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Cross Talk on SARS-CoV-2 and Human Immunity

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of article.

Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes coronavirus disease 2019 (COVID-19) is now the leading cause of death globally. This review elaborated the human immune response to SARS-CoV-2 and its immune evasion mechanisms as well as factors that determine the case fatality rate and effective immunity using articles selected from PubMed, Medline, Google Scholar and Science Direct that provided an in-depth knowledge of the immunopathogenesis of SARS-CoV-2. Findings from the forty eligible reviewed articles revealed that the host-viral interaction to SARS-CoV-2 involves the recognition of SARS-CoV-2, recruitment of adaptor proteins and antigen presentation which activates both innate and adaptive immunity involved in inhibition of viral replication (interferons), destruction of virus-infected cells (natural killer cells and CD8 cells) and viral clearance. However, SARS-CoV-2 subverts human immunity using multiple strategies such as production of double membrane vesicles, repression of adaptor proteins, interferons and antigen presentation. Accumulating shreds of evidence have shown that several factors such as age, sex, comorbidities, obesity, and lifestyle factors affect immune responsiveness to SARS-CoV-2. Hence, better knowledge of the viral interactions with the host and factors determining prevalence and severity is fundamental to the management and development of effective and biocompatible prophylactic and therapeutic options.

Keywords: SARS-CoV-2; COVID-19; Immunity; Immune response; Immune evasion.

NTRODUCTION

The world has been ravaged by three major human coronaviruses within the 21^{ist} century: Severe acute respiratory syndrome coronavirus (SAR- CoV) in 2002 -2003 and Middle East respiratory syndrome coronavirus (MERS-CoV) in 2011 (Prompetchara *et al*., 2020). Surprisingly, toward the end of 2019, the third outbreak of coronavirus originated from the city of Wuhan Hubei province, central China (Kumar *et al*., 2020; Lin *et al*., 2020). Genomic studies of the novel coronavirus have shown that the isolated β-CoV shows 88 % identity to the sequence of SARS-like coronavirus and about 50% identity in the sequence of MERS-CoV (Li *et al*., 2020b). Based on its similarity with SARS- CoV, it was named severe acute respiratory syndrome coronavirus 2 (SARS –CoV-2) by the International Viral Classification Commission on 11th February 2020. On the same day, World Health Organization named it coronavirus disease 2019 (COVID-19) (Li *et al*., 2020b). Hence, SARS-CoV-2 is the causative agent of COVID-19.

Transmission of SARS-CoV-2 is from human to human through respiratory droplets, close contact, and feces (Tay *et al*., 2020). The transmission of SARS-CoV-2 infection from one person to another resulted in the isolation of people who had contact with infected victims or visited pandemic areas, banning of international and domestic flights, social distancing, use of nose masks, and enforcing lockdowns in vulnerable areas (Hamid *et al*., 2020). All these

measures are targeted at preventing respiratory aerosol/droplet infection generated by patients.

The clinical symptoms identified in patients with COVID-19 disease includes fever, dry cough, sore throat, progressive dyspnea, lymphopenia, and pneumonia which could lead to other complications such as lung inflammation, acute respiratory distress syndrome (ARDS), multiple organs failures, and death (Prompetchara *et al*., 2020; Tufan *et al*., 2020).

Although some reviews have been written on the impacts of immunity on COVID-19 disease, there is still a paucity of information on the interplay between immunity and other major immune factors involved in the pathogenesis of SARS-CoV-2 infection. This review, therefore, tried to elaborate more on the immune responses to SARS-CoV-2 infection as well as various mechanisms employed by the virus to withstand host antiviral response. The factors potentiating immune responses were also extensively discussed to widen the understanding in the search for the appropriate management and therapeutic options.

METHODOLOGY

Methods

Articles that border on the reviewed subject were retrieved from English peer-review journals published from 2000 to 2020 using PubMed, Medline, Google Scholar, and Science direct as search engines. The keywords used for the electronic search include but are not limited to the following: "SARS-CoV-2", SARS-CoV-2 immunopathogenesis", "components of the immune system" "Immune response to coronavirus infection", factors that affect mortality and morbidity of COVID-19" "COVID-19 prevalence and case-fatality rates" A total of 254 retrieved articles were screened and only 40 eligible for the study were included. The exclusion criteria were based mainly on the removal of duplicate publications, articles not published within the chosen year, those that lack originality, articles with abstract not written in English and those with insufficient information/ incomplete data. The findings from the reviewed forty articles were presented in this research

RESULTS AND DISCUSSION

Immune response in SARS-CoV-2.

The entry of SARS-CoV-2 is through binding of its envelope spike glycoprotein on the outer surface to angiotensinogen converting enzyme (ACE2) receptor and transmembrane serine protease 2 (TMPRESS2) mostly in alveolar epithelial cells, airway epithelial cells, vascular endothelial cells, and macrophages (Tay *et al*., 2020). Though, it has a higher capacity of replicating in pulmonary tissues (Garcia *et al*., 2020). Thus, blocking ACE2 has been reported to inhibit SARS-CoV-2 infection (Liang *et al*., 2020). After binding, the virus then fuses to the plasma membrane of the host or through the clathrin-dependent and independent endocytosis (Li *et al*., 2020a). The interactions between innate and adaptive immunity play a pivotal role in COVID-19 pathogenesis.

Innate immunity to SARS-CoV-2

The innate immunity, the first line of defense when SARS-CoV-2 invades the physical barriers is mediated at the cellular level not only by phagocytes including granulocytes and macrophages, but also by antigen-presenting cells (APCs). Evolutionally, the innate immune system has a network of receptors called pathogen-recognition receptors (PRRs) that recognize the viral nucleic acids (single-stranded RNA (s RNA), and double-stranded RNA (d RNA) which are not part of the self (Li *et al*., 2020b; Vabret *et al*., 2020). RNA viruses such as SARS-CoV-2 can be recognized by tolls like receptors (TLR) including TLR3, TLR7, RIG-I, and MDA-5 which are endosomal and extracellular PRRs, and also by cytoplasmic retinoic acid-inducible gene 1 (RIG-1)-like receptors (RLRs) (Henry *et al*., 2020). This will lead to the activation of adaptor proteins such as interferon regulatory factor 3 (IRF3), nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), and activator protein-1 (AP-1). Once these proteins are activated, they move to the nucleus and induce intracellular signaling responsible for both transcriptional and post-transcriptional production of interferons (IFNs), pro-inflammatory cytokines viz a viz interleukins (IL-1, IL-6, and IL-18), tumor necrosis factor-alpha (TNF-α) (Vabret *et al*., 2020). Interferons are effective antiviral agents involved in the innate immune response. When IFNs are released in virally infected cells, they bind to the ganglioside receptor on the plasma membrane of the virus and induce the production of enzymes such as oligo (A) synthetase and protein kinase. All these make the cell resistant to viral replication and degrade viral nucleic acids through the action of endoribonuclease. Some IFNs are involved in the stimulation of the activity of T-cells and natural killer cells (NK cells) which

destroy virus-infected cells. There is also the production of other cytokines including MCP1, CXCL1, CXCL5, and CXCL10/IP101 (Garcia *et al*., 2020). All these cytokines mount antiviral immune response on the SARS-CoV-2 virus and also stimulate the adaptive immune response, the hallmark of which is the elimination of the virus, clearing of debris, tissue repair, and restoration of the body to its homeostasis (Ribero *et al*., 2020).

Adaptive immunity to SARS-CoV-2

Antigen presentation by major histocompatibility complex (MHC) usually stimulates activation of cellular and humoral immunity to SARS-CoV-2 infections.

Cellular immunity

Both classes I and II MHC bind and present foreign particles to inform the immune system of the presence of non-self. Class I MHC molecules bind to peptides that originate in the cytoplasm from replicating viruses, and the bound peptides are then carried to, and anchored in the plasma membrane. In this way, the host presents the antigen to a subset of T-cells called CD8+ or cytotoxic T-lymphocytes. CD8+ cells are involved in attacking and killing virus-infected cells (Qiu *et al*., 2017; Tay *et al*., 2020;). However, class II MHC usually bind to fragment from antigens outside the cell which is taken up by endocytosis by macrophages, dendritic cell, or B- cell. Unlike, CD8+ cells, CD4+ cells do not directly kill target cells. Instead, they respond by proliferating thereby increasing the number of CD4+ cells that can fight the antigen, or priming of CD8+ cells and B cells and also cytokines which will inhibit viral replication (Tay *et al*., 2020). Activated T-cells can lyse viral cells or release chemicals (cytokines) that enhance adaptive immunity and innate defenses such as phagocytosis and inflammation. Effective T-cell activation is the key strategy in avoiding immunopathology associated with its deregulation (Vabret *et al*., 2020).

Emerging reports show that there is a significant reduction in CD4+ and CD8+ cells count of SARS-CoV-2 infected patients (Xu *et al*., 2020), with hyperactivation as revealed by a high level of HLA-DR (CD4 3.47 %) and CD 38 (CD8 39.4%) double-positive fraction (Li *et al*., 2020b; Soy *et al*., 2020). Reduction in CD4+ T-cells count leads to a subsequent decrease in neutralizing antibodies and cytokines production in pulmonary which delays viral clearance (Li *et al*., 2020a). The low levels of CD4+ and CD8+ T-cells are related to the rate of mortality in COVID-19 patients (Liang *et al*., 2020; Xu *et al*., 2020). Liang *et al*. (2020) reported that SARS-CoV2 induces T-cell apoptosis and autophagic cell death thereby causing lymphocytopenia. The plausible explanation for the observed decrease in T-cells could be its recruitment to the infected cells thereby reducing the number of T-cells in circulation. Studies that tracked this from the clinical examination of dead COVID-19 patients identified an abundance of lymphocytes in the lungs (Vabret *et al*., 2020).

Humoral immunity

Reduction in number of B-cells was also observed in COVID-19 patients (Tufan *et al*., 2020). Undoubtedly, this could be associated with the resultant decrease in CD4+ required for its activation. Humoral immune response in SARS-CoV-2 infection involves the production of neutralizing antibodies (Nabs) which inhibit viral infection and also limit the rate of re-infection (Prompetchara *et al*., 2020; Vabret *et al*., 2020). Ideally, under a normal immune response, the neutralized viruses are phagocytosed by macrophages (Tay *et al*., 2020). The receptor-binding domain (RBD) on the S protein is one of the main targets of Nabs against coronaviruses. Clinical reports show that patients have peak IgM at the onset of the infection which switches later to IgG with both targeting the viral nucleoprotein (Liang *et al*., 2020; Prompetchara *et al*., 2020). The response of B-cells in COVID-19 patients arises earlier about 1 week after onset of symptoms unlike what was observed in SARS-CoV (Tay *et al*., 2020). However, recent researches have reported that patients with COVID-19 may not develop long-lasting antibodies, hence increasing the chances of re-infection (Tay *et al*., 2020). Hence, there is a great need to measure the antibodies titer of survivors of COVID-19 disease to determine the time frame the immune memory remains active (Garcia *et al*., 2020).

Immune evasion

SARS-CoV-2 has developed multiple mechanisms to avert the immune response of the host to survive, replicate, and cause COVID-19 disease. The immune evasion strategy starts with the downregulation of PRR activation and antagonizing its action through the formation of membrane-bound vesicles (Chukwuma *et al*., 2021; Li *et al*., 2020b). This is achieved by modification of viral RNA to resemble host mRNA through guanosine-capping and methylation by non-structural proteins (nsps) (Vabret *et al*., 2020). This will ultimately prevent the recognition of the viral RNA as part of non-self which enhances their ability to hijack the body machinery to replicate unnoticed. Even when successfully recognized by PRRs, SARS-CoV2 ORF9b has been reported to counteract the signaling of adaptor proteins through TOM 70 or other signaling intermediates thereby circumventing innate immune response (Vabret *et al*., 2020).

Another potential strategy is by inhibiting the expression of interferon stimulating genes (ISG) involved in the activation of antiviral response (Ribero *et al*., 2020). Sequel to this, SARS-CoV-2 down-regulates IFN production and signaling, induces high production of pro-inflammatory cytokines which will delay antiviral activity and induce a severe cytopathic effect on the host (Henry *et al*., 2020). This hypothesis is strongly anchored on the decreased IFNs signature seen in COVID-19 patients (Ribero *et al*., 2020). The biochemical basis behind the inhibition of IFNs production is through inhibition of phosphorylation of repressed adaptor proteins using viral structural and non-structural proteins (Tay *et al*., 2020) thereby preventing their translocation to induce ISG expression in the nucleus (Ribero *et al*., 2020). Inhibition of IFNs induction in SARS-CoV-2 infection can also be achieved through activities of nsps specifically nsp1, nsp3, and nsp15. The inhibitory activity of nsp1 is by degrading host mRNA and also by preventing translation of host mRNA through the binding on 40s subunits of the ribosome (Ribero *et al*., 2020), nsp3 down-regulate the innate immune response and also accelerate the production of cytokines (Priyadarsini and Suresh, 2020), while nsp15 has endoribonuclease activity responsible for cleaving 5¹ polyuridine of SARS-CoV-2 viral RNA (Ribero *et al*., 2020).

Inhibition of innate immunity could also be attributed in parts to irregular polarization of dendritic cells, monocytes and macrophages, and natural killer cells to induce type 2 response while adaptive immunity is inhibited by interfering with an infected antigen-presenting cell which will, in turn, hinder T-cell response (Maggi *et al*., 2020).

Factors affecting human immunity to SARS-CoV-2 infection

The factors that affect the prevalence and severity of SARS-CoV-2 infection include but are not limited to the following: Age, sex, comorbidities, obesity, and lifestyle factors.

1. Age

There are many compelling shreds of evidence that an increase in age is an independent risk factor for the severity and mortality of COVID-19. This corroborate with observations made in previous coronaviruses (SARS-CoV1 and MERS-CoV) (Zhou *et al*., 2020). Age-related factors are considered along with chronological and biological age which is modified by diet, comorbidities, and exercise (Marquez *et al*., 2020).

Results from studies carried out shows that the case fatality rate (CFR) in China is 3.6, 8, and 15 % for patients aged 60, 70, and 80 years respectively while 25 and 31 % death were recorded in 70 and 80 years respectively in Italy (Marquez *et al*., 2020). According to Mueller *et al.* (2020), 74 % of death observed in COVID-19 patients occurred within the age range of 65 and above especially those with other comorbidities. In a retrospective multi-center study conducted on 202 COVID-19 infected patients, only 6 (3%) were children or adolescents (Huang *et al*., 2020b). Another study among 191 COVID-19 patients recorded 137 survivors with an average age of 52 while 54 non-survivors had an average age of 69 (Zhou *et al*., 2020). In the same vein, a multi-center study on 1464 patients, those aged < 65 were 757 (51.7 %) out of which 692 (55.3%) survived while 65 (30.7%) died. However, in the same study, patients ≥ 65, 707 (48.3%), 560 (44.7 %) survived while 147 (69.3%) died (Yu *et al*., 2020). Based on available data, children are less prone to both SARS-CoV-2 infection and mortality (Taghizadeh-Hesary and Akbari, 2020) due to lower expression of ACE2 and the competition of the virus with other viruses inhabiting their respiratory tract, though this needs to be validated experimentally (Garcia *et al*., 2020).

This is in tandem with what was observed during the outbreak of SARS-CoV, where 54 % of patients above 65 years of age died while no death was recorded in people below 24 years (Zhou *et al*., 2020).

This remarkably observed increase in prevalence and severity with age could be attributed in part to the observed decline in immune response in old age. Immunity declines with age leading to immunosenescence and inflammaging. Immunosenescence reduces antiviral activity in old age due to reduced PRR recognition, a decline in both T and B- cells response as a result of the decreased thymic output of naïve T cells, reduced proliferation of T-cells, and diversity of B-cells repertoire (Damiot *et al*., 2020; Garcia *et al*., 2020).

It is worth noting that inflammaging, increase inflammatory response through deregulation of innate and adaptive immunity is the leading cause of cytokine storm, which is the major cause of death in patients (Muller *et al*., 2020; Chukwuma *et al*., 2021). This is attributed in part to the age-related loss of the naïve cell population which helps to avert the harmful effects of the over-stimulated inflammatory response (Marquez *et al*., 2020). Besides, clonal hematopoiesis as a result of somatic mutation of hematopoietic stem cells (HSCs) and other progeny of immune cells which increases with age is a major predisposing factor to the high case fatality rate recorded in older COVID-19 patients (Marquez *et al*., 2020). All these factors will

result in alveolar macrophages defect, decrease in neutrophil activity, thymic atrophy causing defective immune surveillance and exhaustion of helper T-cells, cytotoxic T-cells, and B-cells (Mueller *et al*., 2020).

Hence, age influences both the cellular content and functions of both innate and adaptive immune cells which prevents effective antiviral activity thereby making older people more susceptible to SARS-CoV-2 infection (Tay *et al*., 2020; Marquez *et al*., 2020). These changes in immune response with age are caused by the influence of genetic, pathogenic, and lifestyle factors such as smoking on the diversity of some immune cells and epigenetic status of the cell (Mueller *et al*., 2020).

2. Sex

Sex-linked severity and death for COVID-19 have been studied extensively as shown in **Figure 1** below. Across the globe, the rate of death is relatively 1.5 to 2 men per female death (Mueller *et al*., 2020). Researchers have reported that males have a higher ACE2 cell ratio and TMPRESS2 required for viral entry compared to females (Maggi *et al*., 2020). Besides, males are prone to have immune-dysregulation after infection (Taghizadeh-Hesary and Akbari, 2020). This is consistent with the earlier observation made in SARS-CoV and MERS-CoV (Xie and Chen 2020).

The disparity in immune response in males and females is mainly attributed to genetic and hormonal differences. Genetic studies have reported that most of the genes responsible for immune response are located on the X chromosomes (Marquez *et al*., 2020). The lower-case fatality rate in females could be linked to the presence of alleles on the X chromosome which offers resistance against ACE2 (Tay *et al*., 2020). Additionally, the presences of two X chromosomes in females equip them with immune markers including FOXP3, CD40L, and regulatory markers. Also, in terms of viral recognition, TLR3, TLR7, and TLR9 which recognize SARS-CoV2 (viral) infection are higher in females unlike TLR2 and TLR 4 seen in men which are involved in bacterial recognition (Taneja *et al*., 2018).

Hormonal differences seen in both sexes have a ripple effect on sexual dimorphism in males and females. Generally, estrogen found in females enhances immunity through the induction of T-cell homing, modulation of B-cells function which leads to Th2 response and greater antibody production (Taneja *et al*., 2018). But testosterone such as androgen present in males performs the immunosuppressive activity by downregulating activation of TNFα, natural killer cells, and enhances the production of IL-10 which is an anti-inflammatory agent. A study conducted by Marquez *et al*. (2020) with older men having a higher level of IL-6 and ILIRA when compared with females which connotes higher inflammation, and also reduced T-cells and antibody production which reduces their chances of eliminating the SARS-CoV-2 virus. Hence, men experience inflammaging than females which increases the prevalence and severity of infectious diseases.

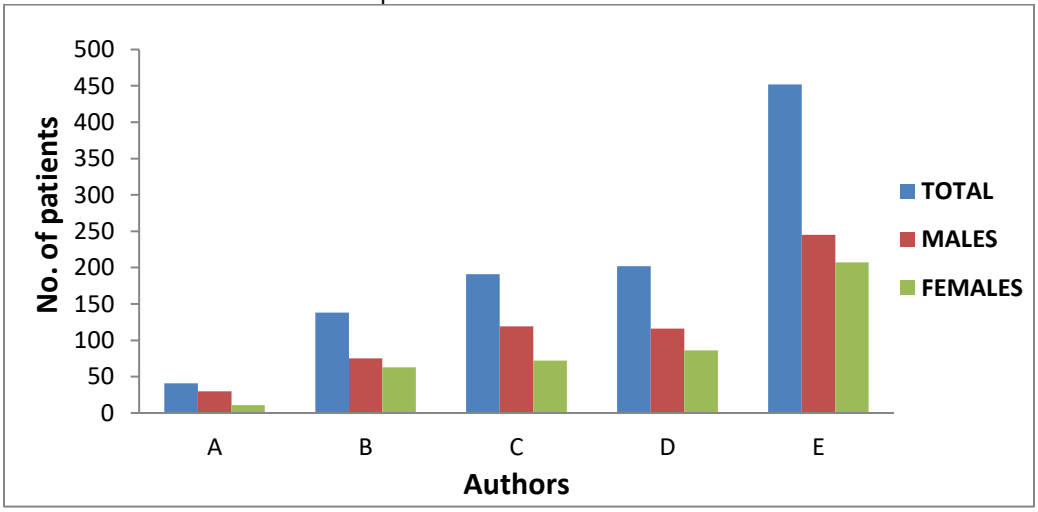

Figure 1: Sex disparity in SARS-CoV-2 prevalence.

Results of different research works conducted by five authors labeled A-E: A (Huang *et al*., 2020a), B (Wang *et al*., 2020), C (Zhou *et al*., 2020), D (Huang *et al*., 2020b), and E (Marquez *et al*., 2020) showed that the prevalence of SARS-CoV-2 is higher in males

3. Presence of comorbidities

The rate of infection and severity of SARS-CoV2 is very high in people with other comorbidities such as diabetes, hypertension, coronary heart diseases, chronic obstructive pulmonary diseases, cancer, kidney, and renal diseases (Huang *et al*., 2020b; Marquez *et al*., 2020; Wang *et al*., 2020; Yu *et al*., 2020; Zhou *et al*., 2020). In a study among 191 COVID-19 patients, 91 (48%) had health challenges with 36(67%) of them not-surviving (Zhou *et al*., 2020). Wang *et al* (2020) reported that out of the 31 patients that required ICU in their study, 26 (72.2 %) had comorbidities. Also, a cohort study conducted on 1464 COVID-19 hospitalized patients in China revealed that 38.8 % of the patients had at least on health challenges in the order of hypertension (20.9%), diabetes (14.4 %), and coronary heart disease (8.0%) (Yu *et al*., 2020). Clinicians and researchers who studied the impacts of health challenges on COVID-19 patients recorded hypertension followed by diabetes to be the leading cause of infection as shown in **Figure 2**.

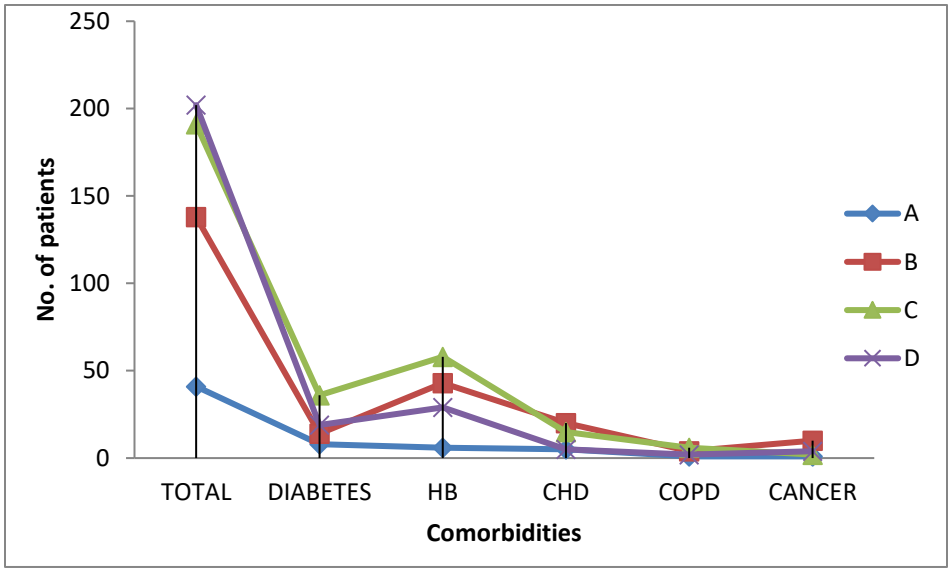

Figure 2: Comorbidities affecting SARS-CoV2 infection

The major comorbidities which determine the prevalence of SARS-CoV2 infection by four authors labeled A-D. A (Huang *et al*., 2020b), B (Wang *et al*., 2020), C (Zhou *et al*., 2020), and D (Huang *et al*., 2020a). This showed that hypertension and diabetes are the two major comorbidities that determine the prevalence of SARS-CoV2 infection

These disorders make an individual more vulnerable to infection because they down-regulate key players of the innate and adaptive immune response leading to a poor prognosis for SARS-CoV-2 infection (Priyadarsini and Suresh, 2020).

Though, there are still limited studies deciphering the underlying mechanisms behind the impact of these comorbidities on the immune system. Imperatively, this might be due to their associated alteration in innate immune response and the shift in Th1 to Th2 which has anti-inflammatory activities thereby sustaining viral survival (Badawi and Ryoo, 2016). Emerging reports have attributed this to weaken immune cells and high level of pro-inflammatory cytokines, decrease in viral clearance, impaired T-cells function already present in their system even before infection with SARS-CoV-2 which facilitate cytokine release syndrome and ultimately death (Priyadarsini and Suresh, 2020; Yu *et al*., 2020). To lead credence to this hypothesis, Priyadarsini and Suresh (2020) reported a high level of IL-6 in patients with co-morbidities.

Concerning diabetes, patients with diabetes have enhanced cellular binding which undoubtedly facilitates viral entry (Badawi and Ryoo, 2016). The rate of mortality in patients with cardiovascular disease could be attributed in a part to the high rate of clonal hematopoiesis which increases the levels of ILs (IL-1β and IL-6) and cells and macrophage inflammatory reactions (Marquez *et al*., 2020). It is also worth noting that some of the drugs used in the management of these health challenges such as ACE inhibitors and angiotensin receptor blockers in hypertensive patients stimulate ACE 2 expression thereby increasing the chances of SARS-CoV-2 infection (Garcia *et al*., 2020). So, people with health challenges have higher chances of being infected and also dying from COVID-19.

4. Obesity

Obesity has been identified as one of the dependent factors that influence the prevalence and severity of COVID-19 (Huang *et al*., 2020b; Lighter *et al*., 2020;

Simonnet *et al*., 2020). In a retrospective analysis carried out by Lighter *et al*. (2020) with 3615 COVID-19 patients, 775 (21%) had BMI within the range of 30-34 while 595 (16%) had BMI ≥ 35. They also realized that patients with BMI ≥ 30 had a higher severity of COVID-19. Also, analysis of 124 patients admitted in ICU by Simonnet *et al*. (2020) to ascertain the relationship between BMI and the need for use of invasive mechanical ventilation (IMV) revealed that the requirement for IMV increases with BMI, with the demand being higher in those with BMI > 35 (85.7%). A high level of a hormone known as leptin in obese people interferes with the body's ability to mount an effective antiviral response. Also, abdominal obesity not only causes the unregulated secretion of some cytokines (IFNs and TNFα) and adipokines that suppress immunity but also reduces ventilation of the lung which results in hypoxemia (Simonnet *et al*. (2020). Obesity is a leading factor in the mortality of COVID-19 patients as a result of its ability to activate low-grade inflammation and an increase in the activity of NLRP3. So, people with obesity should observe all the safety guidelines strictly to reduce their chances of contracting the virus but peradventure they contact it, they should be monitored properly to reduce the disease severity.

5. Lifestyle factors

Several life factors affect the rate of infection and severity of SARS-CoV-2 infection. But the most documented factors are alcohol intake and cigarette smoking.

a. Alcohol intake

Several myths abound on the influence of alcohol on COVID-19 such as "drinking alcohol destroy SARS-CoV2". However, it is worthy to note that alcohol passes from the throat to the gastrointestinal (GI) system where it is later absorbed into the bloodstream, unlike SARS-CoV-2 that moves from the throat to the bronchial tubes and then the lung (Mueller *et al*., 2020). Unfortunately, in the GI system, alcohol alters the integrity of the endothelium and natural microbiomes found in the intestine which assists in the maturation and function of the immune system. Also, it causes leaky endothelium thereby enhancing the chances of infecting other cells expressing ACE2 (Mueller *et al*., 2020). Apart from the ability of alcohol to trigger inflammation in the gut which destroys beneficial micro-organism, it also destroys the immune cells and fine hairs that clear pathogens out of the airway. Chronic alcohol intake leads to a decrease in T-cell number, activation, function, and ultimately increases T-cell apoptosis as well as promoting the loss of peripheral B-cells (Pasala *et al*., 2015). Additionally, chronic alcohol consumption not only led to alcohol induced liver injury (Panigrahy *et al*., 2020) but also decreases the production of cytokines such as IL-10, and TNFβ needed to counterbalance the observed high level of pro-inflammatory cytokines in COVID-19 patients (Szabo *et al*., 2015) which could trigger cytokine storm.

b. Cigarette smoking

Smoking is an independent risk factor for both viral and respiratory infections (Grundy *et al*., 2020). Cigarette smoke has been reported to elicit an inflammatory response, enhance cellular damage, and suppress the immune system (Jaspers, 2014). It alters the innate immune response by activating neutrophils and macrophages which leads to increased stimulation of TNFα, IL-8, and MCP-1. Also, it alters the number and functions of DCs, and NK cells which enhance viral infection (Jaspers, 2014). However, adaptive immune cells mostly affected by smoking are not limited to CD4+and CD8+ T-cells, B-cells, and T helper cells (Qiu *et al*., 2017). A recent study also showed that smoking is an independent risk factor for COVID-19 development and severity (Jaspers, 2014; Grundy *et al*., 2020). A report from China confirmed that chain-smoking increases the activity of ACE2, making smokers more vulnerable to contracting SARS-CoV-2 infection (Marquez *et al*., 2020). The possible explanation for this could be due to the reported activation of goblet cells by cigarette smoke which increases the level of ACE2 in the lung (Polverino *et al*., 2020). A meta-analysis study carried out by Cai *et al*. (2020) recorded a 25 % increase in expression of ACE2 in current and ever smokers which invariably will facilitate binding and entry of SARS-CoV-2 in Smokers.

CONCLUSION

Immunocompetent cells and the physiologic interplay between innate and adaptive cells remain a sure way of remaining afloat in the SARS-CoV-2 storm. The human immune system is well equipped with numerous cells and mediators that guard the body against infections. Unfortunately, viruses such as SARS-COV-2 have developed multiple mechanisms of invading this immune network to cause COVID-19

The rate of infection, duration, and severity of COVID-19 are dependent on several factors with older men with other health challenges and obese being at higher risk of not only contracting the infection but also developing severe complications. Robust knowledge of the immunopathogenesis of SARS-CoV-2 is very imperative not only as a preventive measure and also as a guide on how to avert

complications on those at higher risk of having severe complications and not-surviving but also in the development of appropriate prophylactic and therapeutic agents.

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