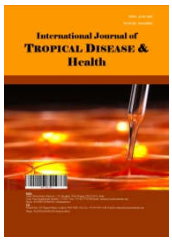

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Age Pattern Related Moribity and Mortality among COVID-19 Patients: Indian Chapter

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Author's contribution

The sole author designed, analysed, interpreted and prepared the manuscript.

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ABSTRACT

The COVID-19 till date has groped in around million lives across the globe that includes children and elderly who became a victim of this pandemic. During course of this pandemic, there has been discussion of age related vulnerability to the disease and the preventive measures and policies implemented by various countries across the globe. The elderly have suffered a disproportionate burden of COVID-19. Patients associated co-morbidities pose a greater threat to that group as compared to general population. The epidemiological data and Case Fatality Ratio (CFR) collected from countries vary significantly but give a vivid picture of the situation of the pandemic in each region. Hence, the author reviewed the published data from several countries to investigate relationship between age and COVID-19 mortality and morbidity. The author also took the time to study briefly about the role of angiotensin converting enzyme 2 (ACE2) as a receptor against the new coronavirus SARS-CoV-2. The author also reviewed the literature for studies explaining the difference in the physiological inflammatory response to SARS-CoV-2 infection according to age.
Thus, the information achieved from these data will prove to be useful in determining the precautionary and preventive policies irrational treatment of COVID-19.

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Keywords: COVID-19; SARS-CoV-2; age; CFR; mortality; morbidity; ACE2; pandemic.

1. INTRODUCTION

The world today is fighting against an epidemic related to acute respiratory syndrome in humans, whose source remains unknown and was first reported in Wuhan, China in December, 2019. On March 11, 2020, the World Health Organization declared coronavirus disease (COVID-19), caused by the novel coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a pandemic concerned both by the alarming rate of spread and severity and by the alarming levels of inaction [1].

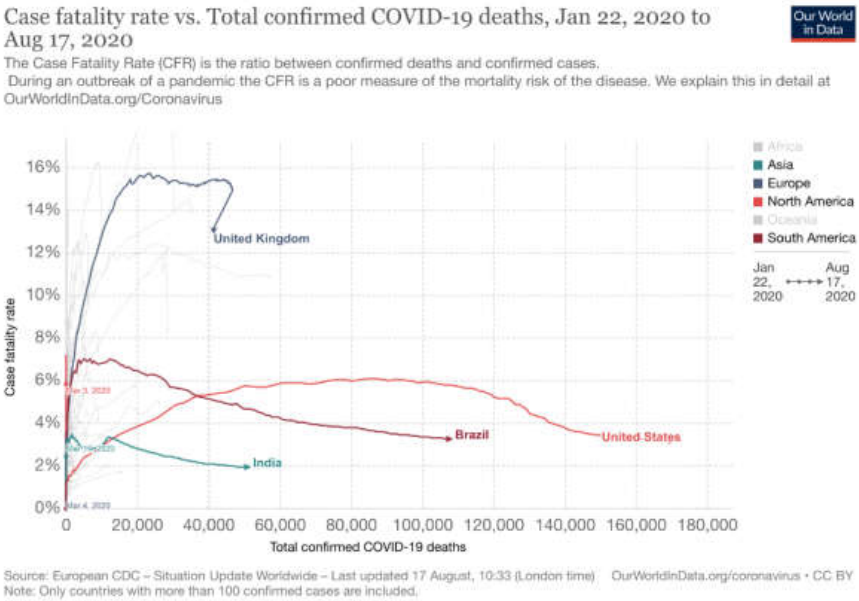
Till date COVID-19 has caused deaths of 770,314 people across the globe, India ranking 3rd with the total number of cases recorded and 4th for the number of total deaths recorded as of 17 August, 2020 according to the WHO [2]. The surge of infected patients beyond the limits of medical systems has raised social concerns on whether age should be considered in determining treatment intensity [3].

COVID-19 fatality rates vary significantly from country to country [3]. It was 3.1% for United States with total deaths recorded 170,052 as of 17 August, 2020 [4]. It was 4th highest for United Kingdom with fatality rate of 13% and total deaths recorded of 41,366 people dated on 17 August, 2020. The CFR in India stands at 1.9% with total number of cases 2.65 million and total deaths recorded 50,921 as of 17 August, 2020. Yemen holds the highest Case Fatality Rate of 28.4% [4].

In another analysis of cases in China diagnosed as of February 11, 2020, the overall CFR was 1.92%. However, the CFR was 8.0% in patients aged 70 – 79 years and 14.8% in patient's aged ≥80 years [5].

This variation in fatality rates may be due to differences in healthcare adequacy and/or epidemiological characteristics of patients. The frequency of diagnostic screening in asymptomatic or mildly symptomatic patients may also influence the rate [6].

During the course of this pandemic, the age-associated vulnerability has been discovered and is quite in discussion. Understanding the degree of vulnerability in mass populated countries is of paramount importance, especially during the pandemic. The perception that young people have lower morbid conditions, result in lowered degree of awareness of preventing infection in some regions making them vulnerable of getting in contact and participating in the cluster formation. The disease affects all age groups and is exacerbated in individuals with underlying comorbid diseases [7].



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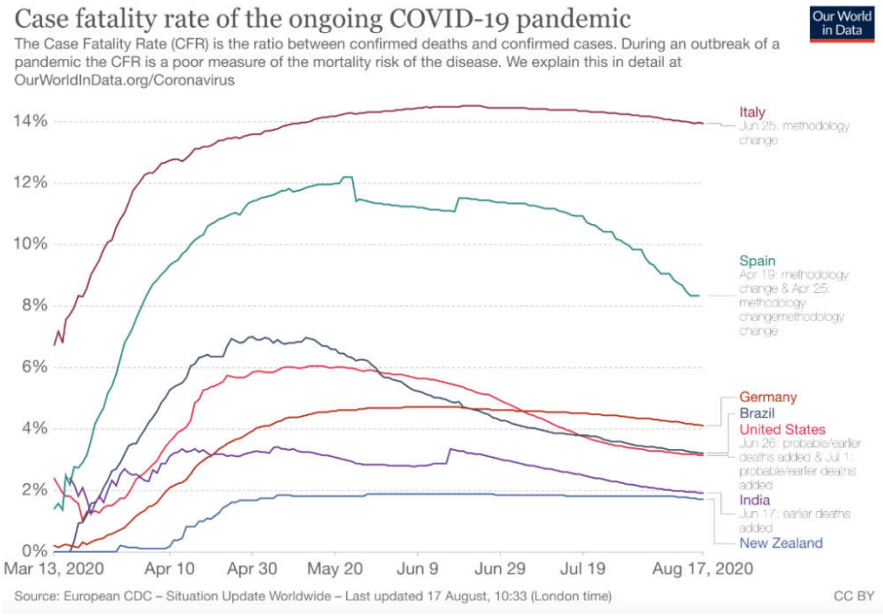


(B)

Fig. 1. (A) Case fatality by total number confirmed COVID-19 deaths recorded of January 22 to August 17, 2020 [4]. (B) Case fatality rate of the ongoing COVID-19 pandemic Italy>Spain>Germany>Brazil>Unites States>India>New Zealand [4]

India holds 2nd highest place in terms of population totaling up to 1.2 billion.

For India, the total deaths recorded per million were 23 and case fatality rate (CFR) of 2.38 % with 30,601 total deaths of 1,337,021 recorded cases as of 24 July, 2020 [3,8].

Due to early initiation of lockdown and decision of keeping people in quarantine by the Indian Government, showed a delayed transmission of COVID-19 in India as compared to other nations.

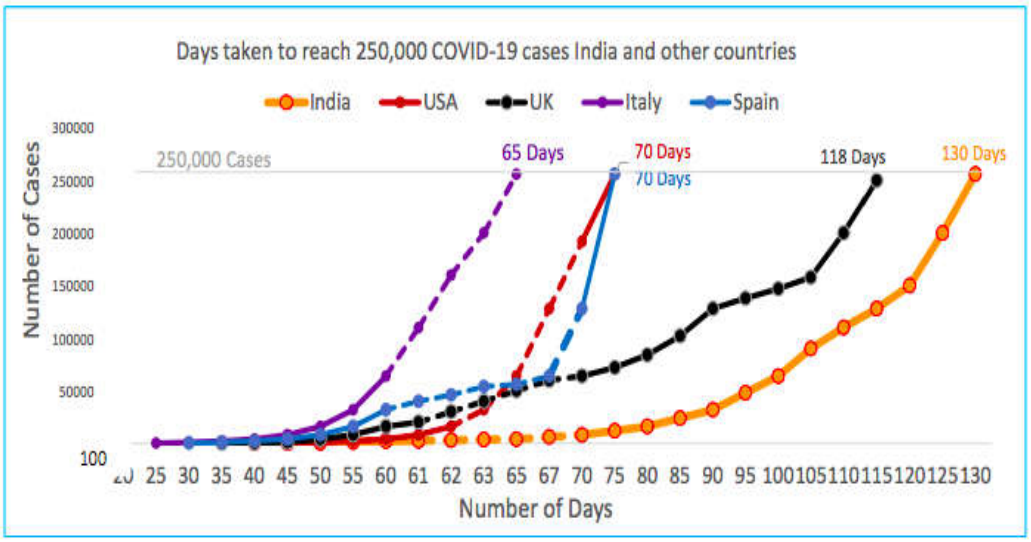
According to the population census recorded by the Indian Government, huge chunk of population of the country is contributed by age group 25-44 (27.6%) [8]. Following which lie the age group of 45-64(13.5%) which are most prone to COVID-19 associated death [9,10]. Indicated in Table 2.

Age associated CFR trend analysis in India indicated people above 45 years of age which comprises about 25% of Indian population are at a higher risk from coronavirus infection, accounting for 85% deaths so far [9]. Within this age group, most deaths (71%) were among those in 45-74 age group as per the Indian Health Ministry data. But the data also revealed that people of the age groups 30-44 and 45-59 years, comprising 37% of total population registered 43% COVID-19 deaths as of 10 July, 2020 [9].

The total number of adjusted cases in India were distributed as per the distribution of total cases for which age is known and total number of confirmed cases. Findings suggest that about 60% of COVID-19 cases were in the age group of 30-64. About 2.3% deaths were under 15 years, 12.8% were in15-44 age group, 48.2% deaths were in 45-64 age group and 36.8% were in 65+ age group. A major share of the COVID-19 deaths is in the working age group. The age specific case fatality ratio increases sharply from age 45 years and above [10].

In terms of death per 100,000 individuals in the population (as of July 10, 2020, data from the New York City Department of Health and Mental Hygiene, and as of July 10, 2020, data from the Office for National Statistics of United Kingdom), clear patterns of age-based significant exponential increase in fatality has been observed [11,12].

Case fatality ratio (ratio of death to confirmed cases) is low in United States followed by India and Pakistan and Russia. It is much higher for United Kingdom.



Source: WHO Situation Reports as received by WHO from national authorities by 10:00 CEST, 14th June 2020

Fig. 2. This depends upon various factors such as population of country, population density, government rules and policies against pandemics, test conduction rate, date of first COVID-19 case reported, initiation of quarantine and lockdown strictness. India took long enough to reach 250,000 cases (130 days) due to early lockdown and quarantine procedures

Table 1. Comparison of CFR at varying ages across India, a hike in COVID-19 deaths recorded in gap of 60 days

Age	Share in Total Population(%)	% share in all COVID-19 deaths	
		Till July 9	Till May 21
<=14 years	35	1	0.5
15-29	18	3	2.5
30-44	22	11	11.4
45-49	15	32	35.1
60-74	8	39	40.2
>=75	2	14	10.3

India's recovery rate is lower than countries such as Switzerland, Russia, Turkey and Iran where duration is even lower or similar to India. Recovery-death ratio (number of recovered per death) is a good indication of chance of recovery from the disease [10].

The study of illness spectrum is one of the most critical issues by clinical and public health professionals affecting largely the triage, diagnostic and therapeutic decisions. Therefore it becomes quite important to understand the morbidity and mortality associated COVID-19 according to age.

However, the data published in each country are inconsistent because of multiple reasons such as different populations, extent of available laboratory tests, and medical systems.

Hence, it becomes important to review the COVID-19 epidemiology data published from several countries to detect any consistent trends in the relationship between age and COVID-19-associated morbidity or mortality.

2. COVID AT ELDERLY AGE

Among all Covid-19 patients, elderly population is still at a much higher risk of death due to high mortality rate and high CFR and symptomatic infection rate.

As you get older, your risk for severe illness from COVID-19 increases. For example, people in there 50s are at higher risk for severe illness than people in their 40s. Similarly, people in there 60s or 70s are, in general, at higher risk for severe illness than people in there 50s. The

greatest risk for severe illness from COVID-19 is among those aged 85 or older [13].

Several studies have reported old age to be a significant risk factor for COVID-19 mortality [14,15]. As of 30 April, the case fatality rate in Maharashtra for the 40 to 49 year-olds, for example, was 4%. Italy's fatality rate for the same age group was a tenth of that [16].

Table 2. The CFR is highest for the age group of 75-79 followed by the age group 70-74, then>80 . The age group of 60-69 accounts to 51.51% of CFR. A similar trend was observed in other countries as well [10]

Age group	Deaths	% distribution of COVID-19 cases	Case Fatality Ratio (CFR)
0-4	7	1.37	1.50
5-9	0	0.59	1.70
10-14	2	0.33	0.90
15-19	3	0.72	1.43
20-24	6	0.91	0.76
25-29	5	1.17	0.69
30-34	7	1.76	0.85
35-39	15	2.86	1.73
40-44	22	5.33	3.47
45-49	45	8.32	6.41
50-54	61	11.51	11.60
55-59	71	13.13	14.65
60-64	70	15.21	24.60
65-69	93	13.59	26.91
70-74	46	10.99	49.25
74-79	30	6.76	50.08
80+	28	5.46	48.12
Total	511	100.0	

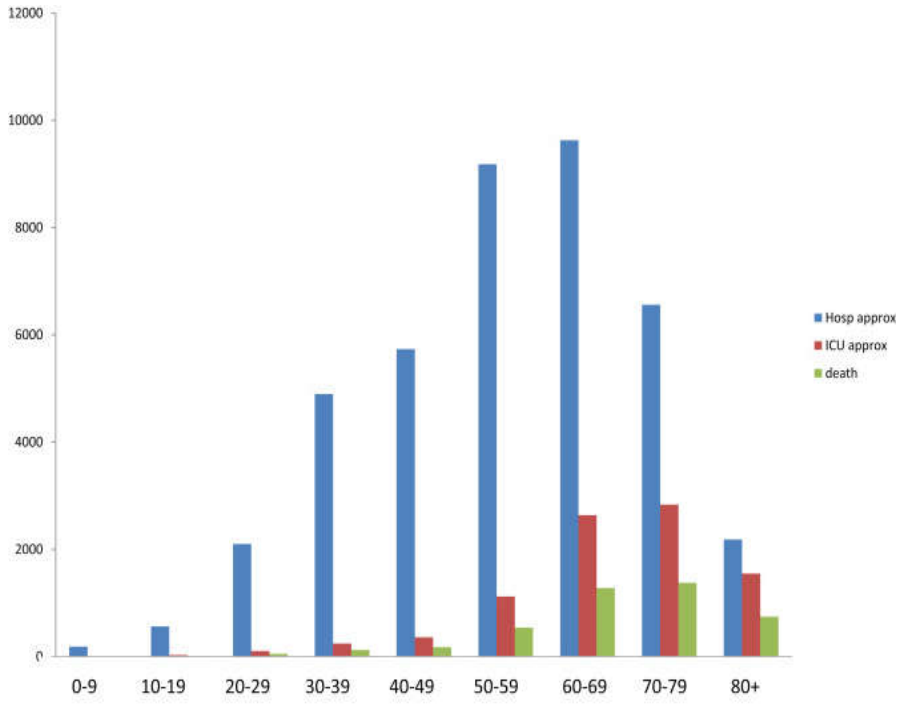


Fig. 3. Age also affects the time from hospitalization to time of viral clearance and discharge with full recovery

Table 3. Projected age-stratified impact of COVID-19 on hospitalization, ICU admission, and fatality, in India [17]

Age group	Indian demographic Distribution(%)	Hospitilization rate	ICU admission rate(%)	Infection fatality rate
0-9	18.4	0.1	5	0.002
10-19	18.8	0.3	5	0.006
20-29	17.5	1.2	5	0.03
30-39	15.3	3.2	5	0.08
40-49	11.7	4.9	6.3	0.15
50-59	9	10.2	12.2	0.6
60-69	5.8	16.6	27.4	2.2
70-79	2.7	24.3	43.2	5.1
80+	0.8	27.3	70.9	9.3

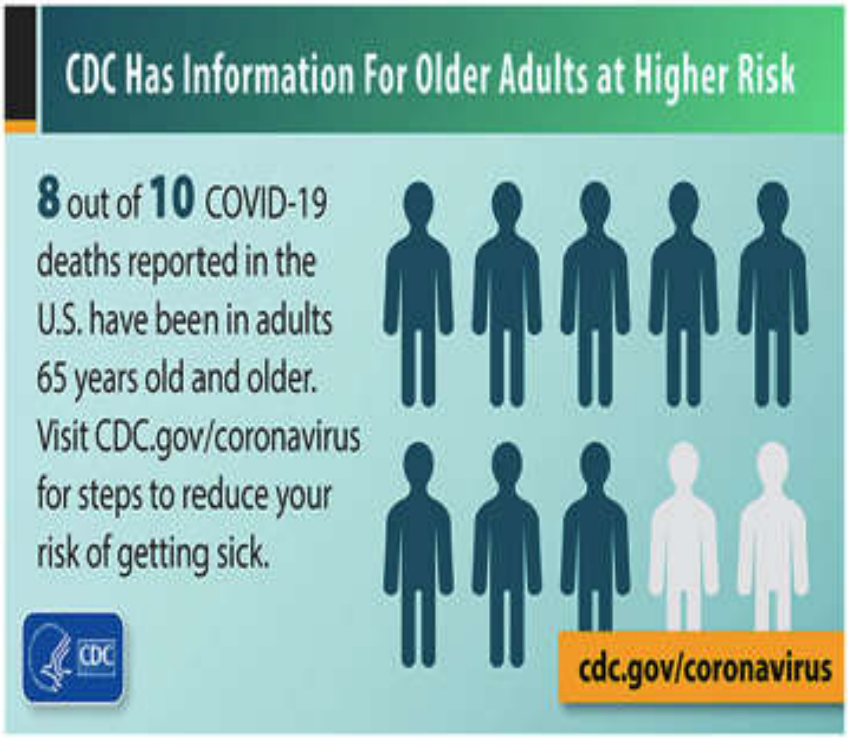


Fig. 4. CDC awaking elderly of the risk of COVID-19

In an animal study, SARS-CoV-2 caused more severe interstitial pneumonia and viral replication in lung tissues of old monkeys than in those of young monkeys [18]. Decreased number of B-lymphocytes, T-lymphocytes and natural killer cells due to aging is one of the best explanation of host's weaker immune response to the virus, compared to other age groups, leading to more severe cases and deaths.

Briefly, in old age, the production of naïve T and B cells decreases, and the function of innate immune cells is impaired; hence, cells involved in the innate immunity do not get activated efficiently during an infection, and progression to an adaptive immune response does not occur in a coordinated manner [19]. These changes reduce the effectiveness of viral clearance and increase the likelihood of triggering a dysregulated immune response in which cytokines are released extensively by activated immune cells, resulting in a cytokine storm [20]. Another well-recognized feature of aging immunity is chronic subclinical systemic inflammation, also known as inflammaging. Inflammation is a key pathogenic mechanism in COVID-19; hence, inflammaging has been estimated to contribute to the poorer outcome in elderly patients with COVID-19 [21].

3. COVID-19 AT ELDERLY WITH CO-MORBIDITIES

Among adults, the risk for severe illness from COVID-19 increases with age, with older adults at highest risk. Severe illness means that the person with COVID-19 may require hospitalization, intensive care, or a ventilator to help them breathe, or they may even die.

According to a press release by the Ministry Of Health And Family Welfare on deaths due to COVID-19, *"It is seen that only 10% of Indian Population (>60 years of age) is contributing to 50% of India's COVID-19 deaths. 73% of COVID-19 deaths in India are people with co-morbidities which include Diabetes Mellitus, cardiovascular disorders and respiratory disease's. Hence these high-risk groups need to be effectively protected"* [22].

73% of COVID-19 deaths in India are associated with co-morbidities. People of age 40 and above were observed suffering from moderate or severe co-morbidities [23].

In reference to the above statement, Indian Government has laid out rules for the welfare and pandemic management that orders senior citizens of age 60 and above to strictly reside indoors and avoid unnecessary contact. On June 2, 2020 the nodal ministry outlined the composition of high-risk groups who require adequate protection.

According to the 2019 IDF Diabetes Atlas, [24] India is home to the world's second largest number of adults diagnosed with diabetes. Of the total adult population (859 million) in India, 77 million (8.9%) have diabetes of various types [24]. Of the total diabetic population, 12.1 million people lie older than 65 years of age [24].

The Global Burden of Disease (GBD) report published in 2017 estimated that 61.8 percent of the deaths in 2016 were due to Non-Communicable diseases (NCDs) [25]. Three-fourths (73.2%) of deaths lie in the age group of 40-69, and 71.6 percent of deaths in the age group of 70 and above in 2016 were attributed to NCDs [26]. The total number of adult deaths in 2016 attributed to NCDs accounts to a total of around 56.9 million [24].

Both the IDF Diabetes Atlas and The India State-Level Disease Burden Initiative [24] provide a snapshot of adult population at risk due to COVID-19. This estimates for population at high-risk lies between the range of 56.9 million to 77 million.

The average number of co-morbid conditions increases with age. According to Liu et al., elderly COVID-19 patients had a significantly higher performance score than young and middle-aged patients [27]. In addition, older adults living in long-term care facilities are at the highest risk because of their chronic illness and the impact of congregate housing [28].

There are also other factors that can increase their risk for severe illness, such as having underlying medical conditions. By understanding the factors that put you at an increased risk, you can make decisions about what kind of precautions to take in your daily life [13].

4. COVID AT EARLY AGES

Based on published reports, SARS-CoV-2 infection seems to affect children less frequently and with less severity. One possible reason behind this is that children have less outdoor activities due to closure of schools and other educational institutions across many parts of the world and undertake less international travel making them less likely to get infected with the virus. This doesn't mean that all children are immune to COVID-19 infection, but is more largely based on precautions undertaken.

Whereas most COVID-19 cases in children are not severe, serious COVID-19 illness resulting in hospitalization still occurs in this age group. Social distancing and everyday preventive behaviors remain important for all age groups as patients with less serious illness and those without symptoms likely play an important role in disease transmission [29,30].

In India, the CFR gathered for children less than 4 years was found to be 1.50% and was highest for age group 5-9 (1.7%) [10]. Refer to Table 2.

There appeared to be proportionally more severe illness in infants, a result that could have be confounded by concomitant bronchiolitis [31].

Children who have medical complexity, who have neurologic, genetic, metabolic conditions, or who have congenital heart disease might be at increased risk for severe illness from COVID-19 compared to other children [13].

History has recorded several cases in the past that shows more or less a similar data and trend

when compared with SARS-CoV-2 virus, responsible for the COVID-19 pandemic.

During the 1918 outbreak of "Spanish flu," those ≥65 years old and children ≤15 years experienced little or no change in excess mortality as compared with that of the previous influenza season. Nevertheless, those aged 15–24 and 25–44 years experienced sharply elevated death rates [32]. On the other hand, several infectious diseases are well known to be less severe in children. Paralytic polio occurred in approximately 1 in 1000 infections among infants, in contrast to approximately 1 in 100 infections among adolescents [33].

The overall case-fatality rate of severe respiratory distress syndrome (SARS) ranges from 7% to 17%. Persons with underlying medical conditions and those older than 65 years of age had mortality rates as high as 50%. However, there was no mortality in children or in adults younger than the age of 24 years [33].

The recent study led by Marc Tebrugge of University College, London addresses the scarce data of COVID-19 in children and adolescent's.

"Our data indicate that the case fatality rate (CFR) in children and adolescents across Europe is less than 1%. Considering that many children with mild disease will never have been brought to medical attention, and therefore, not diagnosed, it is highly probable that the true CFR is substantially lower than the figure of 0·69% observed in our cohort," the authors said [34].

Unlike a greater percentage of adults with co-morbidities, only 25% (145/582) children had a pre-existing condition. Four of 582 (0.69%) children who were infected by the virus died [35]. More active and rapid innate immune response to an antigen and an elevated number of B-lymphocytes, and natural killer cells are also suggested as an immunological mechanism for children to resist an infection [36,37].

Pediatric cases reported during the previous outbreaks of SARS in Hong Kong and MERS in South Korean, were very few [37]. In addition, mortality rate of SARS and MERS in the adults was very high, but there were no fatalities in the pediatric cases [37]. The findings indicated that children appeared to have a milder form of the disease caused by the coronaviruses [38]. Current data about COVID-19, in pediatrics is similar to SARS and MERS in case of disease severity and mortality and shows that children of all ages can get COVID-19, but they seem to be affected less commonly than adults [39].

Thus so far, there is no clear explanation for the children-sparing pattern of SARS-CoV-2 infection. The following hypotheses have been reported in the literature: 1) the possibility that children are less frequently exposed to infection sources due to closure of child care facilities, preschools, and schools, 2) children are less susceptible to the infection itself presumption of safe environment, and 3) children are less likely to be symptomatic or develop severe symptoms; hence, the number of cases is underestimated [40,41,42]. More evidence and studies are needed to prove the hypotheses.

However, recently, Bi et al reported the result of tracing 1,286 close contacts in China; children were as likely to be infected as adults (infection rate in children aged <10 years: 7.4% vs. population average: 6.6%) but less likely to be symptomatic or develop severe symptoms [43].

5. ANGIOTENSIN-CONVERTING ENZYME 2 (ACE2) RECEPTOR

The virus uses the ACE2 receptor to invade cells, which is the same receptor as that for severe acute respiratory syndrome coronavirus (SARS-CoV), and mainly spreads through the respiratory tract. These receptors are present on many cell types in the body including immune cell such as monocytes, neutrophils and lymphocytes.

Specific inhibitors such as angiotensin II type 1 receptor (AT1R) antagonist, losartan, have been shown to be effective in animal models of septic shock [44].

Patients with either very high ACE2 levels (such as in diabetes or cardiovascular disease) or very low levels (animal models of hypertension) can have an abnormal immune response and pulmonary inflammation [45].

Concerns exists that angiotensin-converting enzyme inhibitors (ACE inhibitors) and angiotensin receptor blockers (ARBs) increase susceptibility to coronavirus SARS CoV-2 (the viral agent that causes the disease COVID-19) and the likelihood of severe COVID-19 illness [46].

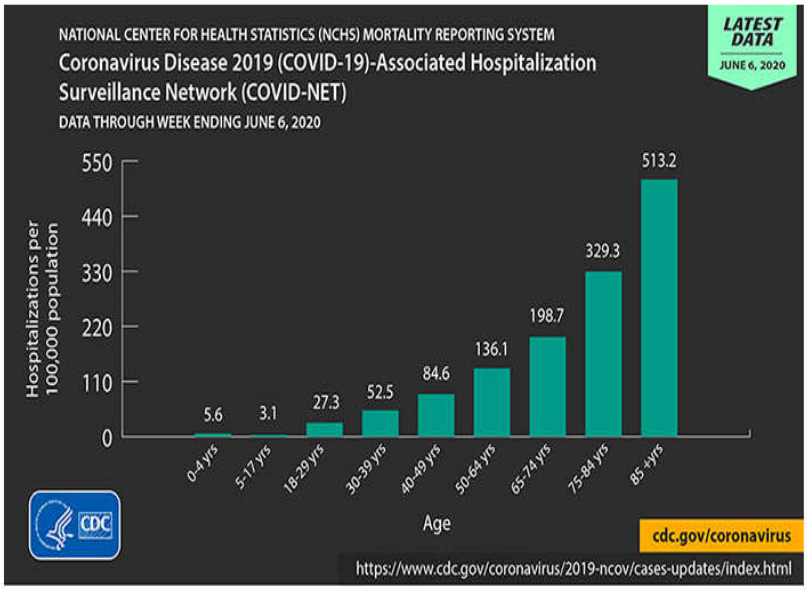


Fig. 5. According to NCHS Mortality reporting system, number of patients hospitalized per 100,000 population. Maximum number of elderly admitted and minimum were observed in age group 5-17

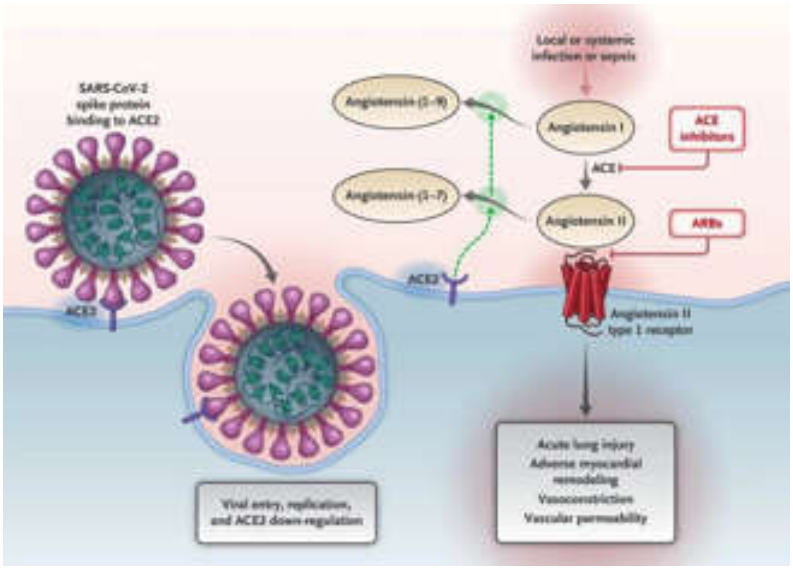


Fig. 6. Interaction between SARS-CoV-2 and Renin-Angiotensin Aldosterone system [47]

In a study conducted by Xie et al., ACE2 expression was observed to dramatically decrease with aging in a rat model [48]. Low levels of ACE2 have been detected in patients with underlying chronic conditions, which generally do not affect the pediatric population [49].

In respiratory syncytial virus (RSV), ACE2 protected against severe lung injury both in children and an experimental mouse model. RSV disease pathogenesis was worsened via activation of AT1R, and a recombinant ACE2 decreased the severity of RSV-associated lung injury (Guo et al., scientific reports) [44].

However, Schouten et al. found that in contrast to preclinical models there are no significant differences in ACE and ACE2 in different age groups from newborns to old age [50,51].

However, studies show that ACE2 is involved in protective mechanisms of the lung. It may protect against severe lung injury induced by respiratory virus infection in an experimental mouse model and in pediatric patients. ACE2 also protects against severe acute lung injury that can be triggered by sepsis, acid aspiration, SARS, and lethal avian influenza A H5N1 virus infection [44].

However, there is low certainty evidence that patients on long term therapy with ACE inhibitors and ARBs are not at higher risk of poor outcomes of COVID-19 patients [52].

6. INFLAMATORY RESPONSES IN VARYING AGES

Inflammatory responses in adults and children differ and vary throughout the lifespan [53].

Schouten et al. found that increasing pro-inflammatory cytokines associated with neutrophil function with age also correlated with severity of acute respiratory distress syndrome (ARDS) and may partially explain age-dependent difference [49].

Levels of myeloperoxidase, interleukin (IL)-6, IL-10 and p- selectin were higher with increasing age, whereas intercellular adhesion molecule-1 was higher in neonates in bronchoaveolar lavage samples.

Thus there are several reasons why children may fare better if infected with COVID-19, which can be further determined by studying the immune responses in varying age groups that will prove as a valuable tool for immunotherapies.

According to a study conducted in China dealing with clinical features observed in COVID-19 patients in elderly and young ages found out that the most common symptoms observed in both groups were fever, followed by cough and sputum [51]. But the PSI (Pneumonia Severity Index) score of the elderly group was higher than that of the young and middle-aged group ($P < 0.001$). The proportion of patients with PSI grade IV and V was significantly higher in the elderly group than in the young and middle-aged group ($P < 0.05$). [51].

7. CONCLUSION

The age pattern of mortality clearly suggests that the COVID19 is likely to affect the adults 45-75, majority in working age group. Beyond age 60, the probability of death due to COVID-19 is at least four times higher among elderly compared with the working age group (18-45).

Social distancing should be mandatory at all times and immunity boosting drugs and remedies should be consumed. Since there is no prescribed therapeutic drug or vaccine, prevention is the only key of safeguarding and is most important for the older adults. The studies dealing in immunotherapies make a promising approach to develop a more effective and preventive approach towards this pandemic. This pandemic can be used to create greater awareness about the rationing of healthcare resources in a time of crisis.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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