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Review Article

Covid-19: An Overview of the Risk Factors in Animals and Humans

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Abstract

The most recently detected anthropozoonotic coronavirus (COVID-19) is a strain that began infecting humans in December 2019, following the reported outbreak of unexplained pneumonia in Wuhan, China. COVID-19 infection can pass from human to human via droplets showing mild (in 80% of cases), moderate or severe illness (in 20% of cases, with 6% of them requires special mechanical ventilation) with multiple organ failure and death. The difference in the disease severity where some people may appear with severe and life-threatening COVID-19 sequelae whereas the others may appear asymptomatic or even with mild symptoms directed us to focus the light on the genome structure and the different genotypes of COVID-19 with regarding the possible risk factors of acquiring the infection in humans (such as: age, gender, occupation, smoking, obesity, pregnancy, race and economic status, alcohol consumption, food consumption, immunological status, residence, travel, contact with pets), animals (such as: species and age), environment (season) and the viral agent itself (such as: infectivity dose and virulence) to be considered during the expected rise of the third wave of COVID-19.

Keywords: *COVID-19; Genome; Genotypes; Risk Factors and SARS-CoV-2*

Introduction

Coronaviruses are positive single-stranded enveloped RNA viruses which are globally distributed in animals and humans. Most of human known coronaviruses causes mild infections. However, two beta-corona-viruses were declared with major outbreaks, the first was the Severe Acute Respiratory Syndrome coronavirus (SARS-CoV) that was represented in the period of (2002 - 2003) causing a fatal pneumonia with a fatality rate of 10% and the second was the Middle East Respiratory Syndrome coronavirus (MERS-CoV) that was represented in 2012 causing a fatal pneumonia but with a mortality rate of 36% [1].

In December 2019, pneumonia of unknown cause was emerged among the inhabitants in Wuhan, Hubei Province, China. Most of these notified cases were previously in a direct contact with the Huanan Seafood Wholesale Market. Afterwards, deep genomic sequencing of the samples taken from the patients' lower respiratory tract showed the presence of a new strain of coronavirus that was previously known as 2019 novel coronavirus (2019-nCoV). Afterwards, the described virus was named as Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2) while the described emerged disease was known as COVID-19. Despite SARS-CoV-2 was phylogenetically

and clinically similar to SARS-CoV, the newly described virus had a higher rate of transmissibility with lower rates of case fatality. Later on, the World Health Organization (WHO) listed the outbreak of COVID-19 as a public health emergency of international concern on 30 January 2020 while the epidemic was upgraded to pandemic on March 11 [2].

The phylogenetic analysis of SARS-CoV-2 showed a close relation with the Bat-SARS-like coronaviruses of order Nidovirales, family *Coronaviridae*, genus *Betacoronavirus* and subgenus *Sarbecovirus* [3]. As well, the zoonotic origin of SARS-CoV-2 was confirmed since it was explained to share nucleotide similarities of 96.3% with bat CoV RaTG13, 89% with SARS-like CoV ZXC21 and 82% with SARS-CoV [4].

Since 31 December 2019 and till 18 March 2021, the global total number of SARS-CoV-2 patients was 120,268,427 with 2,659,802 deaths within 213 countries and territories around the world. In America, the number of patients was 53,497,254 while was 22,641,603 in Asia, was 40,023,320 in Europe, was 4,045,716 in Africa, was 59,829 in Oceania and 705 in an international conveyance in Japan [5].

The current study provided a summarized review on the genomic characteristics of SARS-CoV-2 with a more detailed presentation of the different possible risk factors concerning the host, environment and the viral agent itself that could be a predisposing factor for acquiring of COVID-19. We hope that the current revision would offer meaningful description for other future studies and also spot the light on different critical precautions that should be followed during the expected third wave of the disease.

Genotypes of the SARS-CoV-2 virion

SARS-CoV-2 had 6 identified major clades (basal, D614G, D448del, G392D, L84S and L3606F) and also 14 subclades. D614G variant is the most common identified clade presented in a B-cell epitope with highly immune-dominant portion affecting the vaccine effectiveness. All the strains with a mutation in D614G, have also a mutation in the replication protein (ORF1abP4715L; RdRp P323L) which may affect on the viral speed of replication. Furthermore, D614G clade is the largest one containing five subclades, most samples of D614G clade displayed a non-coding variant 241C>T, ORF1ab P4715L and another synonymous variant 3037C>T. The subclade (614G/Q57H/T265I) is the largest subclade in the D614G clade. On the other side, L84S is the second largest major clade that contained 2 subclades (L84S and P5828L). L3606F contains three subclades (V378I, G251V and G251V/P765S). The basal clade accounted only for a small genomic fraction. The other two clades G392D and D448del are small without any significant subclades [6].

Zhang Liangsheng., *et al*. [7] found that SARS-CoV-2 could be listed into Type I genotype and Type II genotype. Type I could be classified into types IA and IB where the type IA phylogenetically showed a close similarity with the ancestral SARS-CoV-2. On the other side, Type II genotype (which was arised from type I genotype) was suggested to be the source of SARS-CoV-2 outbreak described in the Wuhan Huanan market as well as it was likely evolved from a super-spreader.

Two major SARS-CoV-2 types are described by two SNPs (L and S) which showed complete linkage: The first one is at 8,782 location (orf1ab: T8517C, synonymous) and the second one is at 28,144 location (ORF8: C251T, S84L). The first haplotype "CT" (defined as "L" type as a result that T28,144 is present in Leucine codon) and the second haplotype "TC" (defined as "S" type as a result that C28,144 is present in Serine codon) [8]. Another study showed that the most common SARS-CoV-2 genomic mutations are 8782C>T in ORF1ab gene, 29095C>T in the N gene and 28144T>C in ORF8 gene. These mutations would affect on the viral severity and circulation [9].

Moreover, [10] found an important mutation located within the RdRp protein at the 14408 position which was showed in the European genomes starting from 20 Feb. 2020 and it was related to more viral point mutations in comparison with other genomes in Asia, so RdRp worked in a complex mechanism included proofreading activities (in cooperation with other cofactors as Nsp7, Nsp8 and ExoN), this mutation was expected to decrease its proofreading capability.

Risk factors of COVID-19 infection in the human

Age

Age was well established as a strong risk factor for fatal COVID-19 outcomes. Throughout the pandemic COVID-19, the elderly (of > 60 years) showed higher morbidity and mortality ratios 7 times than the younger people [11]. On the other side, the COVID-19 infected children, were generally asymptomatic or show mild symptoms [12]. Age promotes changes in the immune and the inflammatory systems which would increase the susceptibility of the old people during their exposure to sources of COVID-19 [13].

Gender

Males were also recognized to be twice susceptible for increasing the acquisition and the severity of COVID-19 than females. In UK, 60% of the COVID-19-reported deaths were men [14]. Differences in the activity duties of females and males cause them to show different patterns during their exposure to the infectious pathogens. In addition, men had the habit of tobacco smoking more than women that weakens their immunity and increases their susceptibility for pneumonia and also primes mainly the lungs and also the other vital organs for greater inflammation. Furthermore, the biological differences between males and females immune systems affect their vulnerability to the different infectious diseases since the expression and the activity of the receptor angiotensin I-converting enzyme 2 (ACE2) (that used by the virus to enter the human cells) was shown to be influenced by the sex hormones [15].

ACE2 polymorphisms

Recently, the SARS-CoV-2 spike-protein which combined with human ACE2, is a peptidase molecule presented at the surface of alveolar epithelial cells (types I and II) and other tissues regulating the renin-angiotensin-aldosterone system (RAAS), i.e. it was a hormonal cascade regulating the human physiological processes such as the blood pressure and the volume homeostasis [16]. In addition, ACE2 is a human mono-carboxy-peptidase presented by the oral mucosa, enterocytes, endothelial cells of arteries and veins and even the arterial smooth muscles, they were declared to adjust the representation of the gut antimicrobial peptides [17]. Men were declared to have a higher expression of ACE2 in their lungs than women [14]. As well, Asian people express it often more than the African American and the Caucasian populations [18].

Angiotensin I converting enzyme (ACE) is a commonly circulating protein of 170 kD, altering the inactive ecapeptide angiotensin (Ang) I to an active octapeptide vasoconstrictor Ang II, controlling the blood pressure [19]. As well, liberating the aldosterone which adjusts the renal capacity for absorption of water and sodium. Furthermore, Ang II could stimulate various cytokines that mediate the cell proliferation [20]. On the other side, ACE2 stimulates the regulation of blood pressure via RAAS (converts the octapeptide Ang II to the heptapeptide Ang (1-7) via hydrolysis of the C-terminal residue), Ang (1-7) could further express its action through the MAS-related (MAS1) G protein-coupled receptor (GPGR) that is a soluble catalytic ACE2 ectodomain form able to be passed in the circulation after the cleavage of both 716 and 741 amino acids [21].

When the binding occur between SARS-CoV-2 spike and its ACE2 receptor, reduction of ACE2 catalytic properties would occur in an association with decreased inflammation. The lack of Ang (1-7) generation might increase the injury of both the lung and the cardiovascular system. Under this condition, Ang II accumulates and binds AT1R releasing proinflammatory signals which trigger hypertension and also cause damage in heart and lung [21]. As a result, the mutations which affect on the human ACE2 gene such as: the putative ACE2 protein mutations, transcriptional variation during the ACE2 mRNA expression and also the post-transcriptional modifications on the ACE2 receptor (viral N-glycosylation), would influence the COVID-19 outcome by working on the blood pressure via the RAAS and also possibly would increase the heart and the lung injuries through the oxidative stresses of Ang II [22].

Vitamin D deficiency (hypovitaminosis D)

Vitamin D plays a critical role in the immune system integrity since it was interfered with neutrophils, macrophages, dendritic cells and lymphocytes (B and T) supporting the innate immunity. As well, vitamin D has non-genomic and genomic effects where the genomic effect was induced by the nuclear vitamin D receptor (VDR) that is a factor acts by promoting the expression of the antimicrobial peptides as: Beta-defensins and Cathelicidin against fungi, bacteria and even the enveloped viruses (like SARS-CoV-2). Moreover, vitamin D can increase the production of anti-inflammatory cytokines and decrease the production of pro-inflammatory cytokines. Furthermore, it has a vital role in keeping the integrity of the barriers and tight junctions and also modulating the rennin-angiotensin coordination [23].

Hypovitaminosis D was caused by many physiological causes such as: in case of the low UVB exposure (such as: during the winter season in the northern regions and in case of total body coverage with decreased exposure to the outside), in case of strong pigmentation (in Europe and the USA), in case of reduced synthesis of vitamin D in the skin (in age groups of under 5or even over 65 years, pregnant women, obesity, nursing-home residents and diabetes) and in case of a poor diet of vitamin D (in fish and fortified food) [24].

Hypovitaminosis D (estimated as the level of the transport form of vitamin D in the plasma, 25(OH) D) was a global problem. In Europe, deficits (< 30 nmol) were declared between 20 - 90% in all ages whereas hypovitaminosis D in Asia was shown to be 61% among children in Pakistan and India while was 86% among those in Iran. on the other side, hypovitaminosis D among the Scandinavian population was only 5% as a result of the traditional habit of ingestion of cod liver oil that is high in vitamins A and D or as a result of their genetic expressions, resulting in higher vitamin D synthesis in their skin [25]. On the contrary, severe vitamin D deficiency was declared to be endemic among Arabs individuals especially women since they tend to wear a traditional attire covering more body surface and so, affecting the ability of their body to absorb sunlight and produce vitamin D [26].

Hypovitaminosis D was revealed as a poor prognosis marker of COVID-19 and was independently associated with fatal COVID-19 sequelae since the recorded mortality rate due to COVID-19 in 12 European countries illustrated a significant inverse association (P-value = 0.046) with the mean plasma concentration of 25(OH) D. However, many research indicated that the increased supplementation with vitamin D would reduce the Th2 responses during *Aspergillus* infection among COVID-19 critical cases, enhancing the secondary infection with pulmonary aspergillosis among COVID-19 patients [27].

Residence

Today, more than half of the global human population (about 4 billions) lives in cities (urban districts). From those, 1 billion people live in poor crowded slums lacking the access to drainage, waste disposal, electricity, water, policing and health care. The high density of people crowded together, especially those living in slums in poor slums, increased the risk for contracting of many communicable diseases such as COVID-19 in comparison with those living in rural expanded areas [28].

Occupation

During the outbreak of COVID-19, the workplace played a critical role in increasing or even the stop of the spread of the virus through the workplace policies and practices [29]. Understanding the possible risk of different occupations in acquiring of COVID-19 infection is a critical primary public health goal that aims to prevent the viral spread. Exposure to the disease inside the workplace followed by its spread within the community depends on some factors such as: the number of contacts with the public, the population density within the workplace, the number of hand washing times, the number of contacts with the body fluids, well ventilation, the efficient cleaning and hygiene practices inside the work area and even the usage of proper personal protective equipment (PPE), etc [30].

Baker Marissa G., *et al*. [31] concluded through their study on many workers in the United States that the workers of healthcare support were the most occupational group in a high risk of exposure to COVID-19 infection by 96.1% followed by workers of community and

social services 32.4%, teachers 23.3%, workers of construction 8.3% and workers of business and financial operations 3.9%. They also showed that none of the examined workers of food preparation, sales, farming and fishing workers was evidenced with COVID-19 infection.

Cigarette and waterpipe smoking

The pandemic COVID-19 outbreak is still poorly understood and still also under progression with limited available clinical data about the patients and the risk aspects for acquiring the infection [32]. Tobacco smoking had been reported to be critically related to an adverse COVID-19 prognosis since smoking may have mechanical effects on the respiratory mucosa or structural and functional effects on the host immune response promoting the acquisition or invasion of the infection to the lung. Smoking showed also a detrimental effect on the immunity against different infections, causing the tobacco smokers became twice susceptible to COVID-19 than the non-smokers [15].

Alcohol consumption

Alcohol consumption might be a potential predisposing factor for acquiring COVID-19 and progressing of its fatal complications. Alcohol became absorbed in the bronchial circulation via the ciliated epithelium of the airways. As the air cools the vapors in the trachea, a higher concentration of alcohol occur and causes modification of the airway-epithelium defenses by altering the cytokine release, ciliary function and barrier function. Alcohol also makes oxidative stress and alterations in the functions of the alveolar macro-phage. This alteration in pulmonary defense could enhance the risk of acquiring SARS-Cov-2 infections [33].

Food consumption

Approximately 2 - 10% of the COVID-19 cases showed diarrhea [34]. Two previous studies detected the presence of RNA fragments of COVID-19 in the faecal matter of confirmed patients [35]. It was declared that people were unlikely could acquire COVID-19 from food since coronaviruses cannot multiply in food whereas they need a host (animal or human) to multiply inside their bodies, so SARS-CoV-2 virus causes a pulmonary illness where the primary route of transmission is by direct contact with the respiratory droplets that released during sneezing, talking or coughing from infected persons [35].

Obesity

Obesity was an independent predisposal risk factor for the susceptibility to COVID-19. The excess ectopic fat deposition would reduce the metabolic efficiency, reduce the protective cardiorespiratory reserve in the body as well as potentiate the immune dysregulation and so, causes organ failure and also causes case progression to fatal sequelae [36].

Pregnancy

Pregnant women and their fetuses were considered the most susceptible population throughout the outbreak of COVID-19 infection with no available definite evidence about the occurrence of any notified vertical transmission. The mechanical and physiological pregnancy changes would increase the susceptibility to different infections especially when the gravida cardiorespiratory system is included and promote the quick evolution of the disease to a respiratory failure. Moreover, the circulating T-helper 2 (Th2) system dominates to protect mainly the fetus, leaving the pregnant mother in a danger of COVID-19 infection [37].

Racial/ethnic disparities and economic status

From the studies that concerned the Racial/Ethnic Disparities as an possible aspect in susceptibility of COVID-19, [38] concluded that the people who are black or American Indian and even those with a low-income households had a high opportunity for obtaining

COVID-19 illness with subsequent increased mortality rates in comparison with Latinos, white people and those who were living with higher-income. They explained their result with the fact of the ease accessibility of the second group to the medical facilities. Moreover, the people with low-income were more likely to inhabit in crowded districts and also to work in different industries that were left open during the period of nonessential business closures.

Furthermore, a previous epidemiologic survey was performed in Wuhan and Shenzhen, China, declared that the people with blood group O, showed some resistance to SARS-CoV as a result of their ABO antibodies whereas the people with blood group A, were more related to a higher rate of acquiring COVID-19 illness in comparison with the other people with non-A blood groups [39].

Immunological status

Complications such as: diabetes, liver diseases, chronic kidney disease, hypertension, coronary heart disease, neurological disorders, HIV and even cancer could share in increasing the severity and the fatal sequelae of COVID-19 illness as a result of ACE2 imbalance and the storm of the cytokines stimulated by glucolipid metabolic disorders (GLMD), affecting on both the patients' immunological function and structure. Immunocompromised patients were advised to stay at home with regular washing of their hands to avoid potential exposure to the virus [40].

Throughout the world, diabetes was considered one of the chief reasons of morbidity and mortality. Common infections like pneumonia and influenza, are fatal among older people with type 2 diabetes mellitus (T2DM) [41]. As well, reports from China [42] and Italy [43] declared that older diabetic patients were more susceptible for fatal COVID-19 sequelae since diabetes was considered a chronic inflammatory condition with many vascular and metabolic abnormalities which could affect human response against different pathogens through occurrence of serious immunological defects associated with hyperglycemia.

Furthermore, [44] revealed through their study an increased consequence and fatality among COVID-19 patients who suffered from liver diseases and even chronic kidney disease (CKD) as a result of the immunity dysregulation among those patients. Moreover, people who sometimes take different non-steroidal anti-inflammatory drugs (NSAIDs) like ibuprofen to relief pain of different chronic conditions, would suffer from chronic kidney disease when take these drugs for long time [45].

Moreover, many studies showed that the COVID-19 positive cases who suffered from hypertension and coronary heart disease, were associated with a higher severity of the infection with a higher risk of mortality. It might be related to the imbalance of the first immunological encountered factor (ACE2) which had protective effects for many organs as: the cardiovascular system and lung in case of SARS [21] and [40].

Concerning the neurological disorders, The Center for Disease Control and Prevention (CDC) documented the epilepsy as a predisposing factor for COVID-19. As a result, epileptic patients should require a further cautionary approach concerning COVID-19. Additionally, many autoimmune epilepsy medications (such as: steroids) could affect adversely on the patients' immunity, enhancing the danger of the infectious diseases [46].

Regarding cancer, patients suffering from cancer had a poorer prognosis when infected with COVID-19 more than those without cancer since cancer conducted patients to severe fatal COVID-19 sequelae. In addition, cancer usually causes a blunted immune status showed as suppressed induction of proinflammatory danger signals, over-expressed immunosuppressive cytokines, weak maturation of the dendritic cells and even increased functional immunosuppressive leukocytic populations [47].

Concerning the limited available data of HIV patients, it was believed that the HIV patients who were on effective treatment, had the same risk for COVID-19 as people who do not have HIV [48]. Furthermore, the people who suffered from asthma or even chronic obstruc-

tive pulmonary disorder involved decreased lung function with a greater probability for lung inflammation. As well, those patients when used any corticosteroid immune-suppressing drugs, became more susceptible for biological stresses and inflammation of SARS-CoV-2 [49].

Travelling to the infected countries

The virus of COVID-19 could be transmitted mainly via aerosols, droplets (that arise during coughing or sneezing then inhaled or even ingested by individuals nearby within about 6 feet) and even direct contact, indicating man-to-man transmission. Indirect transmission also could occur by touching a contaminated surface followed by touching the eyes, the nose or the mouth [50].

Many countries applied border closures policy as a key aspect to control the introduction of infected travellers from COVID-19 affected countries and so, to control the pandemic, causing heavy bad implications on the global economy and tourism. In many cases, quarantine was applied on any traveller coming from affected countries instead of the full border closure [51].

Contact with pets

Pets posed a possible risk for COVID-19 transmission, when someone gets in contact with an animal belonged to an infected patient so, COVID-19 patients were advised not to contact with different pets and were also advised to wash their hands regularly before and after touching them and apply physical distancing from people and their pets [52]. Domestic, hospitalised and even stray cats were all tested for prior exposure to the new coronavirus and they produced specific antibodies against the virus by using an antibody-based test [53].

Virus infectivity dose

Although the minimum infective dose causing COVID-19 infection in humans was unknown, it was assumed to be low since the virus transmitted rapidly. The route of inoculation affected the response against the viruses. Infection with the drops informed us about the upper respiratory tract infection whereas the aerosols can inform about the lower respiratory tract infection. The infective dose for COVID-19 was estimated as 300 particles based on the computational analysis of nasopharynx in transmission and inhalation of droplet [54].

Viral virulence

Coronaviruses were old recognized large-sized positive-sense single stranded RNA viruses affecting both animals and humans. In humans, signs of coronaviruses may range from mild cold-like symptoms (that caused by coronaviruses 229E, OC43, NL63 and HKU1) to sever fatal respiratory illnesses (that caused by SARS and MERS) [1] and [6]. Changes in COVID-19 clinical and epidemiological features were related to the virologic changes of SARS-CoV-2 with the aid of the viral spike protein where the surface unit (S1) induces the viral entry to the host via binding with the cell receptor while the other transmembrane unit (S2) drives the union of viral and cellular membranes [3].

The SARS-CoV-2 is an enveloped virus with ability for quick mutation. Eventually, the virus would develop genetically distinct SARS-CoV-2 strains that are clinically different from each other and may further spread easily causing either mild disease or more severe disease [14].

Risk factors in the animal host

More than 400 different species of domestic, laboratory and zoo animals including fish, reptiles, amphibians, birds and even mammals, might possibly acquire the new Corona virus. The International Union for Conservation of Nature reported about 40% of animal susceptible species to be COVID-19 threatened with a possible risk for further human-to-animal transmission [55].

Some animal species were mostly susceptible for SARS-CoV-2 infection such as: primate species (Northern white-cheeked gibbon, Western lowland gorilla and Sumatran orangutan), Chinese hamsters as well as marine mammals (grey whales and bottlenose dolphins). On the other side, the domestic animals such as: cats, sheep and cattle were found to be at a medium risk whereas Dogs, horses and pigs were found to be at a low risk for acquiring the infection [56]. Within the same animal species, the virus causes more severe fatal interstitial pneumonia among old animals than among young animals [57].

Conclusion

The current study highlighted mainly the genotypes of COVID-19 with focusing the light upon different possible risk factors expected rise of the third wave of COVID-19.

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