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ACE2, Expression and It's Role of Mortality and Morbidity in Adults, and Children in Upcoming Newer Variants of COVID-19, Pandemic Waves: A Systematic Review and Meta-Analysis

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Abstract: ***Background*: Human coronaviruses can be divided based on their pathogenicity. The types with high pathogenicity including SARS-CoV, MERS-CoV, and the current novel SARS-CoV2. SARS COV2 has led to possibly the worst pandemic of this century in the form of Coronavirus disease 2019 (COVID-19). Initially recognized as a respiratory system disease, COVID-19 has been found to interact with and affect the cardiovascular system leading to myocardial damage and cardiac and endothelial dysfunction mainly via the Angiotensin-converting enzyme[5] 2 (ACE-2) receptor. In fact, cardiac damage has been noted even without clinical features of respiratory disease. The ACE2 receptors are identified in 72 tissues, ACE2 expression levels were. There are two immune-response phases of COVID-19 disease. *Phase 1*; occurs during the incubation stage of the disease, during which the adaptive immune system works to eliminate the virus; if any defects occur at this stage, SARS-CoV2 will disseminate and induce systemic organ damage, with more significant destruction of organs with higher expression of ACE2 receptors, including lung, endothelial cells, the heart, and the kidneys. This massive damage leads to *Phase 2*: severe inflammation in the affected organs. Diabetes, atherosclerosis, and obesity, which are risk factors for cardiovascular disease, down regulate the immune system. These have been associated with a poor prognosis in COVID-19. In addition, some studies have indicated that person-to-person transmission of SARS-CoV-2 can occur by routes outside of the respiratory tract .A study of patients infected with SARS-CoV-2 showed that females were less susceptible to infection than males. Older males with co morbidities were more likely to be infected with SARS-CoV-2. Taken together, these data indicate that: 1) SARS-CoV-2 may infect other human tissues in addition to lungs, and 2) Males may be more susceptible to SARS-CoV-2 infection than females.***

Keywords: ACE2, mRNA, AT1, Interleukin, TNFα2, Angiotensin ll, SARS COV2, IL, Chemokines, CFR

Aim: To find out the morbidity, mortality in relation to the system wise involvement of the COVID-19 infected patients.

1. Introduction

The possibility that a mild or moderate ACE2 deficiency may protect from viral invasion seems unlikely because of the intrinsically high affinity of corona virus spike protein to ACE2 receptors, Causing Novel Corona viral pneumonia[1,2]. The *ACE2*-expressing lung cells were more abundant in males, potentially explaining the elevated susceptibility of males to SARS-CoV-2 infection. Highest expression in the small intestine, testis, kidneys, heart[3], thyroid, and adipose tissue. Medium expression levels in the lungs, colon, liver, bladder, and adrenal gland, and .Lowest expression in the blood, spleen, bone marrow, brain, blood vessels, secondary lymphoid tissue and muscle. The SARSCOV2 presents with all the signs and symptoms related to these systems like URTI,LRTI,ARDS Myocardial injury, systemic inflammatory disease secondary to cytokine storm all including $TNF\alpha_2$ vasculitis, thrombi ,micro thrombi may cause thromboembolic manifestations like Central venous thrombosis ,pulmonary thromboembolism, GIT manifestations[4] like profuse watery diarrhea[4] ,mesenteric artery thrombosis, elevated liver enzymes, Endocrine "shock" etc . SARS-CoV-2 and the Immune Response.

At lung level, such deregulation would much facilitate the progression of inflammatory and hyper-coagulation processes due to hyper activation of angiotensin ll. This would be due to an *impaired immune* response to *initial viral invasion*, or a genetic susceptibility to hyper-inflammation and thrombosis. Without elucidation exact mechanism and confirmation, it may not plausible to explain why mortality was significantly higher in male COVID-19 patients than females. As reviewed elsewhere, it has been stated that male patients may had higher expression of angiotensin-converting enzyme 2 (ACE2), which may be regulated by male sex hormones rendering them to more risk for SARS-CoV-2 infection and poor clinical outcomes as well In addition, this may be partly because ACE2 expression encoded by the ACE2 gene lays on the X-chromosome, thus allowing females to be potentially heterozygous whereas men who are definitely homozygous.

With all these theories, ACE2[5] receptor expression is the key role of the viral invasion and immune response and pathogenesis leading to mortality and morbidity. In view of upcoming CORONA variants and pandemic waves. In adults with BMI >30 is obesity with high expression of ACE2 receptors are high risk of developing respiratory, metabolic Covid-19-related pancreatic[6] injury and thromboembolic complications.

1) The children will be affected more than adults because most of the adults develop herd immunity, the ACE2 receptors will be competitively blocked by the cytokines and other antibodies, and there would be less chance of viral invasion in adults.
2) The children are not being vaccinated so far, hence viral infection and viral invasion will be more in the children who are from affluent society because of lack of herd immunity and large body surface area(>95 percentile) due to obesity expressing excessive ACE2 receptors than in lean body mass (<5th percentile). Obesity[7,8,11] doubles mortality in patients hospitalized for severe acute respiratory syndrome coronavirus 2 Poor and lower middle class children; moreover these people develop herd immunity because of their living conditions. It was extremely difficult to find age ranges to assess risk of mortality since there was wide variability in reporting clinical outcomes with age ranges. Out of 20 included studies, only 6 studies reported clinical outcomes in such a way that facilitates grouping patients into two arms in which one arm had age <50 years, while the other arm had age ≥50 years. No other suitable age ranges were found to consider for analysis.

To prevent the high mortality and morbidity all age groups of children should be vaccinated. The upcoming variants will be highly infective but non obese children rarely succumb, if they are vaccinated. The main concern is about MIG, and HIG or high affluent obese children will get severe disease and mortality will be more unless vaccinated for SARS COV2.

Cytokine Storm

Cytokines are signalling molecules produced by cell for specific biological functions. For example, interleukin is a type of cytokine. Chemokine is a type of cytokine that is produced as a "chemo-attractant molecules" i.e to attract cells to sites of infection/inflammation e.g. Interleukin 8. Cytokine is a general term used for all signalling molecules while chemokines are specific cytokines that function by attracting cells to sites of infection/inflammation when produced in huge quantities, these pro-inflammatory cytokines, particularly IL-6, generally correlate with respiratory failure and mortality. Cytokine release syndrome occurs in patients with severe COVID-19 infection In many patients who become critically ill, the SARS-COV-2 virus triggers a hyper inflammatory response characterized by excessive cytokine release, often referred to as a 'cytokine storm'. Molecules such as interleukin (IL)-6, IL-1, IL-2, IL-7, IL-10, interferon (IFN)-γ inducible protein, Monocyte chemo attractant protein (MCP)-1, Macrophage inflammatory protein(MIP)1A and tumor necrosis factor (TNF)-α2[10] cause widespread damage, with the cytokine storm proportional to the severity of **COVID-19 produced by white cells.**.

Other Possible Mechanisms

Certain medications such as corticosteroids, antiviral medications, and immunological agents may have cardiotoxic side effects. Electrolyte disturbances can occur in any critical systemic illness and trigger arrhythmias, for which patients with underlying cardiac disease are at higher risk. There is particular concern about hypokalemia in patients with COVID-19, given the interaction of SARS-CoV-2 with the renin-angiotensin-aldosterone system. Hypokalemia is well known to increase vulnerability to various kinds of arrhythmia. The invasion of pancreas[7] by these pro inflammatory cellular molecules may damage the pancreas and produce metabolic complications diabetes mellitus in susceptible individuals. Diabetes mellitus is a high-risk condition for the development of COVID-19 complications and adverse out- comes. Hyperglycemia lowers the immune response thus increasing the risk of mortality (7.3%) and it is associated with organ damage and systemic complications. In the case of SARS-CoV2, it was suggested that the virus could directly damage pancreatic cells, that highly express angiotensin-converting enzyme 2 (ACE2), used as a receptor by the viral spike protein causing acute hyperglycemia. Moreover, SARS-CoV2 was found in pancreatic tissue by using immune-histochemistry and in-situ hybridization. Diabetes will be permanent or SARS-CoV-2 caused a transitory period of hyperglycemia that will resolve with the recovery from the infection.

COVID-19 disease mostly affects middle-aged and elderly patients. Children seem to be asymptomatic or get a mild form of the disease. The mean incubation period is about 5 days from exposure but ranges between 2 to 14 days. A higher risk of infection has been noticed in older patients, male sex, patients with medical co morbidities, patients with chronic pulmonary or chronic cardiac or chronic kidney disease, and patients with diabetes. The symptoms of COVID-19 are akin to other viral upper respiratory illnesses.

Clinical features[9,13] of Patients infected with 2019 novel corona virus alteration of taste and smell, anosmia, is suspected as an early symptom of COVID-19 and is occasionally reported as a phenomenon of upper respiratory viral infection GI symptoms are present in 10% of cases, including nausea, vomiting, or diarrhea. Patients may also experience rarely headaches and confusion. Atypical presentations of infection may be more common in the elderly and immune compromised, who may not mount a febrile response. In current literature, no known reports exist in which the presenting symptoms were exclusively cardiac. Three major trajectories for COVID-19 have been described: a mild disease with upper respiratory symptoms, non-severe pneumonia, and severe pneumonia complicated by acute respiratory distress syndrome (ARDS), necessitating aggressive resuscitative measures. . Clinical course and outcomes[14] of critically ill patients with SARS-CoV-2 pneumonia depends on the category of the disease, The Clinical and computed Tomographic features of novel corona virus pneumonia caused by SARS-CoV-2[17] we

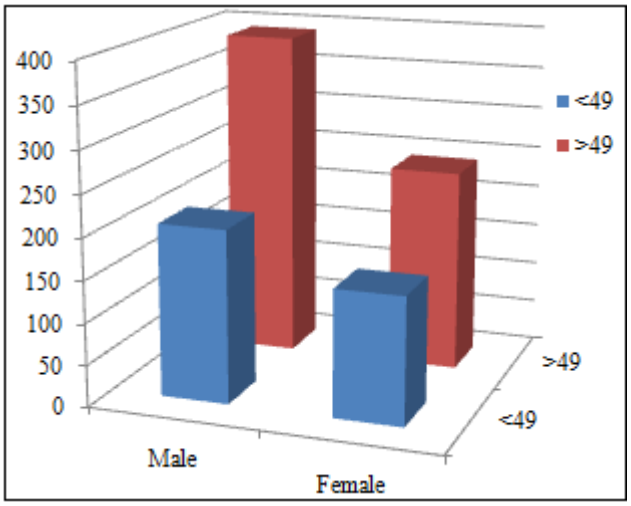
assessed the category and treatment protocol written on the case sheet and send them to respective wards.

2. Materials and Methods

In 4months from 01/04/2020 to 31/07/2020 there were 1045 cases admitted in State designated COVID hospital VIMS, Visakhapatnam, Andhrapradesh, we registered 993 cases 72 cases were discharged against medical advice, absconded, etc., out of 993 cases, Male <49yrs 207,> 49 392, Female <49yrs 152, >49yrs 242. Out of which 170 cases succumbed, 95(55%) cases death were males and 75(44.11%) were females. Out of all deaths, <49 years and >49 years age male 54 (56.84%)> 49yrs, 41(43.14%) <49yrs, female <49 years 13(17.33%),>49, 62(82.66%).

Table 1: Sex and age distribution

Sex	<49yrs	> 49years
Male	207(20.84%)	392(39.47%)
Female	152(15.30%)	242(24.37%)
Total	359(36.15%)	634(63.84%)



Out of which 170(17.11%) cases succumbed, 95(55%) cases death were males and 75(44.11%) were females. Out of all deaths, <49 years and >49 years age male 54(56.84%)>49yrs, 41(43.14%) <49yrs.The remaining 823(82.88%) cases were discharged. Obesity[3] is the independent risk factor in COVID-19, challenges to clinical management from pulmonary, endocrine and immune dysfunctions in individuals with obesity[11].The underlying pathogenesis in obesity is systemic inflammation causing thrombo embolisation and intravascular thrombosis secondary to obesity[7,8,11] induced free radicals, cytokines stored in adipose tissue and ACE_2 receptor expression in perinephric fat.

All the patients with RTPCR positive moderate to severe disease categorized as 1,2,3 and 4, ARDS irrespective of age ,sex ,pregnant were admitted .At the time of Imaging and clinical features[15] of patients with 2019 novel corona virus SARS-CoV-2 admission asses the clinical condition (CAT1,2,3) were sent to ward ,ICU respectively. All the investigations we named as COVID profile including all the inflammatory markers, end organ specific parameters etc., before shifting to the ward. After shifting to wards we did bed side X ray chest, ECG and 2D echo During the hospital stay patients were treated according to ICMR guidelines, ,Patients on oral diabetic treatment ,due to high blood sugar levels, we started them on regular insulin either as drip or intermittent who were hemodynamically stable and able to take meal. Very high pre meal blood sugars with altered sensorium we frequently did ABG and treated accordingly. Hyperglycemia with regular insulin either with infusion pump, or premeal regular insulin, to those who were able to take food , in few we advised RT feeds who were unconscious. Insulin infusion–mediated optimal blood glucose control improves prognosis for hospitalized patients with COVID-19 and hyperglycemia. Hyperglycemia[16] remained a strong prognostic predictor of outcome in hospitalized patients with COVID-19. Patients with COVID-19 who were hyperglycemic versus normoglycemia displayed a higher cumulative incidence of severe disease.

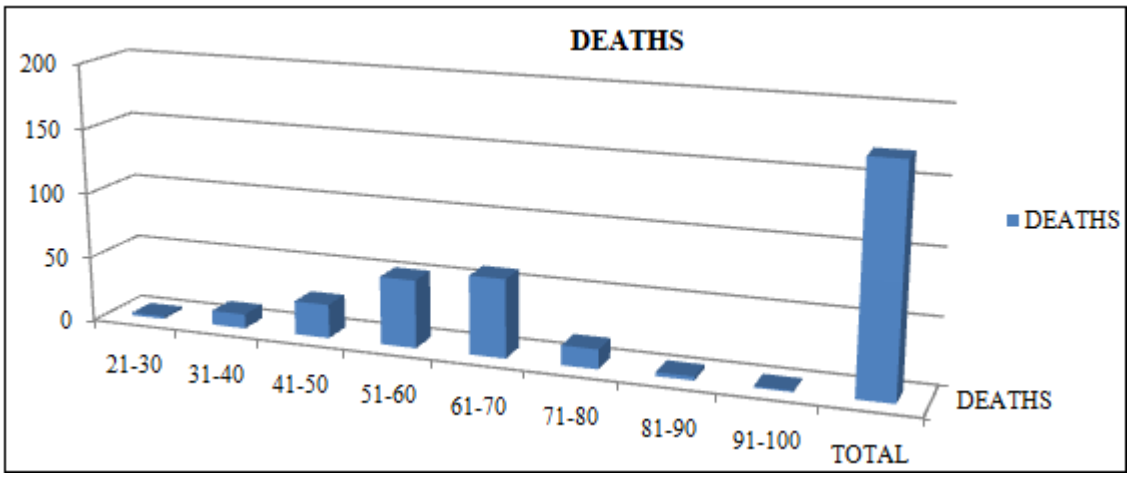
We started on higher antibiotics on NIV or in deeply comatose patients. After getting blood culture of a patient with fever, co morbid conditions, other clinically relevant parameters we treated the patients empirically with two higher antibiotics. We kept the patients in prone posture to improve the SPO_2.. In the discharge plan we followed instant orders of given by the State government Command control. Those patients with 3days SPO_2 > 94% and afebrile for 48 hours and hemodynamically stable we discharged.

3. Discussion

In this outbreak of SARS COV2 we started admitting patients with RTPCR positive ,with co morbidities like T2DM, HTN, CAD, CKD on regular maintenance HD, malignancies on chemotherapy, and Pregnant women. Our hospital was designated as State COVID hospital. The patients were admitted with negative RT PCR with HRCT chest suggesting CORAD 6, **some pitfalls[12] in interpretation of CT-values of RT-PCR in children[12] with acute respiratory tract infections.** Clinically decided if SPO_2 93%, with >60 years with or without co morbid conditions, <60 years with co morbid conditions.

In 4 months from 01/04/2020 to 31/07/2020 there were 1045 cases registered, out which 993 cases were taken into this study. Out of 993 cases, Male <49yrs 207, > 49 392, Female <49yrs 152, > 49yrs 242. Out of which 170 cases succumbed, 95 (55%) cases death were males and 75(44.11%) were females. Out of all deaths, <49 years and >49 years age male 54(56.84%)>49yrs, 41(43.14%) <49yrs, female <49 years 13(17.33%),>49, 62(82.66%). Age distribution of death cases out of 170 deaths 95males,75 females ,60 cases in the age group of 61-70years,52 in 51-60years age,26 deaths in 41-50years age, 15 deaths in 71-80 years age group,3 cases between 81-90years,1 case in age group 91-100years. Higher death rate in 61-70, and 51-60 age groups, might be due to more co morbid conditions, were brought in critical state. Only one case reported in 91-100 age group, she was a female, recovered, and her repeat RTPCR test was negative, but died 12 hours prior to the discharge.

Age	Deaths
21-30	2
31-40	11
41-50	26
51-60	52
61-70	60
71-80	15
81-90	3
91-100	1
TOTAL	170



Among the selected states Gujarat reported highest case fatality rate around 6.3% followed by West Bengal (4.3%) and Madhya Pradesh (4.2%). Kerala showed the lowest case fatality rate i.e. around 0.8%.

The proportion of cases recovered from the disease is around 75.4% in Rajasthan which is highest in the country, followed by Madhya Pradesh 71.1% and Gujarat which is around 69.4%. Delhi showed the lowest recovery rate of around 38.4% followed by Kerala with recovery rate of 44.8%.The recovery rate in our hospital was 82.88% even we were designated as state COVID hospital, referral hospital for 4 districts catered 1.5crore population, the case fatality rate was 17.11% as compared to the case fatality is of other states with high case burden ,Maharashtra (107958) Tamil Nadu (44661) and Delhi (41182). Out of the total cases approximately 51% were either cured from disease or migrated whereas a total of 9520 deaths were reported leading to a case fatality rate of 2.9%.,were reported during the 6 months after starting pandemic in our country. The case fatality is high in our hospital as compared to other hospitals ,recovery rate is also high 82.88% .The reason for high mortality was because of referral hospital ,the cases we received were critically ill, due to cases >60years with co morbid conditions.

Global scenario of COVID-19 fatality rates vary significantly depending on the country; it was 0.06% in Qatar and 16.25% in Belgium as of May 26, 2020 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 .However, there is a consistent and clear pattern of an age-based exponential increase in fatality rate, regardless of the geographic region. According to the Korea Centers for Disease Control and Prevention, the overall case fatality rate (CFR) was 2.37% in 11,344 patients with confirmed cases on May 28, 2020, but it was much higher in the elderly (10.9% in patients aged 70 – 79 years and 26.6% in patients ≥80 years) .In another analysis of 44,672 cases in China diagnosed as of February 11, 2020, the overall CFR was 2.3%. However, the CFR was 8.0% in patients aged 70 – 79 years and 14.8% in patients aged ≥80 years .In the report released by the Higher Institute of Health of Italy, the overall CFR on March 26, 2020, was 9.2%, which was four times higher than that in Korea or China; however, the pattern of increasing fatality with age was similar to that in Korea and China. The CFR was <1% in the age group of <50 years and rapidly increased in the age group of ≥60 years, reaching 16.9% and 24.4% in the age group of 70 – 79 years and ≥80 years, respectively.

4. Conclusion

The SARS COV2 a pandemic started in January 2020, gradually spreading to the community and patients were treated in different hospitals designated as district, state COVID hospitals. Our hospital was designated as STATE COVID hospital. Since the COVID-19 was a newer pandemic in this century with rapid spread, caused serious illness, and high mortality. At the beginning we followed all the protocols of WHO, National and state guidelines. The patients were referred to this hospital in critically ill state. In 4 months from 01/04/2020 to 31/07/2020 1045 cases were registered, but 993 cases were taken for this analysis. Out of 993 cases male (599) dominated than female (394), as per the literature, women in reproductive age will be having protection against SARS COV2, the recovered with minimal or nil complications. The age groups <49,>49 years 392,207 males, 152,242 females respectively. The mortality was high in age groups 51-70 years, less in younger age groups since they were having nil or minimal co morbidities. The

menopause and post menopause females, more likely in middle aged females will get severe COVID 19, may be hormonal imbalance, in one study 'Estrogens' are protective in females. We observed 2 young in 21-30 years age group presented in critical condition were succumbed, might be due to **Obesity,** it's an independent risk factor. Once the RTPCR is positive, depends on age and co morbidities, elderly age with clinical presentation suggesting moderate disease, younger age group with or without co morbidities early start of the supportive care should be started after hospitalization. All the core group specialties, with other equipments handling SARS COV2 cases are essential for the institutions. Preventive measures, mask, sanitizing hands, physical distancing and Vaccination are the gold standard to control spreading of the disease, reduce the complications, and morbidity and mortality.

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