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WHY THE MYSTERY OF COVID-19 STILL REMAINS INTANGIBLE? A MINI-REVIEW

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Abstract:

One of the biggest public health disasters of recent times is none other than COVID-19 caused by the novel coronavirus named as SARS-CoV-2, cause an acute typical respiratory disease. The zoonotic virus transmittable between humans has caused pandemic worldwide still not came to end and cause the major mortality rate globally. There is a range of clinical features from mild to severe life-threatening disease with major complications like severe pneumonia, acute respiratory distress syndrome, acute cardiac injury and septic shock. The mortality rate of different countries forced the government to enforce public social distancing and many versions of lockdown. Lack of specific drugs and vaccine continues the chaotic situation in every sector of a nation. Epidemiological studies showed that elder patients were more vulnerable to severe diseases, while children and middle-age tend to have milder symptoms. In this review, deals with the riddles of COVID-19 based on the current reports of transmission and pathogenesis and contemplate the various factors behind the higher mortality rate in adults.

Keywords: *Transmission, Pathophysiology, COVID-19, Complications, Mortality rate.*

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INTRODUCTION:

Including all endemic, epidemic and pandemic lower respiratory tract infection cause 3 million death per annum and one the fatally contagious infection ranked 4th commonest cause of global mortality [1]. Coronaviruses (CoVs), a large family of single-stranded RNA viruses, can infect animals and humans, causing primarily respiratory infections and they cause gastrointestinal, hepatic, and neurologic diseases [2]. Coronaviruses have caused two large-scale pandemics in the last 20 years, Severe Acute Respiratory Syndrome (SARS) in 2003 and Middle East respiratory syndrome (MERS) in 2012 [3,4]. In late December 2019, doctors of health department belong to the Wuhan city in Hubei province of China, reported group of patients linked to Wuhan seafood market affected by "**Pneumonia of Unknown Etiology**" triggered by a novel β-coronavirus, is responsible for the pandemic is called as "**COVID-19**", has hastily increased in epidemic measure, since it first appeared in china [5-6]. The comprehensive genetic sequence of the COVID-19 on 9th January 2020 and at the end of January 2020, the World Health Organization (WHO) declared the COVID-19 outbreak to be a "**Public-Health Emergency of International Concern**" (PHEIC). As of November 10th 2020, around 51,451,950 cases worldwide have been reported according to the worldometer.info and the death toll was raised to 1,272,404 [7,8]. On February 11th 2020, WHO declared novel coronavirus induced pneumonia named as "**SARS-CoV-2**" due to 79.5% genome sequence comparison with the earlier epidemic of Severe Acute Respiratory Syndrome (SARS) by the same group of coronaviruses in the year 2003[9]. It is believed that the SARS-CoV-2 also originated from bats or pangolin and frequent mutation or by recombination of the virus able infect different species labelled as zoonotic virus [10]. There is a lot of assumption about SARS-CoV-2, its manmade or abrupt natural outbreak, so far there is no ground proof for manipulation in the laboratory. The evidence from current research have found that the virus is 96% identical with entire genome level to a bat coronavirus, which means bats are the most probable host of the SARS-CoV-2 [9] and it belongs to the subfamily of β−coronaviruses and shares 79.5% of the genetic sequence of SARS-CoV [11] and 50% identity with MERS-CoV [4]. Population genetic analysis conducted by Tang et al, resolved by analyzing 103 SARS-CoV-2 genomes and classified out two prevalent evolvement types of SARS-CoV-2, L type (~70%) and S type (~30%). The strains in L type, derived from S type, are evolutionarily more violent and contagious [12].

Epidemiological studies have shown that COVID-19 infects people of all ages, but mortalities are higher in the elder population [13] and the incidence is much lower in children [14]. Mortality rate of the elder patients is mainly due to their underlying comorbidities like those who undergoing immunosuppressive therapy, diabetes mellitus, cardiac respiratory disorders and life-threatening disease like cancer [15]. Each and every country severely affected by the COVID-19, advice the people for using hand sanitizer, social distancing and imposing public lockdown in different versions, but still no end for this horrible story. This review attempts to brief on update knowledge of COVID-19 and discuss the possible facts to explain the pathophysiology of critical stage patients compared with infected children and adult patients.

EPIDEMIOLOGY AND TRANSMISSION:

The capacity of transmission of diseases in the community and the severity of fatality of the disease are the two determinant factors of an epidemic. The rate of transmission of the disease was assessed by reproduction number (*Ro*) and the fatality of the disease was determined by case fatality rate (CFR). The degree of transmission in the public indicates the number of comorbidities due to the initial case and the CFR is proportion of reported cases of a definite disease that are fatal within a quantified time [16]. The reproduction number, or "**R nought**" (*Ro*), is a mathematical term that states the rate of contagiousness [15]. Precisely, it is the number of people that one sick host can infect. If the *Ro* is less than one (<1) the disease will disappear. If the R0 ≥ 1 then the disease will spread between people. Estimates of the *Ro* of SARS-CoV-2 have ranged from median of 2.24 to as high as 3.58 - 5.70 [17] although the WHO evaluations are in between the range was 2.53-6.72 by sensitivity analysis [18]. The slightly higher *Ro* for SARS-CoV-2 maybe because it has a longer prodromal period, increasing the period during which the infected host is contagious. Transmissibility and severity are the two most hazardous factors that determine the public health impact of an epidemic [19].

The estimation of the case fatality rate (CFR) of COVID-19 is defined as the number of deaths divided by the number of confirmed cases. The unique parameter to understand the mortality and epidemiology of infectious disease is CFR [20]. In the case of SARS, the CFR is 9.6% on a global scale [21] and MERS is 34.5% [22]. The overall estimated CFR

for COVID-19 is expected to be at 2.9% to 3.0%. On 17th February 2020 WHO's director general reported that more than 80% of patients with covid-19 have a "mild disease and will recover" and that it is fatal in 2% of reported cases [23]. Among the RT-PCR confirmed cases resulting in death were primarily middle-aged and age patients more than 60 years with pre-existing diseases (tumor surgery, cirrhosis, hypertension, coronary heart disease, diabetes, and Parkinson's disease) [24].

In the case of COVID-19, the human to the human spreading of the virus occurs due to close contact with an infected person, exposed to the droplets of coughing and sneezing in a short distance generally less than 2 m. Airborne transmission, particularly via nascent aerosols from human atomization, is highly virulent and signifies the dominant route for the transmission of this disease [4,25]. However, the airborne route involves much smaller droplets that can float and move longer distances with air flow. Under certain humidity and low-temperature environments, airborne droplets can remain in flight for hours. Generally, pathogens that are transmissible via the airborne route have higher Ro, because infected particles can remain in the air long after the infected individual has left the premises. In the case of measles and chickenpox, *Ro* is in between 12-18 and 3.7 -5 respectively [26,27]. The transmission of the infection also possible when the infected droplets landed on the surfaces of inanimate objects like metals, glasses and plastics up to 2h to even 4 days in colder environment [28,29].

The day from the onset of COVID-19 symptoms to death ranges from 6 to 41 days with a median of 14 days, infected asymptomatic carriers has an average incubation period of 2-10 days. This period is dependent on the age, comorbidity and the immune status of patients. It was shorter among patients more than 70-years old compared with those under the age of less than 40. The most commonly reported clinical symptom in laboratory-confirmed cases is fever (88%), followed by dry cough (68%), fatigue (38%), sputum production (33%), dyspnea (19%), sore throat (14%), headache (14%) and myalgia or arthralgia (15%). Lesser number of patient's experience symptoms like vomiting (5%), diarrhea (4%), running nose, hemoptysis, dyspnea, myalgia, lymphopenia and pneumonia [30-32]. Some of the cases show an infiltrate in the upper lobe of the lung that is associated with increasing dyspnea with hypoxemia and other upper respiratory tract symptoms like rhinorrhea, sneezing and sore throat with pain [33].

In the last stage of pathogenesis gastrointestinal tract (GIT) symptoms and ARDS is the common immunopathological event for SARS-CoV-2, SARS-CoV and MERS-CoV infections [34]. The mortality of the COVID-19 is chiefly due to two fatalities, 70% by ARDS leads to direct respiratory failure and 28% by the vast release of cytokine which causes multiple organ failure, sepsis and finally ends with the death of the patient [35]. In COVID-19, the major earlier symptoms are systematic symptoms and late-stage the respiratory disorder symptoms are dominated. Recently in June 2020 Menni et al, reported that nearly 60% of the COVID-19 infected individual experience the anosmia (loss of smell) and ageusia (loss of taste) and these symptoms are seemed earlier to the typical symptoms like fever [36]. The entire process of successful entry and establish the disease with known symptoms in the host is known as pathogenesis, it includes four different stages. First stage is portal entry into the host cell, second stage is reproduction of virions, third process is accessing the target organ, with specific symptoms of the infection and final stage is systemic spreading, which leads to detectable quantity of viral load in body fluids. The crucial factors pathogenesis is potential of viral accessibility, host susceptibility for viral synthesis sub-cytoplasmic particles and resistance of host immune defense.

MECHANISM OF CELLULAR PATHOPHYSIOLOGY:

Presence of crown like spikes 8 to 12 nm on the outer surface of the virus gives the name for the virus family and it contains positive-sense single-stranded RNA (+ssRNA) ranging from 26 to 32kbs in length, with 5′-cap structure and 3′-poly-A tail, the complete genome of Wuhan-Hu-1 virus is 29.9kb [37-38]. It has been shown that the genome of CoVs contains a variable number (6–11) of open reading frames (ORFs). Two-thirds of viral RNA, mainly located in the first ORF (ORF1a/b) codes two polyproteins namely pp1a and pp1ab, which encodes 16 non-structural proteins (nsp1-nsp16), which form the viral replicase transcriptase complex (RTC) required for the synthesis of virions and completely hijack the host alveolar cell [39].

One-third of the (ORFs) genome near the 3′-terminus encodes at least four main structural proteins: spike (S) protein (~68–78.5 kDa) responsible for specific attachment to host ACE2 receptors [9], membrane (M) protein (~25–30 kDa), which promotes membrane curvature and binds to nucleocapsid [40], envelope (E) protein (~8–12 kDa) involves in virus assembly and release virions during pathogenesis [41] and nucleocapsid (N) proteins (50-55 kDa) helps to

stabilize the replication transcription complex (RTC) and package the encapsulated genome into virions [42]. Besides these four main structural proteins, different CoVs encode special structural and accessory proteins, such as HE protein, 3a/b protein, and 4a/b protein. HE protein acts as a hemagglutinin, which binds sialic acids of surface glycoproteins. It also contains acetylesterase activity, which augment the cell entry mediated by the spike protein and virus spread through the alveolar mucosa [43]. All the structural, nsp and accessory proteins are translated from the ssRNAs of CoVs, which is essential for pathogenesis and virion assembly [44].

The first step of the pathogenesis was done by S-glycoprotein binding it to the specific receptor, lack of this protein loses its pathogenicity it became a non-infectious virus [45]. Binding of spike protein to the ACE2 receptor results in conformational changes in spike protein that leads to the fusion of viral envelope protein with host cell membrane facilitate to entry via the endosomal pathway [46]. The structure of S glycoprotein includes two subunits, S1 and S2. S1 subunit determines the virus-host range and cellular tropism with the key function domain − RBD, while S2 mediates virus-cell membrane fusion by two tandem domains, heptad repeats 1 (HR1) and HR2 [47]. The S1 domain can be further divided into two subdomains, named the N-terminal domain (NTD) and the C-terminal domain (CTD) have receptor binding motif (RBM), both of them act as a receptor binding domain [48]. Binding of the spike protein helps to direct fusion of membrane protein with host alveolar cell plasma membrane [49]. The SARS-CoV-2 might pass through the mucous membranes, especially nasal and larynx mucosa, then arrives the lungs through the respiratory tract. In a fluorescent study, it was confirmed that the SARS-CoV-2 also uses the same ACE2 receptor and similar mechanism as SARS-CoV infection [50-52].

Alveolus of the lung contains three types of cells, Type I pneumocytes cover 95% of the internal surface of each alveolus, mainly facilitating the gas exchange and limit the infiltration of fluid into the alveoli. The second type alveolar cell is Type II alveolar cells are cuboidal in shape, that comprise 15% of total lung cells and maintain the alveolar microenvironment through synthesis and secretion of pulmonary surfactant, transepithelial sodium transport, alveolar fluid homeostasis, proliferation to preserve the epithelium and ultimate trans-differentiation into type I alveolar cells [53]. The third type cell is least number of alveolar macrophages residents in alveoli mainly for chemotaxis and phagocytosis. Even though the ACE 2 receptor expressed in vascular endothelial cells, heart, renal tubular epithelial cells and gastrointestinal tract [55], but the entry of SARS-CoV-2 is mainly in densely populated type 2 alveolar cells of the upper respiratory tract [54]. In 2004 Hamming et al by using the immunohistochemical staining method [55] and recently in 2020 by Zou et al proved that ACE2 is mainly expressed on ciliated type II alveolar epithelial cells favor for the infection [56].

VIRUS ASSEMBLY AND MULTIPLICATION:

Binding of specific receptor facilitates the post membrane fusion of the host cell permits the viral genome RNA (pre-existing single-strand positive RNA) is released into the cytoplasm and the uncoated RNA (negative strand RNA) synthesis positive strand RNA which translates two polyproteins (pp1a and pp1ab) [57], which encode nsp and form RTC in double membrane vesicles (DMV). Synthesis of structural proteins and nsp by the translation of sub-genomic RNA allows the host cell machinery completely for synthesis of new virus [58]. Nucleocapsid protein of the virus binds with synthesized new genomic RNA allows the M protein permits the particle to enclosed in endoplasmic reticulum. The newly formed genetic material capsids to attached with ER membrane and pass through the lumen undergoes post translation modification packed to Golgi vesicles through endoplasmic reticulum-Golgi intermediate compartment (ERGIC) [59-60]. The new virions are now ready to invade the nearby epithelial cells as well as for providing enough infective material for public transmission via fresh nasal and respiratory droplets [61]. During the period of viral replication and increase of local population with a limited immune response with mild symptoms like fever, malaise, throat pain and dry cough. When the infection progress allows the passage of new viral particles to travel to lower respiratory tract.

HOST IMMUNOPATHOLOGICAL RESPONSE:

Innate immunity requires a precise regulation to eliminate the virus in a short interval, to synthesis diverse set of immune mediators against the infected cell and the virus, otherwise the consequence will reflect in dysregulation of immune system against its own organs [62]. On successful establishment of host, within short interval the viral load of the infected cell considerably increased, which leads to high levels of virus-linked highly inflammatory form of programmed cell death called as “pyroptosis” associated with increase of important cytokine IL-1β accompanying with vascular leakage [30]. Based on the clinical stage, symptoms and severity of the

infection, the pathogenesis of COVID-19 is divided into three stages.

1. First Phase: Asymptomatic Stage or Viremia phase:

At the early stage there is lack of visible symptoms and binding of viral particles on the ciliated naso and oropharyngeal cells and starts the process of replication in host cell [52]. Inadequate immune response at this stage, allows the virus to multiply in infected cells and this stage is probable for early detection of virus by nasal swabs. The viral load can be precisely detected by RT-PCR, in the asymptomatic phase. Nearly one-fifth of individuals with COVID-19 positive by RT-PCR method remained asymptomatic. The most common symptoms are cough (40.1%) and remaining patients suffer by hyposmia with hypogeusia and rhinorrhea. Fever (>37.5C) was only observed in 20 (11.6%) individuals [63]. In the case of RT-PCR confirmed elder patients, the most common symptoms are fever 98% (n = 40) and cough 76% (n = 31) [30]. Mild clinical symptoms, such as fatigue, cough, anorexia, malaise, muscle pain, sore throat, dyspnea, nasal congestion, headache reported by most of confirmed cases [64].

2. Second Phase: Airway conducting response stage or **Acute pneumonia phase:**

This phase manifested by triggering of severe innate immune response, after 14 days on the onset of illness, nasal swabs (73.3%) and sputum (88.9%) should yield the positive RT-PCR results [64]. Study increase of viral nucleic acid, inflammatory factors and D-dimer in systemic circulation, along with reduction of T-Cells [65]. Viral infected epithelial cells are a major source of interferons (β and λ) and early secretion of C-X-C motif chemokine ligand 10 (CXCL10) (early marker of covid-19). This stage needs more intensive monitoring with isolation of infected individuals [66]. Within 10 days of the onset of infection, disease progress to exudative phase characterized by necrosis of alveolar, bronchiolar and bronchial epithelial cells, intraluminal edema, fibrin exudation, hyaline membrane formation, hemorrhage and infiltration of inflammatory cells. The severity of this phase fastly moves the patient to pulmonary infiltrate state [67].

3. Third Phase: Progression towards ARDS or Recovery phase:

Nearly 20% of infected patients reach the third phase with breathing difficulties and accumulation of pulmonary infiltrates. Heavy viral load reaches the gas exchanging unit alveolus cause severe diffuse alveolar damage with fibrin rich hyaline membranes and a few multinucleated giant cells. In this phase large number of viral particles are released, and the cells undergo apoptosis and die, to produce viscous infiltrate [67]. Elevated level of d-dimer, fibrinogen and endothelium are seen in severely infected patients, this may be reason for thrombosis and pulmonary embolism in those patients. The increased level of endothelium increases the vasodilation, fibrinolysis, anti-aggregation and increased permeability facilitate further viral invasion [65,68]. In the peripheral blood picture 83.2% patients shows lymphocytopenia, 33-35% shows thrombocytopenia and leukopenia, clearly shows the decreased synthesis of myeloid progenitor cells in bone marrow [30,69].

The combined response of the virus infecting number of cells and it creates a dysfunctional immune response leads to powerful cytokine storm in the immune vulnerable patients cause severe lung inflammation and progressively it starts to affect the function of multiple organs, finally ends with failure of the organ, became a systemic pathology. Release of interleukins (IL-1, IL-6, IL-8, IL-10, IL-12), tumor necrosis factor (TNF-α, TNF-γ and IFN-β), C-X-C motif chemokine ligand 10 (CXCL-10), granulocyte-colony stimulating factor (G-CSF), GM-CSF, monocyte chemoattractant protein-1 (MCP-1) and macrophage inflammatory protein-1α (MIP-1α). This straddling immune response is a powerful to content the spreading of infection beyond this level [63]. During the acute inflammation the first role played by neutrophils, when the inflammatory process persistent due to the macrophages and lymphocytes. The amplified response of entire lungs cells is manifested as acute respiratory distress syndrome (ARDS) [70].

The elevated amount of interleukin IL-8 associated with neutrophils in bronchoalveolar lavage fluid may leads to interstitial pulmonary fibrosis (IPF) and the accumulated T-cells cause infiltration of alveolar cells cause further lung injury [70-71], this cause significant reduction in Th-cells in peripheral blood. The elevated level of IL-6 and IL-8 are act as chemoattractant of CD8+ and CD4+ T cells contribute additional injury to alveolus due to the cytotoxic properties [72]. One of the colony stimulating factor (GM-CSF) stimulate the synthesis of inflammatory monocyte subsets like CD14+ and CD16+ which is responsible for systemic inflammatory immune response by synthesizing pro-inflammatory mediators like IL-6 [73]. Unrestricted inflammatory cell infiltration can itself facilitate the damage in entire lung through excessive secretion of proteases and synthesis of reactive oxygen species (ROS) free radicals, in addition to the direct damage alveolar cells by the virus. On the stimulation of IL-6 and TNFα on neutrophils synthesis free radicals like ROS, in turn hydrogen peroxide stimulate the

production of IL-6 [74]. The major culprits are macrophages and neutrophils release variety of cytokines, cationic proteins, lipid mediators, metalloproteinases and components of the oxygen burst release oxygen free radicals. The ROS that accumulate in the mitochondria may contribute further alveolar damage cause complicated risk to elder patients with cardiovascular health complications.

When pathogenesis progressed to advanced stage cause dramatical increase in virus load, ACE2 receptor is a vital protein for the regulation of renin–angiotensin system (RAS), when the SARS-CoV-2 bind with the receptor, it downregulates the number of receptors [9], which leads to disfunction of RAS system. Which influences blood pressure and fluid/electrolyte balance, and enhance inflammation and vascular permeability in the airways [55]. This cause the additional risk to multi organ failures. Ruan et al research group reported that elevated levels of cytokines such as tumor necrosis factor (TNF) can cause myocardial damage, arrhythmia, acute cardiac injury, circulatory failure, septic shock and multi-organ failure like liver dysfunction and acute kidney injury observed in patients in intensive care unit [75]. About 80% of confirmed cases in China had mild to moderate disease (including non-pneumonia and pneumonia cases), 13.8% had severe disease and 6.1% were critical (respiratory failure, septic shock, and/or multiple organ dysfunction/failure). These patients exhibited pneumonia symptoms with a diffused alveolar injury which lead to acute respiratory distress syndrome (ARDS) exhibits reduce the efficiency of gas exchange, breathing difficulties, reduced pO2 (low blood oxygen level), vulnerable to secondary infections and breathing is only possible by ventilators [76]. When the body of coivd-19 victims are autopsied, shows focal intra-alveolar hemorrhage, necrotic inflammatory debris in small airway and multinucleated syncytial cells were seen in the intra-alveolar spaces [77]. There were abnormal features such as RNAaemia and incidence of grand-glass opacities that led to death [30]. The degree to which SARS-CoV-2 targets these cells remains poorly defined. Understanding the precise drivers of immune dysfunction is crucial area to focus on the application of appropriate immunomodulatory treatments. In the moderately infected patients, chest X-ray of the SARS shows ground glass opacities whereas in SARS CoV-2 patients have bilateral and multilobed ground glass opacities and the alveolar space was filled with blood, pus, water and cell debris, a characteristic finding of viral pneumonia [78-79]. These findings confirmed the advanced stage of the patients with X-ray reports are more useful diagnostic tool in under developing countries where the CT scan facility is not available.

POTENTIAL EXPLANATION FOR CASE FATALITY RATE:

The size of the COVID-19 pandemic shows the emergence and seriousness of the public health problem. Since from the pandemic lot of riddles unsolved around the transmission, severity pathogenesis and fatality of the patients. Still now there is no clear vision to handle the epidemic in future, the fatality of the diseases is not clear and puzzled the whole scientific community. Usually children are the victim of pneumonia caused by the influenza virus than the adults, but children are less capable to develop the adaptive immunity in lungs. Respiratory viruses flourish in bodies where the immune system is either still developing or has started to wear out. In contrast, pediatric COVID-19 patients have fairly milder symptoms in general when compared to elder patients. One of the possible hypotheses is usually children's have less expression of ACE2 receptor when compared to adult, usually human lung and epithelial cells continue to develop only after the birth. This is the one of the reason infants gets less viral load when compared with adult population. Among the confirmed cases in china alone children's accounting for ~2% cases and in Europe it is less than 1%, one in seven cases are asymptomatic and in most common symptoms are fever and cough with zero fatality rate [80-81].

Actually, children have less knowledge about personal etiquettes than adults, the short bronchial tree allows the virus can reach the end of alveoli quickly and less competent immune system makes the respiratory virus more susceptible for infection [82]. At the same time in children, the high plasticity of their adaptive responses, particularly in their B-cell immune response, could more efficiently clear the virus by producing neutralizing antibody (nAb) [83]. In kids and teen agers thymus is active and before puberty there are large sources of progenitors of naive B and T cells, but in elder patients' degeneration of active thymus cell leads to attrition of naïve B and T cells, more memory cells and aged and end stage CD8+ cytotoxic T cells [84]. The cells like CD4 and CD8 focus to eliminate the source of infection by eradicating the infected cells and get rid of the cellular reservoir of the virus [85]. In elder patients, there is an increase of effector T cells and memory T cells due to frequent antigen stimulation and ceaseless activity of thymus in immune response, cause loss of expression of co-stimulatory molecules such as CD27 and CD28, with increased vulnerable to infections, at the same

time CD28 molecules have additional role to terminate unnecessary immune responses and prevent autoimmunity [86].

The less variable COVID-19 antigen within MHC-I most probably share some similarity to antigens of other coronaviruses that have been recurrently encountered by adults but not at the same level by children. Adults are naturally immune to most strains of coronaviruses circulating in the population while children are more prone to infection to common coronaviruses because they are yet lack immunity to most of the circulating coronaviruses [87]. This might largely be due to lack of sufficient memory cells specific to other coronaviruses. These memory cells are expected to be abundant in adults as they have been exposed to many respiratory infections, whether symptomatic or asymptomatic, caused by common flu-causing coronaviruses. COVID-19 proteins share similarity with these of common human coronaviruses [52].

The mortality rate of COVID-19 is less than 4%, in this most of the patients are the age above 60 years and adults with complication, there is a very insignificant percentage of teenagers and progenies. The case fatality rate (CFR) of COVID-19 is depends on age and comorbidities of the patients, averagely CFRs in children appear negligible, in young adults perhaps up to 1%, but in people over 60 rising to 4%, over 70 up to 9% and over 80 even up to 18% [88]. High fatality rate has certain strong independent factors such as age more than 70 years with additional complications such as hypertension, coronary artery disease, chronic pulmonary disease, chronic diabetes, malignancy such as lymphopenia and increased concentration of D-dimer (>1 μg/L) [69]. An individual with strong immune system easily suppresses the virus in the first or second phase without immune over-reaction. In contrast the person is aged or has immune dysfunction may have higher risk to progress towards to final stage called as ARDS, the risk is likely to increase the risk by smoking cigarettes and severity of the comorbidities [30]. When compared with children, ageing is associated with increasing secretion of proinflammatory cytokine, supports with quick progress of ARDS and multiorgan dysfunction (MODS) [80]. When the immune response against the virus is effective and the system is strong enough to overwhelm the infection, it is possible to retrieve the health in early stage.

DISCUSSION:

The foremost delinquent behind the pandemic of COVID-19 is none other than transmission of virus at very high rate between human to human and strategy of treatment. Understanding the epidemiology, transmission and pathogenies is must to resolve the right strategy to break this worldwide pandemic. In the case of transmission frequency, the reproductive number (*Ro*) for COVID-19 (2.2–2.6) is less than the SARS (1.4–5.5) and MERS (<1) shows that it less contagious than previous outbreak by earlier pandemic [4,89]. The spreading nature of the diseases principally by respiratory droplets and aerosols of cough and sneezing [6,19], failure in personal hygiene gets easily contract the disease. Ensuing the safety precaution include wearing a mask when meeting people, avoiding using hands to touch facial parts such as eyes, nose, and mouth, washing hands with soap (recommended) or alcohol (alternative) regularly, as well as proper protection like practicing respiratory hygiene and coughing etiquettes [90]. Speedy transmission of disease entails certain level of people in the area of proximity to acquire the disease. When the travel is necessary it is strongly advised to avoid travelling to highly-populated areas due to risk of being infected. The awareness of personal hygienic among the public is the major preventive measure to halt this pandemic.

Competent humoral and cell mediated immunity individuals are strong enough to resistant to infection and the recovery within 2-3 weeks, on the onset of beginning of mild symptoms. Nearly 85% of the infected individuals have mild to moderate infection and half of them are asymptomatic. Remaining 15% are severely infected are aged and individuals have comorbidity, among this only 5% is admitted in intensive care unit and half of them are die [91]. When compared with influenza virus is COVID-19 is not highly virulent and mortality rate of infected individuals shows that virus is not much aggressive causing death. When considering the mortality rate on gender bases, the rate is much lower in females, the men (70.3%) who died by the COVID-19 is 2.4 times more than females (29.7%), but the prevalence of the disease between the sex is almost insignificant [92]. This is possibly due to movement of males for social and personal responsibility in society, which makes them easily contract the infection in crowded places, workplaces and during public transport. One of major criteria for the CFR is age and comorbidity, in these individuals the innate and adaptive arms of their immune system are sub-optimal, when compared with children and adults. The shortcomings of immunity in these patients make cell-mediated immunity to mount a vigorous attack at very dangerous area, the alveoli. This factor favors the acute pneumonia due to spreading of virus in lower respiratory tract [5]. This

kind of factors not support for pediatric when compared with elders. In healthy individual the alveoli were surround by good blood circulation have lot of powerful alveolar lymphocytes and macrophages, which prevent the accumulation of virus in alveoli as commonly seen in aged and individual with comorbidities. Alveoli are abundantly guarded by alveolar lymphocytes and macrophages which are the pillars of cell mediated immunity [82]. In contract children are more vulnerable to respiratory viruses then elders but short bronchial tree gives less space for viral access and multiplication. Moreover, less developed immune system, suppressed adaptive immunity and lack of memory T cells in children fails to attach its own body cells but in adults dysfunctional over active innate immunity (immune senescence) seen only in adults [93].

Among the 80% of the RT-PCR confirmed affected individuals recovered in the first phase of the infection and half of them are asymptomatically recovered. Most of the old and sick entered into the second and third phase of the infection, become immunopathogenic and severe inflammatory response due to heavy viral load and dysregulation of immune response creates unusual flow of assortment of cytokines creates "Cytokine storm" which cause more CFR [69]. Similar kind of CFR seen in SARS pandemic, simply hijack the host cells and produce inflammatory chemicals cause the disaster to whole system end with death [94]. Acute surge of cell mediated cytokine leads to activate the T-Cell subsets to vigorously eradicate the infected alveolar cells cause interstitial inflammation leading to damage of lung tissue and filling alveoli with inflammatory exudates. The combined effect of cytokine storm, inflammation and destruction of alveolar cells progress to severe hypoxia, respiratory failure, collateral damage of liver and kidney [95,87]. This kind of effect is unusual in pediatric due to lack of memory T cells and underdeveloped immune system, this may due to less exposure to common coronavirus infection [96]. The strong health condition and an active immune response plays crucial role in protecting the body and retrieve the individual those who are infected mildly.

CONCLUSION:

The rate of recovered patients from the pandemic COVID-19 is positively increasing worldwide, but still, now the normal social life of people was affected by this international health emergency and lockdown policy of the government. The etiology and pathogenesis of COVID-19 is entirely depending on the interaction between the stage of infection and the strength of the individual's immune system. The pandemic shows a clear distinction between the treatment strategy between pediatric and elder patients. Treatment and quarantine of patients based on their age, symptoms, comorbidity and severity of the affected individual. Early diagnosis and specific prognostic markers helpful to treat the patients and recovery from the diseases. There should be good awareness in every individual about building a strong immune system for a healthy society.

Available data suggest there is no need for discrimination in treatment based on the gender of the patient. Enough awareness and strict adherence in individual health, safe handling of animals, public hygiene and social responsibility support to create a diseases free community. In addition, to finding the effective drugs and vaccine, a curriculum of handling the emergency of an outbreak should be encompassed in the educational curriculum. The policy of government focus to build a healthy society and establish a required infrastructure to handle an emergency outbreaks in future. A standard guideline should be distributed to medical practitioners, healthcare workers, paramedical staffs, community health examiners and the researchers who involved in eradicating the epidemic.

REFERENCE:

1. World Health Organization. Consensus document on the epidemiology of severe acute respiratory syndrome (SARS), 2003.
2. Weiss S.R, Leibowitz J.L., A 30-hour old infant in Wuhan diagnosed and mother-to-child infection suspected. Coronavirus pathogenesis, Adv Virus Res., 2011; 81; 85–164.
3. Centers for Disease Control and Prevention 2003 Update. Outbreak of severe acute respiratory syndrome—worldwide 2003, MMWR Morb Mortal Wkly Rep., 2003; 52; 241– 248.
4. Zaki A.M., Boheemen S.V., et al., Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia, N Engl J Med., 2012; 367; 1814–20.
5. Zhu N., Zhang D., et al. A novel coronavirus from patients with pneumonia in China, N Engl J Med 2019; 382; 727–733.
6. Li Q., Guan X., et al., Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia, N Engl J Med., 2020; 382 (13); 1199-1207.
7. WHO Director-General's Opening Remarks at the Media Briefing on COVID-19—11 March 2020.

8. Https://www.worldometers.info/coronavirus/coronavirus-cases.
9. Zhou P, Yang XL, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin, Nature 2020; 579: 270–273.
10. Cui J, Li F, Shi Z-L. Origin and evolution of pathogenic coronaviruses. Nat Rev Microbiol, 2019;17(3);181–92.
11. Lu R, Zhao X, Li J, et al. Genomic characterization and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding, Lancet 2020; 395(10224): 565-574.
12. Tang X., Wu C., et al., On the origin and continuing evolution of SARS-CoV-2, Natl Sci Rev., 2020; 7(6); 1012-1023.
13. Zhou F., Yu, T., et al., Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study, Lancet., 2020; 395; 1054–1062.
14. Lu X., Zhang L., et al. Chinese Pediatric Novel Coronavirus Study, SARS-CoV-2 infection in children, N Engl J Med., 2020.
15. Wang B., Li R., et al., Does comorbidity increase the risk of patients with COVID-19: evidence from meta-analysis. Aging (Albany NY)., 2020; 12; 6049–57.
16. World Health Organization. Cholera case fatality rate. Accessed March 8, 2020. https://www.who.int/gho/epidemic_diseases/cholera/case_fatality_rate_text/en.
17. Zhao S., Lin Q., et al., Preliminary estimation of the basic reproduction number of novel coronavirus (2019-nCoV) in China, from 2019 to 2020: A data-driven analysis in the early phase of the outbreak, Int J Infect Dis., 2020; 92; 214–217.
18. Talukder H., Debnath K., et al., Estimation of Basic Reproduction Number (Ro) of Novel Coronavirus (COVID-19) from SEIR Model in Perspective of Bangladesh, J Infect Dis Epidemiol., 2020; 6(4);144.
19. Swerdlow D.L., Finelli L., Preparation for possible sustained transmission of 2019 novel coronavirus: lessons from previous epidemics, JAMA., 2020; 323;1129-1130.
20. Battegay M, Kuehl R, et al., 2019-novel coronavirus (2019-nCoV): estimating the case fatality rate – a word of caution, Swiss Med Wkly. 2020; 150; 20203.
21. Donnelly A., Azra G., et al. Epidemiological determinants of spread of causal agent of severe acute respiratory syndrome in Hong Kong, Lancet 2003; 361; 1761-1766.
22. Fisman D., Rivers C., et al., Estimation of MERS-coronavirus reproductive number and case fatality rate for the Spring 2014 Saudi Arabia Outbreak: insights from publicly available data. PLoS Curr., 2014; 6.
23. Elisabeth M., Coronavirus: covid-19 has killed more people than SARS and MERS combined, despite lower case fatality rate. BMJ., 2020; 368; m641.
24. Li T., Wei C., et al., Beijing Union Medical College Hospital on "pneumonia of novel coronavirus infection" diagnosis and treatment proposal (V2.0). Med J Peking Union Med Coll Hosp., 2020.
25. Zhanga R., Lib Y., et al., Identifying airborne transmission as the dominant route for the spread of COVID-19, PNAS Latest Articles 2020; 1-7.
26. Guerra, F.M., Bolotin S., et al., The basic reproduction number (R0) of measles: A systematic review, Lancet Infect. Dis., 2017; 17; 420–428.
27. Marangi L, Mirinaviciute G, et al., The natural history of varicella zoster virus infection in Norway: Further insights on exogenous boosting and progressive immunity to herpes zoster, PLoS One., 2017; 12; 0176845.
28. Kamp G., Todt D., et al., Persistence of coronaviruses on inanimate surfaces and their inactivation with biocidal agents. J. Hosp. Infect., 2020; 104; 246–251.
29. Warnes S.L, Little Z.R, et al., Human Coronavirus 229E Remains Infectious on Common Touch Surface Materials, mBio., 2015; (6); e01697-15.
30. Huang C., Wang Y., et al., Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China, Lancet., 2020; 395; 497–506.
31. Wang W., Tang J., et al., Updated understanding of the outbreak of 2019 novel coronavirus (2019-nCoV) in Wuhan, China, J. Med. Virol., 2020; 92 (4); 441–447.
32. Carlos W.G., Dela Cruz C.S., Cao B., et al., Novel Wuhan (2019-nCoV) coronavirus, Am. J. Respir. Crit. Care Med., 2020; 201 (4); 7–8.
31. Hussin A., Rothan., et al., The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak, J Autoimmun., 2020; 109; 102433.
33. Tang P., Louie M., et al., Interpretation of diagnostic laboratory tests for severe acute respiratory syndrome: the Toronto experience, Can Med Assoc J 2004; 170; 47–54.
34. Xu Z., Shi L., et al., Pathological findings of COVID-19 associated with acute respiratory distress syndrome, Lancet Respir Med., 2020; 8; 420–22.
35. Zhang B., Zhou X., et al., Clinical characteristics of 82 death cases with COVID-19. Plos One., 2020; 1-9.

36. Menni C, Valdes A, et al., Loss of smell and taste in combination with other symptoms is a strong predictor of COVID-19 infection, medRxiv., 2020.
37. Muhammad A.S, Suliman K., et al., COVID-19 infection: Origin, transmission, and characteristics of human coronaviruses, Journal of Adv. Res. 2020; 24: 91–98.
38. Wu F., Zhao S., et al., A new coronavirus associated with human respiratory disease in China, Nature., 2020; 579; 265-267.
39. Fehr A.R., and Perlman S., Coronaviruses: an overview of their replication and pathogenesis, Methods Mol. Biol., 2015; 1282; 1-23.
40. Neuman B.W., Kiss G., et al., A structural analysis of M protein in coronavirus assembly and morphology, J Struct Biol., 2011; 174(1);11-22
41. Schoeman D., and Fielding B.C., Coronavirus envelope protein: current knowledge. Virol J., 2019; 16; 69. doi: 10.1186/s12985-019-1182-0.
42. Cui L., Wang H., Ji Y., et al., The nucleocapsid protein of coronaviruses acts as a viral suppressor of RNA silencing in mammalian cells, J Virol., 2015; 89(17); 9029-9043.
43. Klausegger A., Strobl B., et al., Identification of a Coronavirus hemagglutinin-esterase with a substrate specificity different from those of influenza C virus and bovine coronavirus. J Virol., 1999; 73; 3737–43. doi: 10.1128/JVI.73.5.3737-3743.1999.
44. Chen Y., Liu Q., Guo D., Emerging coronaviruses: Genome structure, replication, and Pathogenesis. J Med Virol., 2020; 92; 418–423.
45. De Haan C.A.M., Kuo L., et al., Coronavirus particle assembly: primary structure requirements of the membrane protein. J Virol 1998;72(8); 6838-50.
46. Coutard B., et al., The spike glycoprotein of the new coronavirus 2019-nCoV contains a furin-like cleavage site absent in CoV of the same clade, Antivir. Res., 2020; 176;104742.
47. Xia S., Zhu Y., et al., Fusion mechanism of 2019-nCoV and fusion inhibitors targeting HR1 domain in spike protein. Cell Mol Immunol. 2020.
48. Li F., Structure, function, and evolution of Coronavirus spike proteins. Ann Rev Virol., 2015; 3;1–25.
49. Simmons G., Reeves J.D., et al., Characterization of severe acute respiratory syndrome-associated coronavirus (SARS-CoV) spike glycoprotein-mediated viral entry. Proc. Natl. Acad. Sci. U.S.A., 2004; 101; 4240-4245.
50. Harmer D., Maureen Gilbert., et al., Quantitative mRNA expression profiling of ACE 2, a novel homologue of angiotensin converting enzyme. FEBS Letters., 2002; 532;107-110.
51. Yan R., Zhang Y., et al., Structural basis for the recognition of the SARS-CoV-2 by full-length human ACE2. Science., 2020; 367(6485); 1444-1448.
52. Ksiazek T.G, Erdman D, et al., A Novel Coronavirus Associated with Severe Acute Respiratory Syndrome. N Engl J Med., 2003; 348; 1953–1966.
53. Ochs M., Nyengaard J.R, et al., The number of alveoli in the human lung. Am J Respir Crit Care Med., 2004 Jan 01;169(1);120-4.
54. Mason R.J., Biology of alveolar type II cells. Respir. Suppl., 2006; 11; S12–S15.
55. Hamming I., Timens W., et al., Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. J. Pathol., 2004; 203; 631–637.
56. Zou X., Chen K., et al., The single-cell RNA-seq data analysis on the receptor ACE2 expression reveals the potential risk of different human organs vulnerable to Wuhan 2019-nCoV infection. Front Med., 2020; 14; 185–92.
56. Ding Y., He L., Zhang Q., Huang Z., et al., Organ distribution of severe acute respiratory syndrome (SARS) associated coronavirus (SARS-CoV) in SARS patients: implications for pathogenesis and virus transmission pathways. J. Pathol., 2004; 203 (2); 622–630.
57. De Wilde A.H., Snijder E.J., et al., Host factors in coronavirus replication. Curr Top Microbiol Immunol., 2018; 419; 1–42.
58. Hussain S., Pan J., et al. Identification of novel sub-genomic RNAs and noncanonical transcription initiation signals of severe acute respiratory syndrome coronavirus. J Virol., 2005; 79(9); 5288–95.
59. Knoops K., Kikkert M., et al., SARS Coronavirus replication is supported by a reticulo-vesicular network of modified endoplasmic reticulum. PLoS Biol., 2008; 6; e226.
60. Gosert R., Kanjanahaluethai A., et al., RNA replication of mouse hepatitis virus takes place at double-membrane vesicles. J Virol., 2002; 76; 3697–3708.
61. Cascella M., Rajnik M., et al., Features, evaluation and treatment coronavirus (COVID-19). Stat pearls [internet]. Treasure Island (FL): Stat Pearls Publishing, 2020.
62. Takeuchi O., Akira S., Innate immunity to virus infection. Immunol Rev., 2009; 227(1); 75–86.
63. Kim G.U., Kim M.J., et al., Clinical characteristics of asymptomatic and symptomatic patients with

mild COVID-19. Clin Micro Inf., 2020; 26; 948.e1e948.e3.
64. Yang Y., Yang M., et al., Evaluating the accuracy of different respiratory specimens in the laboratory diagnosis and monitoring the viral shedding of 2019-nCoV infections. MedRxiv,. 2020.
65. Cao W., and Li T., COVID-19: towards understanding of pathogenesis. Cell Res., 2020; 30; 367–369.
66. Tang N.L., Chan P.K., et al., Early enhanced expression of interferon-inducible protein-10 (CXCL-10) and other chemokines predicts adverse outcome in severe acute respiratory syndrome, Clin Chem., 2005; 51; 2333–2340.
67. Tian S., et al., Pulmonary pathology of early phase 2019 novel coronavirus (COVID-19) pneumonia in two patients with lung cancer. J. Thorac. Oncol., 2020; 15 (5); 700-704.
68. Wang M., Hao H., et al., Early Career, Thrombotic regulation from the endothelial cell perspectives, Journal., 2018; 38; 90–95.
69. Chen N., Zhou M., et al., Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet., 2020; 395; 507.
70. Moldoveanu B, Otmishi P, et al., Inflammatory mechanisms in the lung. Journal of Inflammation Research 2009;2: 1–11.
71. Liu S., Su X., et al., Neutrophil extracellular traps are indirectly triggered by lipopolysaccharide and contribute to acute lung injury, Journal., 2016; 6; 37252.
72. Fang M., Siciliano N.A., et al., Perforin-dependent CD4+ T-cell cytotoxicity contributes to control a murine poxvirus infection, Journal., 2012; 109; 9983–9988.
73. Zhou Y., Fu B., Zheng X., et al., Aberrant pathogenic GM-CSF+T cells and inflammatory CD14+CD16+ monocyte in severe pulmonary syndrome patients of a new coronavirus, BioRxiv., 2020.
74. Mehta P., McAuley D.F., Brown M., et al., COVID-19: consider cytokine storm syndromes and immunosuppression, Lancet 2020; 395 (10229); 1033-1034.
75. Ruan Q., Yang K., Wang W., et al., Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med., 2020; 46 (5); 846-848.
76. Chinese Center for Disease Control and Prevention. Epidemic update and risk assessment of 2019 Novel Coronavirus 2020 [updated 29 January 2020; cited 2020 29 February]. Available from: http://www.chinacdc.cn/yyrdgz/202001/P020200128523354919292.pdf.
77. Backer J.A., Klinkenberg D., et al., Incubation period of 2019 novel coronavirus (2019-nCoV) infections among travellers from Wuhan, China. Eurosurveillance., 2020; 25(5); 20-28.
78. Soon Ho Yoon., Kyung Lee., et al., Chest radiographic and CT findings of the 2019 novel coronavirus disease (COVID-19): analysis of nine patients treated in korea, Korean J. Radiol., 2020; 21.
79. Tomas Franquet., Imaging of pulmonary viral pneumonia», Radiology., 2011; 260 (1); 18–39.
80. Statista. Number of novel coronavirus COVID-19 cumulative confirmed and death cases in China from January 20 to April 24, 2020.
81. European Centre for Disease Prevention and Control (2020) Coronavirus disease 2019 (COVID- 19) pandemic: increased transmission in the EU/EEA and the UK-seventh update.
82. Molteni M., Kids Can Get Covid-19. They Just Don't Get That Sick. Available at: https://www.wired.com/story/kids-canget-covid-19-they-just-dont-get-that-sick. 2020.
83. Cossarizza A., De Blasi S., Guaraldi G., et al., For the Modena Covid-19 Working Group (MoCo19). SARS-CoV-2, the virus that causes COVID-19: cytometry and the new challenge for global health. Cytometry., 2020;97A; 340-343.
84. Sullivan K.E., Stiehm E.R., Stiehm's immune deficiencies: Academic Press; 2014.
85. McCloskey B., Heymann D.L., SARS to novel coronavirus – old lessons and new lessons. Epidemiol Infect., 2020; 148; 22.
86. Yokosuka T., Saito T., Dynamic regulation of T-cell costimulation through TCR-CD28 micro clusters, Immunol Rev., 2009; 229.
87. Begley S., Experts envision two scenarios if the new coronavirus isn't contained. Available at: https://www.statnews.com/2020/02/04/two-scenarios-if-new-coronavirusisnt-contained/ (Accessed 15 March 2020).
88. Wang A., Chiou J., Poiron O.B, et al., NHLBI Lung Map Consortium. Single nucleus multiomic profiling reveals age dynamic regulation of host genes associated with SARS-CoV-2 infection, BiorXiv., 2020.
89. Chowell G., Abdirizak F., Lee S., et al., Transmission characteristics of MERS and SARS in the healthcare setting: a comparative study, BMC Med., 2015; 13 (210); 1-12.
90. World Health Organization (WHO)Recommendation to Member States to improve hand hygiene practices widely to help

prevent the transmission of the COVID-19 virus 2020, 1–3.
91. Liu K, Fang Y.Y, Deng Y., et al., Clinical characteristics of novel coronavirus cases in tertiary hospitals in Hubei Province, Chin Med J (Engl)., 2020; 133(9); 1025-1031.
92. Jian-Min Jin., Peng Bai., Wei He., et al., Gender Differences in Patients With COVID-19: Focus on Severity and Mortality. Fron Pub Heal., 2020; 8 (152); 1- 6.
93. Dhochak N., Singhal T., Kabra S.K., Lodha R., Pathophysiology of COVID-19: Why Children Fare Better than Adults? Ind J Ped., 2020.
94. Tian S., Hu W., et al., Pulmonary pathology of early phase 2019 novel coronavirus (COVID-19) pneumonia in two patients with lung cancer, J Thor Onc., 2020; 15 (5); 700-704.
95. Mckeever A., From blood storms to honeycomb lungs, here's an organ-by-organ look at how COVID-19 harms humans. Available at: https://www.nationalgeographic. com/science/2020/02/here-is-what-coronavirus-does-tothe-body/ (Accessed 10 March 2020).
96. Hui D.S, E IA, Madani T.A, et al., The continuing 2019-nCoV epidemic threat of novel coronaviruses to global health - The latest 2019 novel coronavirus outbreak in Wuhan, China. Int J Infect Dis., 2020; 91; 264-6.