CLINICAL NOTES: NOVEL PANDEMIC DISEASE

Coronavirus 2019 (COVID-19): A Novel Pandemic Disease

Abdulghani Mohamed Alsamarai, Aalborg Academy College of Medicine [AACOM], Denmark. Tikrit University College of Medicine, [TUCOM], Tikrit, Iraq. Email: **galsamarrai@yahoo.com**; **abdulghani.Mohamed@tu.edu.iq**; Mobile: +9647701831295,
ORCID: http://orcid.org/0000-0002-7872-6691
Amina Hamed Alobaidi, Kirkuk University College of Veterinary Medicine, Kirkuk, Iraq [KUCOVM],
Email: aminahamed2006@gmail.com, Mobile: +9647702399175,
ORCID: http://orcid.org/0000-0002-8495-3452
Mohamed Almoustafa Alsamarai, Laboratory Investigation Department, Samara University College of Applied Sciences (SUCOAS), Samara, Iraq. Mobile: +9647718814092
Email: mohamedalmoustafaa@gmail.com
ORCID: http://orcid.org/0000-0002-3051-725X

Correspondence author:
Abdulghani Mohamed Alsamarai, Aalborg Academy College of Medicine [AACOM], Denmark. Tikrit University College of Medicine, [TUCOM], Tikrit, Iraq. Email: abdulghani.Mohamed@tu.edu.iq, galsamarrai@yahoo.com; , Mobile: +9647701831295,
ORCID: http://orcid.org/0000-0002-7872-6691

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Abstract

Coronaviridae is a viral family that includes a large number of viruses that cause diseases in animals and human. The human diseases ranged from mild common cold to severe lower respiratory infections.

The first alarm of the severity of the disease that induced by coronaviruses is the outbreaks of Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS). Coronavirus most recent disease outbreak in Wuhan, China in December 2019. The virus called initially as 2019-nCov and subsequently the ICTV termed it as SARS-CoV-2, while the disease is termed COVID-19. This new virus is very contagious and thus induces pandemic infections.
Keywords: SARS-CoV-2, SARS-CoV, MERS-CoV, COVID-19, 2019-nCoV, Coronaviruses, Pandemic COVID-19.

Introduction

Coronavirus first isolated in 1937 [1] and was with global distribution and form the 2nd common cause of common cold after Rhinoviruses. Coronaviruses infect animals and human but it characterized by induction of mild diseases with a little rate of case severity. Infected animals include bats, cats and camels. In 1965, the 1st human coronavirus was isolated from individual with common cold. Human infection is of zoonotic viral infection [2]. However, in human the coronaviruses are present for at least 500-800 years, and all originated in bats [3,4].

Coronaviruses recognized for a long period as important veterinary pathogens, responsible for infections in birds and mammals [5]. Before the outbreak of COVID-19, only six coronaviruses reported that are with ability to infect human: MERS-CoV, SARS-CoV, HcoV-HKU1, HCoV-229E, HCoVNL63, HCoV-OC43 [6-8]. The last four are endemic locally and associated mainly with mild, self-limiting disease, while the first two can cause severe illness [9-11]. MERS-CoV and SARS-CoV are betacoronaviruses [12], and are among the pathogens included in the World Health Organization's Blueprint List of Priority Diseases [6]. Coronaviruses form continuous threat to human health because of their genetic diversity, genome frequent recombination, high prevalence rate and animal-human interface increasing activity [13,14].

The health threat became obvious in December 2019 and early 2020 as the novel coronavirus (SARS-CoV-2) was identified as the etiology of rabidly and large outbreaks of respiratory disease, including potentially fatal pneumonia, in Wuhan, China [15]. The virus--provisionally designated 2019-nCoV and later given the official name SARS-CoV-2, due to its similarity to SARS-CoV--was isolated

and the viral genome sequenced. SARS-CoV-2 was characterized as a betacoronaviruses and recognized as the seventh discrete coronavirus species capable of causing human disease [14].

The phenomenon of evolution of coronaviruses of animal origin in human and their transmission among people was the outbreak of Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV), and Middle East Respiratory Syndrome Coronavirus (MERS-CoV). According to WHO reports, SARS mortality rate was 10% and MERS mortality rate was 37% [16,17]. Both SARS and MERS were spread between people with close contact. MERS outbreak still occurring and spread outside Middle East region such as South Korea [18].

Viral infections are public health problem that are with continuous emergence. The respiratory viral diseases are the common viral infections that are spread frequently among people. Coronaviruses are not taken any interest unless the appearance of SARS-CoV and MERS-CoV. On December 31, 2019, the country office of WHO in China reported an epidemic unexplained lower respiratory tract infections in Wuhan [19]. The etiology of such outbreak was a coronavirus (CoV) and termed COVID-19 [20]. In the last two decades, three coronavirus strains that induced respiratory diseases outbreaks [21]. SARS-CoV-2 was different from SARS-CoV and MERS-CoV as it leads to pandemicity, while the other two were epidemic. The 3 viruses share pathogenicity and clinical spectrum, however, the epidemiology of COVID-19 was different and not as firstly believed that it was similar to SARS-CoV and MERS-CoV [22,23]. Genetically, COVID-19 [(SARS-CoV-2; Novel Coronavirus 2019] is with 90% amino acid identity with SARS-CoV [24] and sequence identity with SARS-CoV as compared to MERS-CoV [25]. COVID-19 is more contagious the other two strains and thus in a short period transmitted from endemic in to a pandemic disease. The virus initially termed 2019-nCoV, but the International Committee on Taxonomy of Viruses (ICTV) called it SARS-CoV-2

Initially, the new virus was called 2019-nCoV. Subsequently, the task of experts of the International Committee on Taxonomy of Viruses (ICTV) termed it the SARS-CoV-2 virus as it is very similar to the one that caused the SARS outbreak (SARS-CoVs). This virus belong to coronaviruses , which is an enveloped single stranded RNA that affect animals and human [26,27]. The virus crosses barriers of species and infected human to induce disease ranged from mild

common cold to severe respiratory infections as in SARS and MERS [11,28].

Coronavirus grouping

Coronaviruses are single-stranded RNA viruses, positive sense, enveloped and large group belonging to the order Nidovirales, family Coronaviridae, subfamily Coronaviridae, family Coronaviridae and the order Nidovirales. [29]. More than two dozen different species are known and have been divided into four genera (alpha, beta, gamma and delta) characterized by different antigenic cross-reactivity and genetic makeup. Human and some mammals infected by strains that belong to alpha and betacoronaviruses genera, Table 1. [11,30].

Table 1. Pathogenic Coronaviruses

Genus	Strain	Discovery date	Receptor	Host
Alpha-coronavirus	HCoV-229E	1966	Human aminopeptidase (CD13)	Bats
	HCoV-NL63	2004	ACE2	Palm Civets, Bats
Beta-coronavirus	HCov-OC43	1967	9-O-Acetylated sialic acid	Cattle
	HCoV-HKU1	2005	9-O-Acetylated sialic acid	Mice
	SARS-CoV	2003	ACE2	Palm Civets, Bats
	MERS-CoV	2012	DPP4	Bats, Camel
	SARS-CoV-2	2019	ACE2	Bats

Replication and genomic characterization

The replication of coronaviruses was studied extensively [12,30,31] and it was characterized by no DNA step in their replication cycle. However, the virus – host interaction is of vital importance in the influence of replication cycle steps [31,32]. SARS-CoV-2 is single-stranded RNA, positive-sense and with a genome of

thirty kilobase that encodes viral proteins (14 open reading frames, Orfs) [12,33,34]. At the genome 5' end, a single Orf encodes a polyprotein that auto-proteolytically cleaves into sixteen non-structural proteins (Nsp1-16) that form the replicase-transcriptase (RTase) complex.[34]. These sixteen proteins RTase composed multiple enzymes essential to viral genome replication, including the viral RNA-dependent RNA polymerase and other enzymes such as endo- and exonucleases essential to nucleic acid metabolism [34]. The 3' end of the viral genome, expressed 13 Orfs which includes four major viral structural proteins such as: Envelop (E), Spike (S), Nucleocapsid (N) and Membrane (M) [35]. SARS- CoV-2 viral capsid that encapsulates the genome consists of structural proteins, which facilitate entry to human cells through ACE2 receptors [34].

Previous MERS-CoV infection research indicated that mTOR-P13K signaling is a fundamental host component in replication of coronavirus [36]. The ubiquitin system of the host plays an important role in the utilization of autophagy pathways of MERS-CoV during infection. Specific kinases (SPK) blocking is important in autophagy and reduced replication of MERS-CoV by 28 000 fold in vitro [37]. Vesicle trafficking within the endoplasmic reticulum of host cells is an important host pathway in MERS-CoV and SARS-CoV replication. Viral structural proteins grouped within the host ER, while coronavirus RTase machinery grouped at the host ER. Thus this assembly step is an important component of host cell and potential drug target for the inhibition of the replication of viral genome and assembly of the capsid in the process of new virus particles formation [35].

Gordon et al [34] screen all SARS-CoV-2 proteins against human cell lines to determine high confidence viral-human protein interactions. With the genome sequence of SARS-CoV-2 available, they cloned, tagged and expressed 26 of 29 viral proteins in HEK293 cell lines .*In genetic composition, the SARS-CoV-2 genome is very similar to SARS-CoV: each has an Orf1ab encoding 16 predicted Nsps and each has the four typical coronavirus structural proteins. However, they differ in their complement of 3' open reading frames: SARS-CoV-2 possesses an Orf3b and Orf10 with limited detectable protein homology to SARS-CoV16, and its Orf8 is intact while SARS-CoV encodes Orf8a and Orf8b* [38-40]. Gordon et al [34] identified 332 high confidence SARS-CoV-2 human protein-protein

interactions. The SARS-CoV-2 interactome reveals novel aspects of SARS-CoV-2 biology. Gordon et al study [34] highlighted interactions between SARS-CoV-2 proteins and human proteins with a variety of functions such as deoxyribonucleic acid replication , gene expression regulators and epigenetic, trafficking of vesicle, modification of lipid (Spike), Ribonucleic acid regulation and processing, signaling, ubiquitin ligases (Orf10), nuclear transport machinery, mitochondria, cytoskeleton, and extracellular matrix. Modifications of lipids and trafficking of vesicle were responsible for most of the interactions. Apparently, the protein of the Spike (S) interacts with the GOLGA7-ZDHHC5 acyl-transferase complex, which likely mediates palmitoylation on its cytosolic tail [41]. Membrane fusion by SARS-CoV Spike is facilitated by Palmitoylation and this may forms a sound target for therapeutic inhibition [42]. ZDHHC5 enzyme inhibition was with a broad utility [43]. Host interactions of signal recognition particle (Nsp8), endoplasmic reticulum quality control (Orf8), golgins (Nsp13), and ER structural morphology proteins (M) may facilitate the dramatic reconfiguration of ER/Golgi trafficking during coronavirus infection. Peripheral compartments interactions by Orf3a (HOPS), Nsp6 and M (vacuolar ATPase), Nsp10 (AP2), Nsp7 (Rabs) and E (AP3) may also modify endomembrane compartments to favor coronavirus replication. Gordon et al [34] identified protein-protein interactions with the main protease Nsp5, using both catalytic dead (C145A) and wild-type constructs. For wild-type Nsp5, they identified the epigenetic regulator histone deacetylase 2 (HDAC2), one high-confidence interaction and predicted a cleavage site between the HDAC domain and the nuclear localization sequence, suggesting that main protease (Nsp5) may inhibit HDAC2 transport into the nucleus, induce an impact on the functions of HDAC2 in influencing interferon response and inflammation [44,45]. An interaction of tRNA methyltransferase 1 (TRMT1) with Nsp5 (C145A) was identified [34], which is responsible for synthesis of the dimethylguanosine (m2,2G) base modification on both mitochondrial and nuclear tRNAs [46]. Nsp5 cleaved tRNA methyltransferase 1, through removing its zinc finger and nuclear localization signal and likely resulting in an exclusively mitochondrial localization [34].

Lu Roujian et al [33], reported the genomic characterization of the 2019 novel coronavirus (2019-nCoV), the studied 10 genome

sequences were with homology of > 99.98% sequence identity and were with 88% identity to two coronaviruses isolated from bats with SARS (bat-SL-CoVZC45 and bat-SL-CoVZXC21) in 2018, China. While they were with about 79% homology with SARS-CoV and about 50% homology with MERS-CoV. They concluded that 2019-nCoV is a new human infecting betacoronaviruses as it adequately divergent from SARS-CoV and the original host of the virus might be bats depending on the phylogenic analysis. Additionally, structural analysis indicated that 2019-CoV able to bind to angiotensin converting enzyme 2 receptor (ACE2) in humans.

Schoeman and Fielding [47] in an extensive review *indicated that coronavirus envelop protein play a central multifunctional role which includes viral pathogenesis, release and assembly.* The coronavirus E protein play potential role in budding, assembly, envelope formation, and pathogenesis [48-55]. SARS-CoV-2 envelope interacts with bromodomain proteins [34] and binds to BRD4 and BRD2 and attributed to BRD –histone binding disruption through histone structure mimicking mechanism. Previous study reported that gene transcription was regulated by BRD2 [56]. There was a matching region between envelop protein transmembrane segment and histone N- terminus [57] and thus envelop protein mimic the histone and obstruct its interaction with BRD2, lead to host protein expression changes which are of benefit to virus.

The coronavirus spike protein is another important viral structure with a potential molecular multifunctional role that regulates CoV entry into the host cells. Spike protein S1 subunit responsible for 1st binds to host cell receptor and S2 subunit regulates the fuses of host and viral membrane [58].

Origin and evolution

The sequence databases indicated that all human coronaviruses were of animal origin. HCoV- NL63, HCoV-229E, SARS- CoV, and MERS- CoV are considered to be of bats origin, while HKU1 and HCoV- OC43 and HKU1 are of rodents origin.[59,60]. Previous studies documented the spillover of coronaviruses from animal to animal and from animal to human [61-66]. The MERS- CoV strains isolated from human were identical to that isolated from camels [66-71]. Analysis of gene sequences suggest that HKU4 bats coronavirus, HKU5 bats coronavirus and MERS- CoV are phylogenetically closely related [72].

Cui J et al [73], review indicated that SARS-CoV was originated in bats as result of SARSr-CoVs sequential recombination and then introduced to civets or other mammals before transmission to human. In addition, MERS-CoV Orf1ab is highly similar to that of MERSr- CoVs, HKU4 and HKU5 bats species. East-African bats reproduction may guide risk reduction of coronavirus spillover [74].

Before the outbreak of SARS-CoV-2 in 2019 in China, 6 strains of coronaviruses were identified as pathogenic to human. The HCoV-229E, HCoV-NL63, HCoV-HKU1 and HCoV-OC43 caused mild respiratory infection, while SARS-CoV and MERS-CoV induced more severe and respiratory infections [14,75]. SARS-CoV-2 genome sequence is 96.2% and 79.5% identical to a bat CoV RaTG13 and SARS-CoV respectively. Thus bats suspected as natural host of virus origin, and SARS-CoV-2 might be transmitted via unknown intermediate hosts from bats to human [76]. Both SARS-CoV and SARS-CoV-2 (2019-nCoV; COVID-19) using the same angiotensin-converting enzyme 2 (ACE2) to induce human infection [77].

Wuhan coronavirus isolate show some phylogenetic and genomic similarity to SARS-CoV, especially in receptor- binding domain (RBD) and S-glycoprotein gene, indicating the capability of direct human transmission [38]. Most genomic encoded proteins of SARS-CoV-2 are similar to SARS-CoVs [25]. Concerning proteins, there are substitution in underpinning subdomain, spike protein, NSP2 and NSP3 [25].

Angeletti S et al [78] suggest that SARS-CoV-2 differentiation mechanism and infectious capability may be influence by NSP3 and NSP2 mutation. Thus the difference between SARS-CoV and SARS-CoV-2 in their transmission, contagiousness and host tropism and research conduction for effective antiviral agents may be attributed to these changes.

SARS-CoV-2 isolates in different patients from several provinces indicated a mutation in different patients in China [79]. However, the mutation of H7N9 was larger than the diversification of SARS-CoV-2 [80]. SARS-CoV-2 community-based genetic analysis indicated 2 prevalent evolvement types of SARS-CoV-2, S type (about 30%) and L type (about 70%) [81]. The L type SARS-CoV-2 strains are evolutionally more contagious and aggressive and this warranted further investigations to illustrate their effect on virus epidemicity and virulence. In human, SARS-CoV receptors in

respiratory tract, heart and kidney are ACE2 [82], and this receptors regulate human to human transmission and cross-species transmission [83]. SARS-CoV-2 used the same receptor for cell entry (ACE2) as in SARS-CoV [77].

Coronavirus surface S-glycoprotein attached to the angiotensin-converting-enzyme 2 on human cell surface [84]. There are two subunit in S-glycoprotein, S2 and S1 [85]. Virus cell membrane fusion mediated by S2 through 2 tandem domains, HR2 and HR1, while S1 determined host-virus range and cellular tropism with RBD [86,87].

de Wilde AH et al [88], the viral genome ribonucleic acid is released into the cytoplasm after membrane fusion, and the uncoated ribonucleic acid translates two polyproteins (pp1ab and pp1a), which encode non-structural proteins, and form replication-transcription complex (RTC) in double-membrane vesicle [89]. A nested set of subgenomic RNAs replicated and synthesized continuously by replication-transcription complex [90], which encode structural proteins and accessory proteins. Arranging Golgi apparatus and endoplasmic reticulum and Golgi [91], newly formed genomic ribonucleic acid, nucleocapsid proteins and envelope glycoproteins assemble and form viral particle buds. Finally, the virion-containing vesicles fuse with the plasma membrane to release the virus. SARS-CoV-2 cellular entry was enhanced by human respiratory cells of ACE2, rather than Aminopeptidase N or Dipeptidyl peptidase -4 [92]. Song W, et al [93], found that ACE2 and S protein with binding efficiency of 10-20 fold higher in SARS-CoV-2 than in SARS-CoV.

The mechanisms for SARS-CoV-2 membrane invagination in the process of endocytosis still unknown [77], however, for SARS-CoV trimer S protein cleavage is triggered by cathepsin and the cell surface-associated transmembrane protease serine 2 (TMPRSS2) [94,95]. Although, scientists suggest that SARS-CoV-2 is less virulent than SARS-CoV and MERS-CoV depending on the mortality rate wich is 2-4% , which lower than MERS (around 35%) and SARS (9.6%) [16,17], still there is no explanation for the pandemicity of the disease globally. Andersen et al [96] *identifies two notable genomic features of SARS-CoV-2: (i) on the basis of structural studies [83,92,97,98] and biochemical experiments[77,92,98], SARS-CoV-2 appears to be optimized for binding to the human receptor ACE2; and (ii) the spike protein of SARSCoV-2 has a functional polybasic (furin) cleavage site at the S1–S2 boundary through the insertion of 12*

nucleotides[97] , which additionally led to the predicted acquisition of three O-linked glycans around the site.

There are different ideas concerning the origin of SARS-CoV-2, however, the two main suggestions: firstly, the SARS-CoV- 2 is laboratory manipulated virus, secondly, it is a naturally selected virus either in human or animals. Anderson et al [96] concluded that SARS-CoV-2 is not emerged from manipulated SARS-CoV in laboratory. The SARS-CoV-2 receptor binding protein domain in the spike protein is optimized for binding to human ACE2 with an efficient solution different from those previously predicted [83,99]. Additionally, if laboratory genetic manipulation was done, at least one of ß coronaviruses available reverse genetic systems was used [73]. The SARS-CoV-2 genetic data indicated that it was not derived from previously used backbone [100]. Accordingly, Andrews et al proposed two plausible theories to explain the origin of SARS-CoV-2: (i) natural selection in humans following zoonotic transfer; and (ii) natural selection in an animal host before zoonotic transfer. [96].

There is global ongoing research work used passage of bat SARS-CoV-like coronaviruses in cell culture and/or animal models [101], with a documented escape of SARS-CoV from laboratories [102]. SARS-CoV studies shows RBD mutation following repeated cell culture passage and this may occur for SARS-CoV-2 [99].

Pangolins SARS-CoV-like coronaviruses from pangolins with nearly identical RBDs in SARS-CoV-2 provides a much stronger but more parsimonious explanation of how SARS-CoV-2 acquired these via mutation or recombination [73]. In addition, acquisition of both the predicted O-linked glycans and polybasic cleavage site another issue against culture-based viral manipulation [96]. Progenitor virus prior isolation, which is with very high genetic similarity to SARS-CoV-2 is required to the generation of SARS-CoV-2 by animal passage or cell culture and no such research work is reported [96]. In addition, polybasic cleavage site generation need continuous passage in animals or cell cultures with ACE2 similar to those of human and such work is not previously reported. Lastly, the predicted O-linked glycans generation is also unlikely to have occurred due to cell-culture passage; as such features suggest the involvement of an immune system [103]. The balance of evidence to favor one hypothesis over another is swing depending on new and more scientific data [96]. Available genetic information suggesting that SARS-CoV-2 origin is

from animal sources. However, the future evidence may confirm or exclude this hypothesis.

Immune response

SARS-CoV-2 interacts with multiple innate immune pathways [104-129] and multiple SARS-CoV-2 viral proteins targeted signaling of cellular proteins that play a role in innate immune response [34]. Nsp13 interacts with two key players of IFN signaling pathway including TANK-binding kinase 1-binding protein 1 (TBKBP1/SINTBAD) and TANK-binding kinase 1 (TBK1). Interferon regulatory factor dependent transcription induction mediated by SINTBAD which acts as an adaptor protein between TBK1 and IKKi [104]. In addition, Transducin-like enhancer family multiple proteins interacts with Nsp13 and influence NF-κB inflammatory response [105-107]. Nsp15 targeted E3 ubiquitin ligase (RNF41) /Nrdp1) and activate IRF3 and TBK1 and lead to increase in the production of INF- I [108]. MIB1 and TRIM 59 regulate antiviral signaling of innate immune response and are taken over by Nsp9 and Orf3 respectively [109,110].

Multiple proteins that influence NF-kB and IkB kinase signaling pathway interact with Orf9c protein with an including NLRX1, NDFIP2 and F2RL1 [111-113]. In addition, there is an interaction between Orf9b and mitochondrial import receptor (Tom70), which is an important adapter that links TBK1/IRF3 with MAVS resulted in IRF-3 activation [114]. Innate immune response induced by N targets stress granule protein G3BP1through multiple mechanisms [115-117].

Stress granules (SG) and related RNA biology is commonly manipulated by coronaviruses, and may lead to stress granules suppression and shutoff of host translation [118]. This functionality attributed to viral replication, as stress granules are inhibitory to MERS-CoV replication [119] and other viruses [120]. Many host mRNA binding proteins, including the protein kinases CK2, SG related factors G3BP1/2 and the mTOR translational repressors LARP1, are included in SARS-CoV-2 nucleocapsid (N) interactome [34]. Once viral dsRNA recognised the protein kinase R (PKR)-mediated phosphorylation of eIF2α lead to induction of SGs [120]. Zotatafin (eIF4A inhibitor) promote the aggregation of G3BP [121,122] or inhibition of CK2 by Silmitasertib [123] which lead to disassembly of SG warranted studies for SARS-CoV-2 treatment [34].

Rapamycin, an mTOR inhibitor prevent LARP1 binding to mTORC1 [124] and in vitro reduction of MERS infection by about 60% [125]. Host interferon signaling antagonized by Orf6 of SARS-CoV [126]. Gordon et al [34] reported the identification of novel, high-confidence interaction between SARS-CoV-2 Orf6 and NUP98-RAE1, an interferon-inducible mRNA nuclear export complex [127] that is degraded by multiple viruses [Influenza-A, KSHV, VZV and Polio) [121,123,125,128]. Interferon antagonized by SARS-CoV-2 by targeting the RNA nuclear export activity of RAE1 [34].

Both humoral and cell mediated immune response to COVID 19 are with protective role against infection in human [130,131]. The copiously expressed proteins and most immunogenic during SARS-CoV-2 infections are N protein and S protein [131]. Zheng et al [132], China, reported neutropenia in 74.3%, lymphoprenia in 89.2%, and thrombocytopenia in 24.3%. in 94.5% of the cases are with ratio of neutrophil-to-lymphocyte ratio of more than 5. Additionally, all patients show increased CRP, 89.2% of cases with high systemic immune inflammation index of more than 500, increased D dimer in 97.1%, increased lactate dehydrogenase in 93.2% and high level of interleukin-6 [132]. Other studies show a high levels of proinflammatory cytokines such as TNFα , IL-2, IL-7, IL-10, IP-10, G-CSF, MIP-1A, and MCP-1 and induction of cytokine release syndrome (CRS) or "cytokine storm" [133,134].

The disease severity was correlated with lymphocytopenia and neutrophilia [38,135]. Innate immune response antiviral response augmented by the recognition of viral invasion produced molecular structure (pathogen-associated molecular patterns, RAMPs). In coronavirus infection, RAMPs found in replicating double stranded RNA or single-stranded RNA, which is recognized by TLR7, TLR8 and the endosomal RNA receptors in single stranded RNA, and retinoid- inducible gene, cytosolic RNA sensor and melanoma differentiation associated gene 5 [130,136,137].

Transcription factors and several signaling pathways activated as a consequence of this recognition and include activator protein 1 (AP-1), nuclear factor κB (NF-κB), , interferon response factor 3 (IRF3), and IRF7 accompanied by their nuclear translocation . AP-1 and NF-κB and AP-1 stimulate the expression of genes encoding many of the molecules required for inflammatory responses, including

inflammatory cytokines (eg, tumor necrosis factor [TNF] and IL-1), chemokines (eg, CCL2 and CXCL8). IRF3 and IRF7 promote the production of type I interferon (IFN-α and IFN-β), [138] which are important for antiviral innate immune responses and able to suppress viral replication and dissemination at an early stage.[139,140]. In SARS-CoV-2 infection, the type I INF mediated response to viral infection was suppressed [138].

The major host-virus interaction include: Th1/Th17 is induced and specific antibodies are produced, delay or suppression type I interferon response during initial infection, influex of activated neutrophils and inflammatory monocytes/ machrophages and viral replication triggers hyperinflammatory conditions [141]. Neutralizing antibody produced during SARS-CoV-2 infection and limit infection and may prevents re-infection [142]. After 4 days of SARS-CoV-2 infection, IgG antibody against N protein was detected and seroconversion achieved by day 14 [143,144]. Previous studies on SARS infection suggested memory B-cells decreased level with time [145,146] and this may be the case for SARS-CoV-2 [145]

T-cell mediated immune response against SARS-CoV-2 is of vital importance for infected cells recognition and killing [147]. CD4+T cell response number and function was lower than CD8+T cells [130]. The cytokines production and regulation was correlated to the disease severity and this influence the course and outcome of the infection [145,148-153].

Wu F. et al [154] studied immune response in 175 subjects recovered from COVID-19 found that neutralizing antibody (Nabs) to SARS-CoV-2 were unable to cross-reactive with SARS-CoV virus. Specific Nabs to SARS-CoV-2 were detected in COVID-19 patients after 10-15 days from the onset of the disease and remained thereafter. Neutralizing antibodies titres among COVID-19 patients correlated with the spike-binding antibodies targeting S1, RBD, and S2 regions. Additionally, different patients show variable NAbs titres. The plasma spike binding and neutralizing antibodies were significantly lower in younger patients than elderly and middle-aged patients. At admission time, lymphocyte count was inversely correlated with NAabs title, however, CRP levels were positively correlated with NAabs. These finding indicating cellular immune and humoral response association. They suggested that NAabs may play a role on disease progression

based on SARS-CoV-2 specific NAbs variations in recovered COVID-19 subjects. Blood CRP, age and lymphocyte counts correlation with neutralizing antibodies titres suggest that host and virus immune response interaction in SARS-CoV-2 infection need more investigations in order to develop effective vaccine [154].

Shi Y. et al [155] suggested that immune response against SARS-CoV-2 infection is of two phase. During the incubation period and nonsevere stages, SARS-CoV-2 specific adaptive immune response is needed to induce viral elimination and prevent the development of disease severe stage. The second phase is the inflammation driven damage phase. Thus it is important to potentiate immune response in the first phase to clear viral infection and suppression of it in the second phase to prevent lung damage. However, the immune response is not similar in all individuals; there are variations in the immune response to virus infection, which may be attributed to genetic differences.

Qin et al [156], China, studied 452 COVID-19 patients, and reported that immune response dysregulation, especially T lymphocytes, may be involved in SARS-CoV-2 infection pathogenesis. Screening of neutrophil-to- lymphocytes ratio and lymphocyte subsets is of predictive value in disease diagnosis, treatment and prognosis. Both TCD8+ and TCD4+ were below normal levels. Additionally, monocytes, basophils and eosinophils with lower percentages. TNF-α, IL-1 and IL-6 (pro-inflammatory cytokines) and IL-8 (Chemokines) serum levels were higher in severe COVID-19 than in mild cases and this was similar to the finding of MERS and SARS [133,157]. These chemokines and cytokines play a role in immunopathology and immune response during viral infection [137,157]. COVID-19 disease severity and outcome was correlated with increased NLR and serum elevation of chemokines and cytokines suggest that hyperinflammatory responses may play a role in SARS-CoV-2 infection pathogenesis. Additionally, disease severity may be attributed to viral evasion of host immune response and viral induced direct cytopathic effects [137,157]. Innate immune response form the first defense line against viral infections, but when dysregulated it lead to excessive inflammation and may cause death [158]. The aggravation of inflammatory responses and cytokine storm production may be due to consumption of CD8+ and CD4+ T cells and induction of tissue damage [156]. CD8+ and CD4+ T cells play role in

dampening and weakening of innate immunity over activity during viral infection [158]

Host Th17 inflammatory responses play a critical role in the pathogenesis of SARS-CoV-2 infection [159,160]. Key cytokines released that include GM-CSF and IL-17 [160] and virus immunopathogenesis exacerbation elements through Treg cells downregulation [160,161]. Allergic and eosinophilic responses induced by IL-17 through extravasation and recruitment of eosinophils into the lung and promoting bone marrow production of eosinophil [162-164]. IL-6 play a role in induction of SARS infection associated lung pathogenesis [165] and promote differentiation of Th17 [166]. IL-6 is induced by SARS N protein and thus influence lung pathology in coronavirus infection [167]. The role of IL-6 in SARS-CoV-2 infection lung pathogenesis may represent a target for the development anti-IL-6 monoclonal antibody as COVID19 treatment approach [168]. Additionally, under Th17-polarizing conditions, IL-8 production is also generated [169]**,** which play a critical role ARDS pathogenesis [170]. Other studies reported the increase plasma levels of IL-1, IL-2, IL-4, IL-7, IL-10, IL-12, IL-13, IL-17, GCSF, macrophage colony-stimulating factor (MCSF), IP-10, MCP-1, MIP-1α, hepatocyte growth factor (HGF), IFN-γ and TNF-α [171-173].

Pathogenesis

COVID-19 is an infectious disease caused by SARS-CoV-2. The infection ranged from mild cases which low morbidity and good prognosis to a severe cases that characterized by multiple organ destruction with high mortality [174]. The pathogenesis of SARS-CoV-2 infection in humans remains unclear. Based on the published literature and clinical observations of COVID-19 patients, Lin L. et al [174] proposed a hypotheses about the pathogenesis of SARS-CoV-2 infection in humans. After the viral entry through the nasal and laryngeal mucus membrane and reached to lungs induced fever and cough and subsequent viraemia [175]. Lungs, renal, heart and gastrointestinal tract which express ACE 2 are attached by SARS-CoV-2 [92,176]. Fecal SARS-CoV-2 detection [175] mostly comes from blood as the pH of the stomach kills the virus. The median time for the onset of ARDS symptoms was about 8 days [177]. Thus Lin L. et al consider that second viral attack occurs in the second week after disease onset and aggravated patient condition [174]. The count of WBC in the early disease stage was slightly low or normal [175], but

with lymphopenia [177]. Lin L et al [174], guess that reduction in B lymphocyte count occur early following infection and affect the production of antibody.

Lymphocyte counts inversely correlated with disease severity i.e. reduced in severe cases [177] and this may be due to continuous reduction in WBC count with disease progression. However, the mechanisms that induced WBC count reduction are unclear [174]. Interleukin-6 as inflammatory factor increased in SARS-CoV-2 infection and may play a role in disease aggravation in the 2nd week of disease onset [178]. Survivor's patients had lower levels of D-Dimer, neutrophil, creatinine and blood urea nitrogen than non-survivors [177]. According to the information Lin L et al [174], divided the clinical phase of the COVID-19 into 3 phases, the viremia phase, the acute phase (pneumonia phase) and the recovery phase.

The SARS-CoV-2 suppressed in the acute phase if the host immune response is effective and an absence of risk factors. While the patient condition proceeded to more severity or critical state if the immune response is not competent or there is a risk factors (older age, diabetes, hypertension e.t.c) [174]. Because unavailability of SARS-CoV-2 antiviral agent, the management of COVID-19 concentrate on symptomatic treatment and oxygen therapy to prevent cytokines storm [174]. Low molecular weight heparin and intravenous immunoglobulins are indicated in cases with continuous reduction in B and T cells; increased IL-6; increased D-Dimer, and lung lesion expansion [174,179,180].

Cui S. et al [181] in a retrospective study that included 81 severe novel coronavirus pneumonia (NCP) patients in the Intensive Care Unit (ICU) of Union Hospital (Wuhan, China) reported that the incidence of venous thromboembolism was 25%. This data is related to poor prognosis and D-dimer significant increase in severe NCP patients is a good index for identifying high-risk groups of VTE. An alternative hypothesis was proposed to explain the pathogenesis of SARS-CoV-2 infection. Liu and Li [182] used conserved domain analysis, homology modeling and molecular docking to compare the biological roles of novel coronavirus proteins. They reported that viral surface glycoprotein and Orf8 bind to porphyrin. Additionally, Orf1ab, Orf3a and Orf10 proteins regulate attack the heme on the 1-beta chain oh Hb and detach iron to form the porphyrin. Subsequently,

Hb losses its capacity to bind with oxygen and thus major organs not supplied by oxygen. High level of free iron in the circulation is toxic and lead to oxidative damage to lung. These lung damage sites appeared mistakenly in CT scan as pneumonia. Body compensates mechanism lead to increase in Hb synthesis and this explains the high level of hemoglobin. Other compensatory mechanisms to deal with iron load such as increasing ferritin level explain the increased ferritin level in SARS-CoV-2 infected patients. Chloroquine prevent heme attach by Orf10, Orf3a and Orf1ab to form porphyrin and inhibit surface glycoprotein and Orf8 binding to porphyrin and guide to respiratory distress symptoms relieve. Structural proteins inhibition is not obviously induced by chloroquine and this reflect the variation in therapeutic response between patients. Orf7a protein and envelop protein binding to porphyrin was inhibited by favipiravir and prevent viral entering to host cells and catching free porphyrin. This may explain the unresponsiveness of ARDS cases to ventilation. The above finding is a theoretical explanation of the processes during SARS-CoV-2 infection which need laboratory documentation.

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