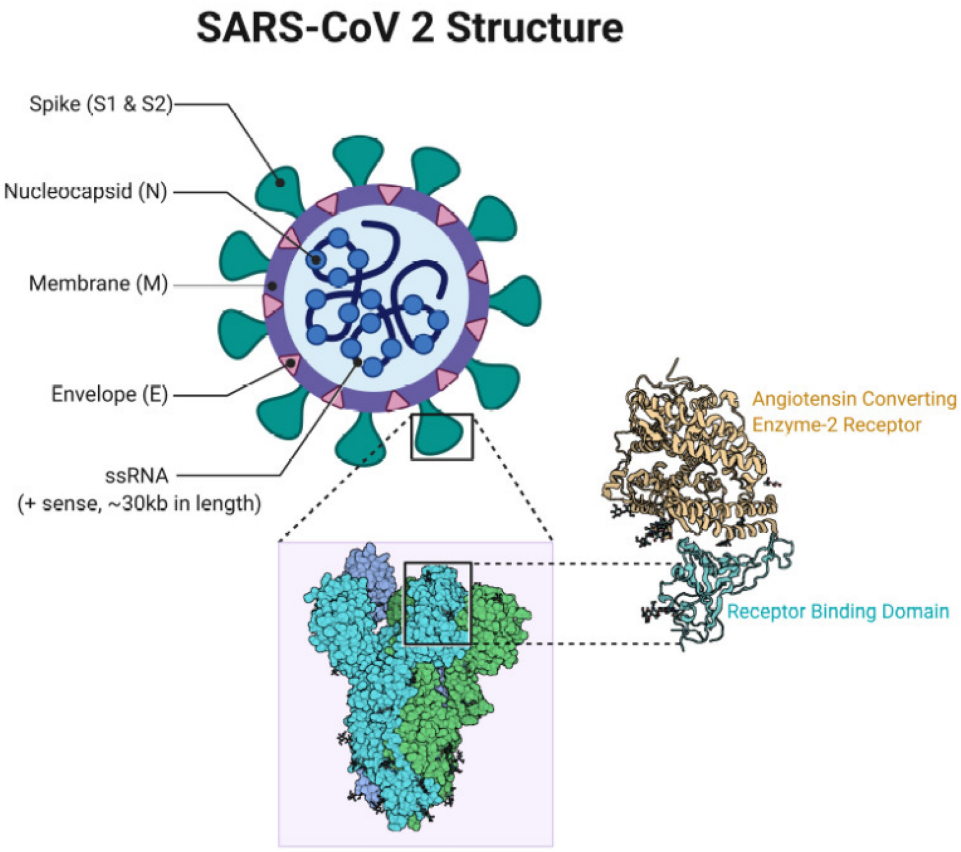

Figure 1 SARS-CoV-2 structure.
Notes: Reproduced from StatPearls Publishing LLC. Copyright © 2020. Cascella M, Rajnik M, Cuomo A, Dulebohn SC, Di Napoli R. *Features, Evaluation, and Treatment of Coronavirus (COVID-19)*. StatPearls (http://creativecommons.org/licenses/by/4.0/).[65]

immune response is mediated by T lymphocytes and B lymphocytes. T helper cells (i.e. CD8+ and CD4+) predominantly play the fight against the virus. The CD4+ initiate B lymphocytes to produce antigen-targeted antibodies, while the cytotoxic cells (CD8+) attack viral diseased cells.[32]

The fact that most infected children experience mild symptoms and have a better prognosis continuous to hold.[33,34] Although the reason is not yet clear, several theories have been proposed to explain it. One of the likely reasons is that children are thought to have fewer ACE2 and TMPRSS2 receptors in their nasal tissue than adults. These receptors help the virus entry in to host body. That is the reason why pneumonia and ARDS is not common in kids with COVID-19 compared to adults.[35] Another possible explanation is tied to immune response, overzealous pulmonary inflammatory mediators, termed as cytokine storm is rare in children. An exaggerated immune response may end up in extreme inflammation, thereby eventually causing more severe damage. Children, with immature immune systems, appear to be less capable of mounting cytokine storms suggesting why children do not seem to be getting severely ill.[36] It has also been suggested that early childhood vaccines provide some protective immunity against SARS-CoV-2 in children. Studies have suggested that, in contrast to adult vaccines can protect children from acquiring COVID-19 disease.[37] The overall pathogenesis is indicated in Figure 2.

Clinical Manifestation

Children of all ages can be affected by COVID-19 disease.[38] They may show symptoms within 2–14 days after being infected by SARS-CoV-2.[39] The symptoms have been reported to be milder than adults.[40] Male children constitute a greater proportion than females.[41] A study conducted on children with COVID-19 delineated a spectrum of clinical appearances from no symptom to sever condition. The manifestation can be categorized in to five stage depending on the severity of clinical progression: (i) the initial characteristics is no apparent clinical signs, (ii) minor clinical symptoms such as cough, fever, myalgia, fatigue (iii) subclinical pneumonia, (iv) Severe pneumonia characterized with hypoxia, dyspnea and

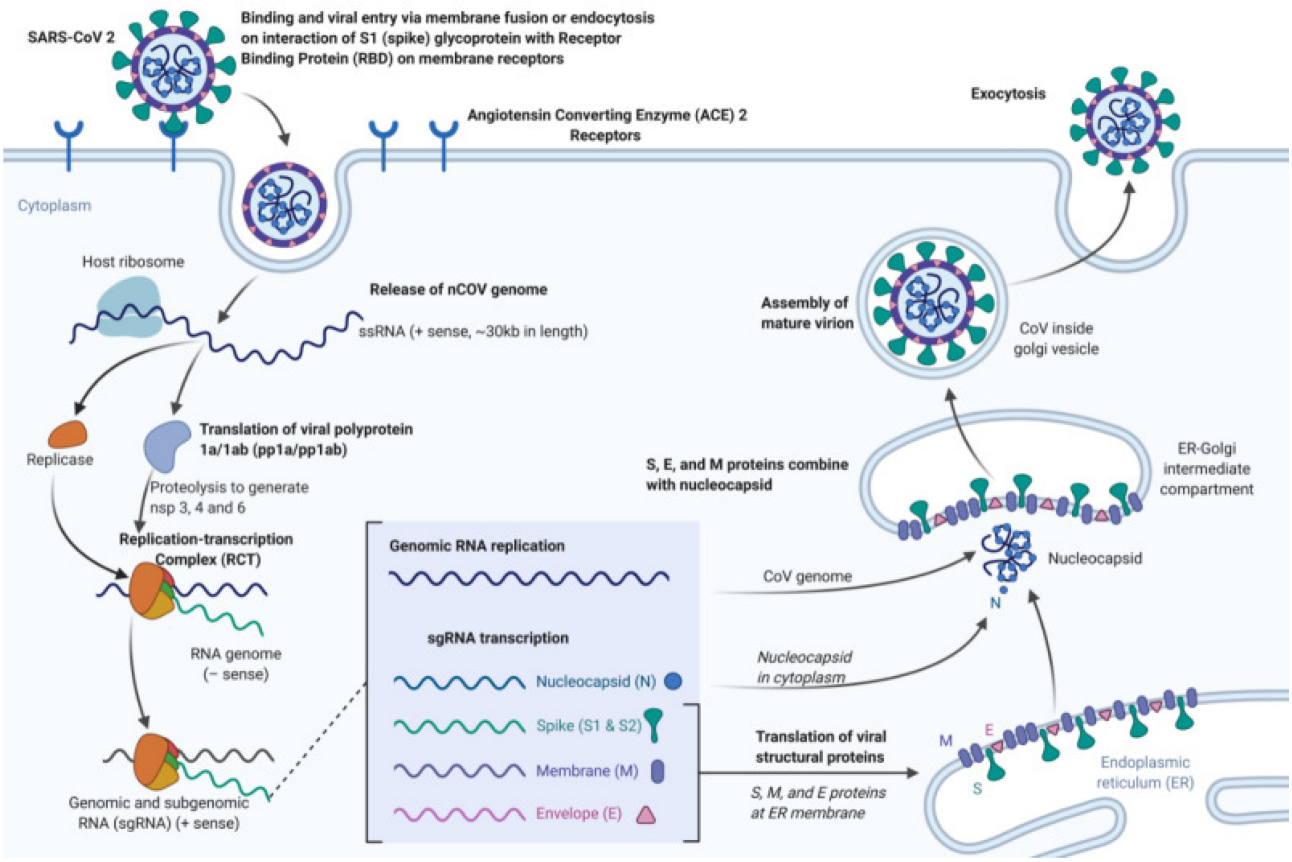

Figure 2 Pathogenesis, corona replication.
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central cyanosis, and (v) Critical stage involving complication like shock, ARDS and multi-organ failure.[13] The clinical feature in children is somehow different from adults. The most common symptom is fever, like in adults, but the incidents of productive cough, vomiting, and diarrhea are much higher than in adults.[42] Unlike adults, dry cough and phlegm are not the most common symptoms.[43] Children rarely progressed to acute respiratory distress syndrome than adults.[44]

Although children have milder symptoms compared to adults, it is important however to note the clinical feature in children may progress to critical condition.[45] COVID-19 in young infants often has an unexplained fever along with mild respiratory symptoms.[46] The most frequently profiled symptoms for children are cough and fever.[10,11] In a study that evaluated 171 children with confirmed SARS-CoV-2 infection in China, the most common reported symptoms were: fever (41.5%), cough 48.5%), and pharyngeal erythema (46.2%).[47] Recently, a systematic review that identified 131 studies comprising 7780 pediatric patients across 26 countries indicated, most common clinical manifestations. They reported that the frequently encountered symptoms are rhinorrhea (20.0%), fever (59.1%), myalgia/fatigue (18.7%), and cough (55.9%).[44] Some children presented with mild or often ignored symptoms such as nasal congestion, nausea, abdominal discomfort, diarrhea, vomiting, and abdominal pain.[48,49] Rash was also documented as infrequent sign among children with COVID-19. Dyspnea or hypoxemia and, sign and symptoms of multi-organ failure were rarely described.[18] Moreover, ARDS and pneumothorax were indicated in children with COVID-19 very rarely.[50]

Laboratory Findings

The viral antigen (SARS-CoV-2 nucleic acid) is identified using real-time reverse transcriptase-polymerase chain reaction (RT-PCR). The preferred sample comes from nasopharyngeal swab. The American CDC recommends the swab must be introduced into the nostril and left inside for some seconds. Soon after sample collection, the sample has to be kept in sterile tubes containing 2–3 mL of viral transport media. Samples have to be kept at 2–8°C for

about 72 hours after collection.[51] The virus can also be detected in stool, sputum, urine, and blood.[52]

Based on current data, a consistently similar result of laboratory findings has not yet been reported in children. The laboratory result varies with the severity of COVID-19 disease.[53] It has been noted that in the early time following the disease onset, either normal or decreased white blood cell count and marginally elevated lymphocyte count have been observed. The majority of patients have normal neutrophil counts.[54,55] Severe cases may be accompanied by; increased serum inflammatory markers such as D-dimer, procalcitonin, creatine kinase, and interleukin-6 and progressively decreased lymphocyte.[44,56] Table 1 summarizes the laboratory changes observed in mild and sever cases of COVID-19 in children

Myoglobin, muscle and hepatic enzymes appeared to rise in kids. Increased CRP and erythrocyte sedimentation rates have also been reported.[57] On the other hand, an observational cohort study from China reported that elevated creatine kinase, decreased lymphocytes, leucopenia, and elevated procalcitonin are typical abnormal laboratory results among children with COVID-19.[58]

Table 1 Summary Laboratory Changes with the Severity of COVID-19

Mild COVID-19	Severe COVID-19
↔ Lymphocytes	↔ Lymphocytes
↓ ↔WBC Count	↑ ↔ WBC Count
↓ Neutrophils	
↑ ESR	
↑ CK-MB	↑ CK-MB
↑ Procalcitonin	↑ Procalcitonin
↑ ALT	↑ ALT
↑ LDH	↑ LDH
↑ AST	
	↑ IL-10
↑ CRP	↑ CRP
↑ D-dimer	↑ D-dimer

Notes: ↓ Decreased, ↔ no change, ↑ increase.
Abbreviations: LDH, lactate dehydrogenase; WBC, white blood cell count; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ESR, erythrocyte sedimentation rate; CRP, c-reactive protein; IL-10, interleukin-10; CK-MB, creatine kinase-MB.

Table 2 Comparison of Laboratory Finding Among Adults and Children with COVID-19

Laboratory Finding	Children	Adult
White blood cell count	Normal	Abnormal
Neutrophil	Decreased	Increased
Lymphocytes	Increased	Decreased
Abnormal ALT	Higher	Lower
Abnormal AST	Similar	Similar
Abnormal CK	Lower	Higher
Abnormal Myo	Higher	Lower
Abnormal PT	Higher	Lower
Abnormal D-dimer	Similar	Similar
LDH	Significantly increased	Increase
CRP	Decreased	Significantly increase
IL-6	Decreased	Significantly increase

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, c-reactive protein; PT, prothrombin time; CK, creatine kinase; LDH, lactate dehydrogenase; IL-6, interleukin-6.

The laboratory report in children is somehow different from adults.[43] In contrast to adults, the white blood cell counts of children were all normal, with decreased neutrophil counts and increased lymphocyte counts. The value of PCT showed no difference between children and adults, however, an elevated level of CRP and IL-6 was shown in adults, but not in children. Children have higher level of LDH compared to adults.[43] The comparison of characteristics of laboratory result in children and adults is summarized in Table 2.

Complications

So far, studies reported that children appear to be less affected by this new coronavirus. But the report showed this rare case my cause several life-threatening complications. Children under 18 years of age with COVID-19, 5.7–20% were hospitalized compared 10–33% adults aged 18–64 years. Besides, 0.58–2.0% children were admitted to an ICU compared to 1.4–4.5% adults. Children aged <1 year accounted for the highest percentage 15–62% of hospitalization among pediatric patients with COVID-19.[11] A syndrome called pediatric inflammatory multisystem disorder which is associated with COVID-19 has been reported widely. The syndrome appears four to six weeks after infection and manifested by high fever, low blood pressure, and abdominal pain.[59] Some children have experienced kidney injury,

inflammation in the heart, gastrointestinal symptoms, or excessive blood clotting.[60] One study on children with the underlying medical problem has reported that few of them developed failure of two or more organ systems as a result of COVID-19 disease, while many of them developed acute respiratory syndrome and supported with a ventilator.[61,62]

Risk Factors to Severe Disease

Most infected children have had mild symptoms with no fever or pneumonia, and have an excellent prognosis.[63] However; few of them suffer from life-threatening complications. Few studies have tried to show that children with underlying serious conditions appear to be at greatest risk. The most commonly profiled underlying chronic conditions are chronic pulmonary disease, cardiovascular disease, immunosuppression, and obesity. Another conditions that may increase the risk of severe disease are seizure, kidney disease, liver disease, an endocrine disorder, and age less than 1 year.[11,64]

Conclusion

The current COVID-19 pandemic is a global public health concern. Research is progressing at an unprecedented speed. Our knowledge regarding the disease in children is evolving from time-to-time. Despite fewer children with COVID-19 have been reported, they are more at risk than adults to be infected with the virus. In most cases, clinical manifestation of the disease in children is not clearly specific and often mild or asymptomatic. Severe conditions, such as life-threatening complications and death associated with the disease have rarely been reported. On top of that, the presentation of COVID-19 disease in children is not intensely studied. An intense investigation of the clinical presentation in children is very important.

Ethical Approval

Ethical approval was obtained from the College of Health Science, Mizan Tepi University Ethical Review Board.

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