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Research Article

A Descriptive Study of SARS-Cov-2 Outcome in Children

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Abstract

The pandemic of SRAS-CoV-2 has infected millions and cost many lives since an outbreak that began in the city of Wuhan of Hubei province of China. Number of cases and severity of disease has been high in older age groups. However, incidence of the disease and the disease severity in the children worldwide has been reported low. The present study investigated the possible factors responsible for low mortality and morbidity in children in India by analyzing the COVID-19 data available from S.M.S Medical College and attached hospitals, Jaipur and www.covid19india.org as of 4th May 2020. The data was categorized into different age groups and distribution in terms of percentage of COVID-19 cases among different age groups was assessed. Fatality rates due to COVID-19 (in%) among different age groups in India was also analyzed.

COVID-19 infection seems to spare the pediatric age in terms of number of infected children and the disease severity possible due to healthier immune system and frequent respiratory infections that might account for enhanced immunity against the novel corona virus. Previous exposure to coronavirus antigen in children and a weaker cytokine storm in response to the viral infection could also underlying the lesser disease severity. Fewer comorbid conditions and a healthier respiratory tract that has not yet been exposed to smoking or environmental pollution, could also be attributed for lesser susceptible to SARS-COV-2 infections. A higher concentration of ACE 2 receptors in children might have a protective role against severe clinical manifestations of the disease.

Keywords: *Children; Age; SARS-Cov-2; Immunity and ACE2*

Introduction

In the month of December 2019 an outbreak of pneumonia due to some unknown agent emerged in the city of Wuhan of Hubei province of China, serving as an epicenter of the disease, that rapidly transformed into a pandemic. The agent, later reported to be a novel coronavirus, was designated as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or coronavirus disease 2019 (COVID-19) by World Health Organization (WHO) during February, 2020 [1,2]. Coronavirus disease may present clinically as common cold or in severe cases as a fatal illness. Past two decades have already witnessed the severity of illness, caused due to corona viruses such as severe acute respiratory syndrome (SARS) in China (2002) and middle east respiratory syndrome (MERS) in the Arabian region (2012) [3]. The usual presentation of novel coronavirus disease (2019) in adults include fever, cough, myalgia, shortness of breath, headache and diarrhea.

A study of more than 72,000 COVID-19 patients in China showed that majority (81%) of the cases presented with a mild illness and about 14% had severe manifestations (like dyspnea or $SPO_2 \leq 93\%$). Only 5% were critically ill (respiratory failure or septic shock, MODS) [4]. Elderly individuals and those with underlying illnesses presented with a poor outcome. The case fatality rate in China was reported to be 2.3% [4], however, the actual situation might be worse, with a possibility of overestimation as mild or asymptomatic cases might have been missed.

Transmission of COVID-19 primarily occurs through respiratory droplets during coughing and sneezing, that may infect any close contact within a range of 6 feet. Virus transmission, though less likely, can also occur through fomites or fecal-oral route. The median incubation period is 5 days (ranging from 2 - 14 days). Non-availability of any US Food and Drug Administration-approved therapeutics leaves the only management option of severe COVID-19 illness to be supportive therapy only. Although, intensive research has been ongoing for vaccine development, but it is expected that a vaccine for wide distribution may not be available for at least a year [5].

Confirmed cases of novel coronavirus worldwide have been 3,442,181 as of 4th May 2020, with 2,39740 cumulative deaths reported. However, incidence of disease in children was lower in terms of number and the available literature also showed lesser severity in this age group. Asymptomatic infections were not uncommon. Disease severity in children seems to be relatively mild and rare under 19 years of age, contributing only 2.4 percent of the total cases. As per the report published on 28th February by WHO during the SARS epidemic in 2003, mortality in children was reported nil, and the majority out of the 800 deaths in the outbreak were aged above 45 years, with men at a higher risk. Out of 8,000 cases of SARS, there were only 135 infected children according to a published report of Centers for Disease Control and Prevention.

Zhou., *et al.* (2020) observed a positive correlation between age and death in patients with COVID-19 [6]. Moreover, research has demonstrated a strong host innate responses to virus infection, reduced expression of type I interferon beta and increase in differential expression of genes associated with inflammation in SARS-CoV inoculated older macaques as compared to the compared to younger adults [7]. The T-cell and B-cell show age-related defects in function and there is higher production of type 2 cytokines that lead to more prolonged proinflammatory responses but poor control of viral replication and a poor outcome [8]. The mean age of those who died in Italy was 81 years and more than two-thirds of these patients either had diabetes, cardiovascular diseases, cancer, or were former smokers. It is therefore true that these patients had underlying health conditions, but it is also worth noting that they had acute respiratory distress syndrome (ARDS) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pneumonia, needed respiratory support, and would not have died otherwise [9].

Materials and Methods

The present study was conducted at S.M.S. Medical College and attached hospitals, Jaipur (Rajasthan) analyzing the COVID-19 data available from www.covid19india.org as of 4th May 2020. Present research design was an observational descriptive type of study. The data was categorized into different age groups and distribution in terms of percentage of COVID-19 cases among different age groups was assessed. Fatality rates due to COVID-19 (in%) among different age groups in India was also analyzed.

Observations and Results

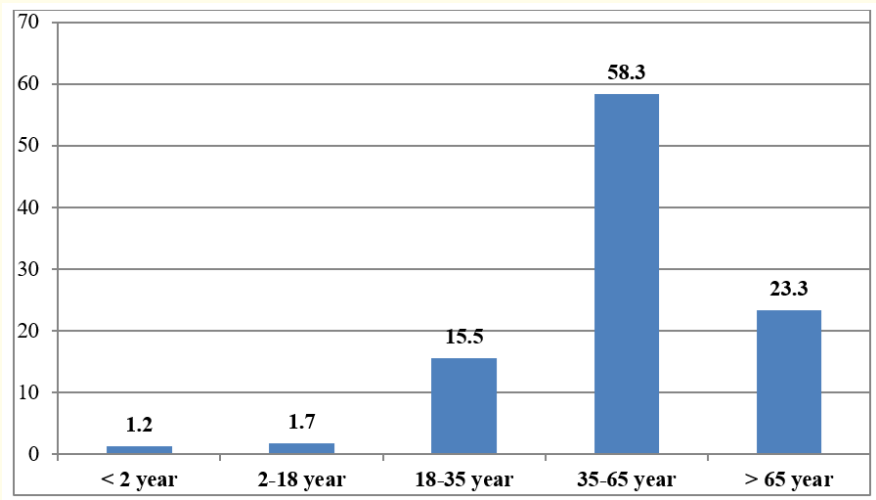

Figure 1: *Distribution (in %) of COVID-19 cases among different age groups in India. Source: www.covid19india.org.*

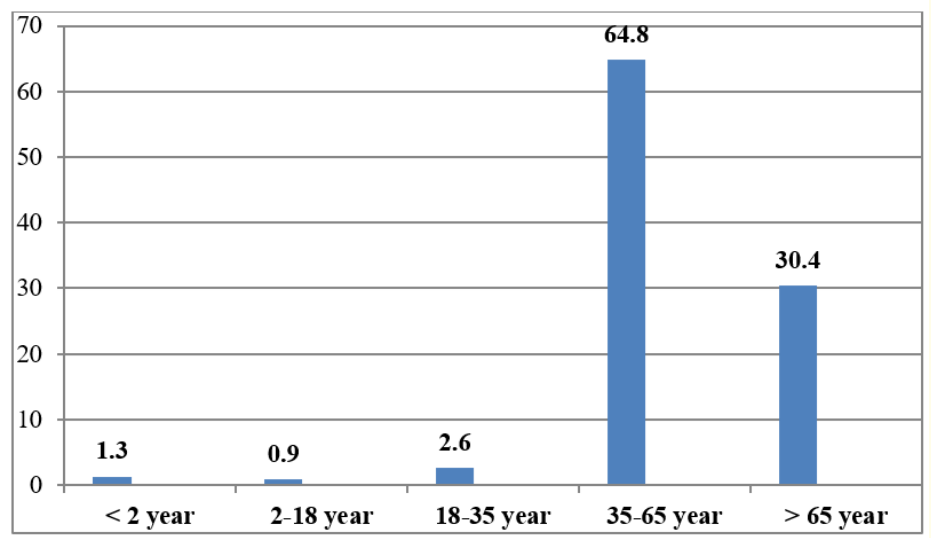

Figure 2: *Fatality rates due to COVID-19 (in %) among different age groups in India. Source: ww.covid19india.org.*

Discussion

Presentation of coronaviruses in children has been not so severe as observed in during epidemic of SARS in past. Mortality rate were also low in patients having age 12 years or younger. A milder disease developed and requirement of ICU, supplemental oxygen therapy or steroid were less likely than adults. Clinical presentation of SARS in patients above 12 years has not been much different to that in adults. There were zero deaths reported among children or adolescents with SARS, and minimal residual changes were reported in exercise tolerance and pulmonary function [10].

The COVID-19 data of India as of 4th May 2020 shows that there were 46,437 positive cases with 1566 deaths reported. Age wise distribution in percentage among COVID-19 cases in India indicates only 1.2% cases reported below 2 years, and only 1.7% cases in the age of 2 - 18 years. 15.5% cases had age between 18 - 35 years, 58.3% have age between 35 - 65 years and remaining 23.3% were aged above 65 years. On observing the age distribution for deaths, it was found that 1.3% cases who died were aged below 2 years, 0.9% cases were aged between 2 - 18 years, 2.6% cases were aged between 18 - 35 years, 64.8% cases were between 35 - 65 years and remaining 30.4% of the cases had age above 65 years (Figure 1). Clinical profile of pediatric patients as observed at a tertiary care center in Jaipur (Rajasthan, India) has shown that up to 22nd April 2020 there were 45 confirmed pediatric cases of COVID 19, out of which only one patient presented with fever and no radiological abnormality was found in any pediatric patient. One death was reported of a pediatric patient who had peritonitis with septicemia as co-morbid condition.

Studies have demonstrated this difference in disease severity among younger and aged mice also. Variability in pulmonary host responses, as evident by higher upregulated immune response and cell-to-cell signaling genes, and continued expression of many genes even after clearance of virus (exaggerated host response to virus) in aged mice, whereas, downregulation of genes related to cellular development, cell growth, and cell cycle during peak viral replication, and restitution after viral clearance in young mice [11].

Analysis of COVID-19 data suggested low intensity of infection in children as compared to adults in terms of symptoms, radiological abnormalities, and laboratory finding. The underlying cause behind this finding remains unknown. It is speculated that a fully active and functional thymus in children might be a factor behind it. Thymus functions as a center for T-cells development, the lymphocytes, that are responsible for so called active immunity [12]. A phenomenon termed immunosenscence is gaining acceptance, that indicates deterioration of immune functions with age in many species including human beings, that underlies higher susceptibility of aged individuals

to infections, cancers and various autoimmune disorders [13]. Ageing has been associated with higher production of pro-inflammatory cytokines by macrophages and fibroblasts, that might be responsible for various age related diseases like diabetes, osteoporosis and coronary artery disease [14,15]. 'Inflamm-ageing' is the term used to describe the process of development of inflammatory disease, as a consequence of production of inflammatory markers due to constant bodily antigenic challenge. The balance between pro- and anti-inflammatory cytokines might prove as an indicator of morbidity and mortality in older individuals [16].

Available literature on susceptibility of children towards COVID-19 infection has shown some conflicting results. However, respiratory viral infections occur very often this age group [17,18] and it has been shown that infants and children are also as vulnerable to get infected with COVID-19 as adults [19,20]. The pathophysiological mechanism underlying the host and viral interaction, remains unknown.

Angiotensin-converting enzyme 2 (ACE2) has been linked with SARS-CoV and SARS-CoV-2 infections. It is a functionally important protein for maturation of angiotensin II to angiotensin 1-7 in many organs such as lungs, myocardium, kidneys and intestine [21,22]. SARS-CoV and SARS-CoV-2 utilize this mechanism and cause downregulation of ACE2 expression [22-24]. Angiotensin 1-7 has protective roles such as, anti-hypertensive and profibrotic effects [25,26] and disruption of this mechanism by SARS-CoV-2 can lead to hypertension and lung injury. SARS-CoV-2 could disorganize Ang II/Ang1-7 level and thus lead to inflammation and hypoxia [27] and blunt the protective effect of ACE2. This dysfunction seems to spare the pediatric age group [26-28]. This is also evident by a negative association between ACE2 expression and SARS-CoV-2 outcome in young individuals [29]. Moreover, estrogen and androgen, that decrease with age have shown to upregulate ACE2 expression [29,30].

A phenomenon termed cytokine storm has been reported previously in SARS-CoV and MERS-CoV infections. The similar storm is also seen in SARS-CoV-2 cases with raised proinflammatory cytokines, type I INF levels. This exaggerated immune response is less prevalent in children [31]. Adult patients with a severe disease, had lymphocytopenia [33-35] whereas, infected children showed normal lymphocytes, suggesting lesser immune dysfunction [36,37]. Frequent viral infections in children may account for higher lymphocyte count apart from inherent high lymphocyte count as compared to adults [38].

Such frequent respiratory infections and the vaccinations in pediatric age group might be a cause of effective and enhanced innate immune defense system against various microbes [39]. This training of immune system through prior antigen exposure might serves as a memory for future infections and subsequently causing enhanced response to reinfection and also provides cross protections to other infections [36]. Vaccination might also contribute as a training of innate immune system providing cross reactivity and subsequent mild disease in pediatric patients [39,40].

The higher prevalence of COVID-19 in adults could be attributed to the associated comorbidities. A previous study indicated 3.4-fold higher risk of developing acute respiratory distress syndrome in patients with H7N9 infection when associated with any comorbidity [41].

Lower than expected rate of children affected by COVID-19 could also be due to previous infections with coronaviruses or decreased likelihood of disease, even when infected with the virus [42]. Another factor might be healthier respiratory tracts of children, that has not been exposed to much cigarette smoke and air pollution as seen in adults [43].

Conclusion

COVID-19 infection seems to spare the pediatric age in terms of number of infected children and the disease severity. The available literature supports the role of immunosenescence in adults making them more susceptible to SARS-CoV-2 infection. Children also get frequent respiratory infections that might account for enhanced immunity against the novel corona virus. There might be a possibility of previous coronavirus antigen exposure in children that may provide better ability of their immune system to handle the viral load. Moreover, a weaker cytokine storm in response to the viral infection could also be the cause underlying lesser disease severity. Children also have fewer comorbid conditions and a healthier respiratory tract that has not yet been exposed to smoking or environmental pollution, making this age group lesser susceptible to SARS-COV-2 infections than the adults. A higher concentration of ACE 2 receptors in lung pneumocytes in children might have a protective role against severe clinical manifestations of SARS-CoV-2 infection. Thus, it can be concluded on the basis available data on SARS-CoV-2 infection, that although children are susceptible but the disease severity is lesser in this age group.

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Volume 9 Issue 8 August 2020