



Severe acute respiratory syndrome Coronavirus-2 infection: A synopsis of the host immune responses and viral immune evasion strategies involved

Bala, N. Umar^{1*}; Jibril, Adamu¹; Muhammad, T. Ahmad²; Kabiru, H. Ahmad³; Ochuko, Orakpoghenor⁴; Bashir, S. Aliyu⁵; Nuhu, Mohammed⁶; Aliyu Sada^{1,7}

¹Virology and Immunology Unit, Department of Veterinary Microbiology, Faculty of Veterinary Medicine, Ahmadu Bello University, Zaria, Nigeria; ²Veterinary Teaching Hospital, Ahmadu Bello University, Zaria, Nigeria; ³Diagnostic Laboratory, Department of Veterinary Microbiology, Faculty of Veterinary Medicine, Ahmadu Bello University, Zaria, Nigeria; ⁴Department of Veterinary Pathology, Faculty of Veterinary Medicine, Ahmadu Bello University, Zaria, Nigeria; ⁵Kofar Ran, Veterinary Clinic, Bauchi State Ministry of Agriculture and Natural Resources, Nigeria; ⁶Department of Clinical Pharmacology and Therapeutics, Faculty of Basic Clinical Sciences, Ahmadu Bello University, Zaria, Nigeria; ⁷Central Diagnostic Laboratory, National Veterinary Research Institute (NVRI), Vom, Nigeria



*Corresponding author E-mail: umarningi5@gmail.com

Received: 26 February, 2021; Accepted: 7 April, 2021; Published online: 16 April, 2021

Abstract

The novel coronavirus designated as SARS-CoV-2 is the etiological agent of coronavirus disease 2019 (COVID-19), which rendered the care of the global health powerless and plunged the world economy into a historic decline. This disease is characterized by different clinical pictures; ranging from asymptomatic mild phase to severe illness with acute respiratory distress syndrome (ARDS), in addition to having no specific therapy. The protective immunity involving solid CD4⁺ T-cells, viral specific CD8⁺ T-cells and the neutralizing immunoglobulins have been established in most of the convalescent COVID-19 individuals. On the other hand, the host immune response to severe COVID-19 infection has been attributed to the inflammatory cytokine storm, and to influx of the activated immune cells to the lungs; leading to severe pneumonia, extensive ARDS and finally to death. Despite of this, the protective and pathogenic aspects of the human immunity have not been fully elucidated. Recent attempts conducted by several published research works have focused on information derived from the immune responses to the severe acute respiratory syndrome-related coronavirus diseases (mainly; SARS and MERS). However, these works lack sufficiency due to variations in the transmissibility, virulence, host-virus interactions and the immune evasion mechanisms. Hence, adequate understanding of the host immune response mechanisms to SARS-CoV-2 will generate the impetus towards effective control and preventive measures. The objectives of this article were to provide an overview of the host immune responses to SARS-CoV-2 infection, the viral immune evasion strategies, and to define certain knowledge gaps that require further studies.

Keywords: SARS-CoV-2, COVID-19, T-cells, Immune response, Immune evasion

1. Introduction

Coronaviruses are spherical-shaped enveloped, non-segmented positive-sensed RNA viruses, which belong to the subfamily Coronavirinae of the family Coronaviridae. According to [Su *et al.*, \(2016\)](#); [Chan *et al.*, \(2020\)](#); [Chen *et al.*, \(2020a\)](#), this large family of human, veterinary and zoonotic viruses comprises four different genera mainly: Alphacoronavirus, Betacoronavirus, Gammacoronavirus and Deltacoronavirus. The seven coronaviruses documented to infect humans have been grouped into two main categories on the basis of their pathogenicity. Low pathogenic human coronaviruses (HCoV), which include HCoV-229E, HCoV-OC43, HCoV-NL63 and HCoV-HKU1 viruses that cause mild (common cold-like) respiratory illness, as reported by [Pyrce *et al.*, \(2006\)](#); [Van Der Hoek, \(2007\)](#); [Shurin *et al.*, \(2020\)](#). The second category are the highly pathogenic HCoV viruses, particularly; Severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus (MERS-CoV) and Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Recent studies conducted by [Clери *et al.*, \(2010\)](#); [Naeem, \(2014\)](#); [Rokni *et al.*, \(2020\)](#); [Yang *et al.*, \(2020a\)](#) reported that these viruses are responsible for the major epidemics in the past two decades. Infections with the latter group have been reported to cause severe immunopathological responses, which result in fatal pneumonia.

The novel SARS-CoV-2 that causes the dreaded pandemic coronavirus disease 2019 (COVID-19), is the most contagious of these viruses. As of February 9, 2021, the virus was detected in over 105.4 million confirmed cases, with more than 2.3 million deaths globally, while several nations are still battling with the second wave of the disease ([WHO, 2021](#)). Recently, [Orakpoghenor *et al.*, \(2020\)](#) revealed that clinical presentations of COVID-19 range from the most predominant asymptomatic or mild stage to severe respiratory illness. According to [Inandikhoğlu](#)

[and Akkoc, \(2020\)](#); [Mortaz *et al.*, \(2020\)](#), the majority of patients which progressed to the severe stage exhibited immunological dysregulations, associated with inflammatory cytokine storm (ICS) and lymphopaenia. Most potential therapies currently under evaluations have focused on direct elimination of the virus and/or vaccines development, while ignoring the role of the host immune response ([Liang *et al.*, 2020](#)).

A recent work conducted by [Sariol and Perlman, \(2020\)](#) highlighted that although the protective and pathogenic immune responses in COVID-19 patients have been speculated; the host immune response and viral evasion strategies have not been fully elucidated due to novelty of the virus. The protective solid immunity involving CD4⁺ T-cells, SARS-CoV-2 specific CD8⁺ T-cell responses ([Grifoni *et al.*, 2020](#)), and positive antibody responses ([Bao *et al.*, 2020](#)) have been described in convalescent COVID-19 patients with normal disease course and no hospitalization. On the other hand, [Bonam *et al.*, \(2020\)](#); [Prete *et al.*, \(2020\)](#) reported that the insufficient and detrimental immune responses characterized by ICS, and the influx of activated immune cells to the lungs with eventual development of acute respiratory distress syndrome (ARDS); were observed in severe COVID-19 individuals requiring positive pressure oxygen therapy, and often intensive care hospitalization.

According to [Wu and McGoogan, \(2020\)](#), the pro-inflammatory cytokines-driven ARDS is the most critical stage of SARS-CoV-2 infection that can result in multi-organ failure and death. [Liang *et al.*, \(2020\)](#) reported that limited understanding of the immune responses caused by SARS-CoV-2 makes it difficult for clinicians to avert patients from complications of ARDS and pulmonary fibrosis. Therefore, it is imperative to regulate the aberrant host immune responses when managing severe SARS-CoV-2

infected patients. However, achieving this important task seems to be challenging; hence, there is a need for adequate knowledge of the host immune responses to SARS-CoV-2.

[Liang *et al.*, \(2020\)](#); [Shah *et al.*, \(2020\)](#) reported that although significant efforts have been made to unravel the immunity surrounding this pandemic; however, much of these efforts were predictive knowledge derived from the host immune responses to acute respiratory syndrome-related coronavirus diseases, particularly severe acute respiratory syndrome (SARS) and Middle-East respiratory syndrome (MERS). Recent studies of [Sariol and Perlman, \(2020\)](#); [Shurin *et al.*, \(2020\)](#); [Yang *et al.*, \(2020b\)](#) highlighted that no doubt, this would provide valuable hints toward the fight against COVID-19, owing to the fact that these related viruses share about 80 % of sequence identity; use the same entry receptor and cause similar acute respiratory syndromes. However, the information obtained might not accurately depict the novel COVID-19 dynamics, because of the differences in several epidemiological and biological characteristics including; type of host cells mostly infected ([Liang *et al.*, 2020](#)); virulence, host-virus interactions, immune escape pathways ([Shurin *et al.*, 2020](#)), and transmissibility among these related viruses ([Yang *et al.*, 2020b](#); [Zhang *et al.*, 2020a](#)).

Furthermore, central to the development and identification of excellent vaccine candidates and fine-tuning of COVID-19 control measures depend on good understanding of immunity to the SARS-CoV-2. This has become critical now, as some promising COVID-19 vaccines, notably, Moderna mRNA-1273, Pfizer/BioNtech BNT162b2, Gamaleya Sputnik V, and Sinopharm BBIBP-CorV, have reached the advanced stage 3 clinical trials, and are gaining approval for administration from several countries (<https://covid19.trackvaccines.org/vaccines/>). In addition, excellent knowledge of immunity to SARS-CoV-2 infection might improve the measures for using immune therapy as an adjunct to stop patients from developing ARDS, and helps in combating the

pandemic. Therefore, this review summarizes the host immune responses to SARS-CoV-2 infection, and how the virus evades such responses. It also highlights some gray areas of research requiring further exploration.

2. Host immune responses in COVID-19

Infection with SARS-CoV-2 triggers serious immunological responses from both host innate and adaptive immune systems. Several studies conducted by [Liang *et al.*, \(2020\)](#); [Shah *et al.*, \(2020\)](#) revealed that these complex responses involve recognition of the whole SARS-CoV-2 or its components by pathogen recognition receptors (PRRs); recognition of viral spike (S) and nucleocapsid (N) proteins by the B cells, as well as presentation of the viral antigens by major histocompatibility complexes (MHC) to T cells. These responses lead to type I interferon (IFN) response; increased cytokine secretion, antibody production and cytolytic effects; with the aim of eliminating the invading SARS-CoV-2. Moreover, [Shi *et al.*, \(2020\)](#); [Shurin *et al.*, \(2020\)](#); [Thevarajan *et al.*, \(2020\)](#) added that the host immune responses in COVID-19 seem to be in two-stages; a protective response observed in most patients with mild or no clinical symptoms, and pathogenic response characterized by hyper-activation of some subsets of immune cells; increased viral propagation, ICS, ARDS and massive destruction of the affected tissues, which are observed in severe COVID-19 patients when the protective response is impaired.

2.1. Innate immune responses

A recent work conducted by [Vabret *et al.*, \(2020\)](#) highlighted that an effective innate immune response that involves pro-inflammatory cytokines; IFN type I response and its downstream cascades, which culminates in controlling viral replication and induction of effective adaptive immune response, constitutes the primary line of defense against invading viruses. [Shah *et al.*, \(2020\)](#) added that interferons secreted by most innate immune cells are not only efficient in impeding cell proliferation, but

equally modulate apoptosis, immune response and act as secondary immune messengers to stimulate the other body cells.

In COVID-19, PRRs present on many immune cells; particularly Toll-like receptors (TLR) 3, 7, and 8, are known to be the earliest host factors to identify SARS-CoV-2 surface epitopes ([Shah *et al.*, 2020](#)). Meanwhile, as with SARS and MERS, the pathogen-associated molecular patterns (PAMPs) represented by the viral RNA are recognized by the intracellular sensors such as RIG-I; leading to downstream signaling cascades that eventually activate NF- κ B, and IRF3 transcriptional activities. As reported by [Prompetchara *et al.*, \(2020\)](#), this results in enhanced IFN production and expression of pro-inflammatory cytokines. [Lokugamage *et al.*, \(2020\)](#) demonstrated that SARS-CoV-2 is sensitive to IFN pretreatment. Likewise, [Cai *et al.*, \(2020\)](#); [Chu *et al.*, \(2020\)](#) revealed that increased concentration of types I and II pneumocytes; alveolar macrophages, plasma cells and foam cells, were consistently reported in SARS-CoV-2 infected patients.

A previous work of [Tanaka *et al.*, \(2016\)](#) revealed that in an attempt to clear viral particles and control pulmonary inflammation, cytokines were employed; however, rapid and massive release of cytokines could cause deleterious effects in the host. According to [Wan *et al.*, \(2020\)](#); [Zhou *et al.*, \(2020\)](#), Interleukin (IL)-6, which produces CD14⁺ CD16⁺ inflammatory monocytes, is identified as the key inflammatory cytokine that mediates the frequently reported cytokine release syndrome associated with COVID-19. Recently, [Huang *et al.*, \(2020\)](#); [Mehta *et al.*, \(2020\)](#); [Yang *et al.*, \(2020c\)](#) proposed that a cytokine profile comparable to patients with secondary hemophagocytic lymphohistiocytosis is well documented in severe COVID-19; depicting cytokine storm, due to excessive immune activity. This includes increased levels of IP-10; MCP-3, MCP1, HGF, MIG, MIP-1 α , GCSF, TNF- α , MCF1 (CCL2), IL-2 and IL-7. Furthermore, [Huang *et al.*, \(2020\)](#); [Shurin *et al.*, \(2020\)](#) reported that these cytokines may help in grading the prognosis of each patient; as dissimilar

expression profiles are observed in patients with different COVID-19 severity. For instance, the levels of IP-10; MCP-3, MCP1, HGF, MIG, MIP-1 α , GCSF and TNF- α , are reported to be significantly higher in critical patients, compared to their expression in moderate disease. On the other hand, IP-10 and MCP-3 were found to be outstanding predictors for the progression of COVID-19 infection.

Notwithstanding, there is general paucity of data on innate immune responses to SARS-CoV-2, other than the elevated levels of acute-phase reactants and ICS. Most of the recent reports focused on severe outcomes and adaptive immune responses ([Azkur *et al.*, 2020](#)). Therefore, more intensive studies are required to elucidate these important components of the immune response to COVID-19.

2.2. Adaptive immune responses

In an effort to eliminate the invading SARS-CoV-2 and preclude disease progression to severe stages, the host may employ specific adaptive immune responses. These involve combined induction of humoral and virus-specific T lymphocytes, to provide optimal protective immunity.

2.2.1. Humoral immunity

Virus neutralization is crucial to impede the spread of the invading virus throughout the body tissues. Recent studies conducted by [Bao *et al.*, \(2020\)](#); [To *et al.*, \(2020\)](#); [Wu *et al.*, \(2020\)](#), reported that positive humoral immune response that is characterized by high titer of neutralization antibodies such as; IgM and IgG targeting the viral S and N proteins, are found within the sera of most SARS-CoV-2 exposed individuals. Induction of the IgM is earlier and transient, while IgG possess longer half-life and lower molecular weight, hence provide longer protection with efficient tissue penetration. Similarly, the minority of patients particularly those with either asymptomatic or severe infections mount little detectable antibodies. In fact, potential full recovery in the absence of antibodies has been reported in some cases, as highlighted by [Altmann, \(2020\)](#).

As reported by [Zhao *et al.*, \(2020\)](#), the seroconversion rates of IgM, and IgG observed in COVID-19 patients were documented to be 82.7 % and 64.7 %; respectively, whereas the median seroconversion times were evaluated to be around 12th and 14th days post onset of symptoms, respectively. Thus, most patients become seropositive to the virus and negative for SARS-CoV-2 PCR within 28 days ([Gorse *et al.*, 2020](#)). For how long these antibodies will remain in recovered patients has not been fully delineated ([Liang *et al.*, 2020](#)). However, recently [Long *et al.*, \(2020\)](#); [Seow *et al.*, \(2020\)](#) revealed that for the naturally acquired SARS-CoV-2, the antibodies begin to disappear 2-3 months post infection. Although, [Stephens and McElrath, \(2020\)](#) reported that antibody titers always decrease after an acute phase of infection. Accordingly, in convalescent COVID-19 patients, the decline in IgG neutralizing antibodies to SARS-CoV-2, may fuel the trepidation about susceptibility to reinfection.

[Altmann, \(2020\)](#) highlighted that SARS-CoV-2 spike antigen-binding responses correlate well with the functional virus neutralization. Conversely, some studies conducted by [Jiang *et al.*, \(2020\)](#); [Tan *et al.*, \(2020a\)](#) on antibody responses in COVID-19; have associated higher IgG and IgM titer against viral S and N proteins at different stages of the disease with older age; worse clinical readouts and highly unfavorable prognosis. Accordingly, [Iwasaki and Yang, \(2020\)](#); [Tetro, \(2020\)](#) suggested potentially detrimental effects of the antibodies in some COVID-19 patients in a possible antibody-dependent enhancement (ADE) phenomenon. Therefore, careful and more elaborate researches on subclasses of IgG, IgM and IgA; recognizing at least SARS-CoV-2 specific S or N proteins would unravel the applicability of ADE in COVID-19, provide answers to several unknowns regarding the development and stability of humoral immune response in COVID-19, and might also support the development of fast, reliable and non-expensive alternative means for early diagnosis of SARS-CoV-2 infection ([Shurin *et al.*, 2020](#)). Moreover, beneficial insights gained from studying the

subclasses of these immunoglobulins, which correlate with recovery as opposed to worsening of COVID-19 infection, will inform us the type of antibodies that has to be assessed when selecting the best possible SARS-CoV-2 vaccine.

2.2.2. Cell-mediated immunity

As proposed by [Grifoni *et al.*, \(2020\)](#), a robust of T-cell antiviral immune response comprising solid CD4⁺ T cell response that helps in antibody production, and viral specific CD8⁺ T cells that eliminate virus-infected cells, have been established in average COVID-19 recovered patients; who had a normal disease course with no recourse to hospitalization. The activation of T-cells by N and S proteins of SARS-CoV-2 is documented to occur within the first week of infection, whereas the virus-specific memory CD4⁺ and CD8⁺ T-cells increase about 2 weeks post activation. These reportedly remain detectable although at lower levels for at least 100 days. Therefore, the observed long-lived T-cell responses might dispel the lay press belief about failure of the host immune system to mount protective and lasting response to SARS-CoV-2 ([Stephens and McElrath, 2020](#)).

Active immune response against many viral infections hinges on activation of cytotoxic T lymphocytes to eliminate the virus-infected cells. According to the recent study of [Shurin *et al.*, \(2020\)](#), massive tissue damage associated with ICS and hyper-activation of virus-specific CD8⁺ cells during COVID-19 infection, may dysregulate the peripheral tolerance machinery and allows the development of autoimmune pathology after patient recovery. Moreover, [Diao *et al.*, \(2020\)](#); [Zeng *et al.*, \(2020\)](#) added that a dramatic cytokine release drive depletion, and exhaustion of total CD4⁺ and CD8⁺ T cells is often reported in acute phases of SARS-CoV-2 infection; as patients progressed from prodromal to overtly symptomatic stages. This significant reduction in T cells levels exposes COVID-19 patients to secondary infections; prolonged virus clearance and reduced survival rate, as proposed by [Zheng *et al.*, \(2020\)](#). Therefore, intensive

research on subpopulations of T lymphocytes; for their vulnerability and roles in COVID-19 progression and recovery will be necessary. Furthermore, [Shurin *et al.*, \(2020\)](#) highlighted that very limited information regarding SARS-CoV-2 proteins-specific T cells subsets in COVID-19 patients is known; hence, comprehensive analysis of these cells especially after recovery is needed, to predict and minimize outcomes of immune dysregulation during infection.

[Altmann, \(2020\)](#); [LeBert *et al.*, \(2020\)](#) reported that T-cells from SARS and COVID-19 convalescent patients have been documented to share similar antigen responsiveness to conserved regions of nucleocapsid protein. In addition, exposure to the circulating common cold coronaviruses provides some level of pre-existing immunity to the novel SARS-CoV-2. This has been evidenced through the significant cross-reactive T cells responses in blood samples of people who had never been exposed to the SARS-CoV-2, but have experienced at least three of the four common cold coronavirus infections during their life. However, it is still not clear, whether the observed cross-reactivity provides any kind of protective immunity to COVID-19 ([Grifoni *et al.*, \(2020\)](#)).

3. SARS-CoV-2 immune evasion strategies

Recent studies conducted by [Shah *et al.*, \(2020\)](#); [Sariol and Perlman, \(2020\)](#) revealed that one of the most effective antiviral machineries employed by the immune cells is the secretion of interferons (IFN). An early type I IFN response plays important role in protection against severe diseases, and prevention of aberrant pro-inflammatory cytokine release. However, coronaviruses have developed various immune evasion mechanisms, to prevent detection by PRRs and inhibit IFN-I induction and signaling pathways leading thus to enhanced pathogenesis.

As a member of Betacoronavirus group, SARS-CoV-2 is conceived to develop immune evasion mechanisms similar to those of SARS-CoV and MERS-CoV, which have been extensively reviewed

and discussed by [Kindler *et al.*, \(2016\)](#); [Thornbrough *et al.*, \(2016\)](#); [Kikkert, \(2020\)](#). Briefly, these related coronaviruses suppress type I IFN response ([Cameron *et al.*, 2012](#); [Comar *et al.*, 2019](#)); induce T cells apoptosis ([Yang *et al.*, 2005](#); [Bahl *et al.*, 2010](#)), activate direct elimination of activated T Cells ([Chu *et al.*, 2015](#)) and down regulate antigen presentation via MHC class I and II, leading thus to overall diminished T cells responses ([Shokri *et al.*, 2019](#)). However, whether such SARS-CoV-2 has evolved these evasion strategies and/or ought for additional possible immune escape mechanisms like viral mutations, immune exhaustion and deviation, and biased Th2 type response remain to be elucidated.

The recent study of [Singh *et al.*, \(2020\)](#) revealed that SARS-CoV-2 is able to stay undetected within host cells for longer time than many influenza viruses or other coronaviruses, thus efficiently evading the host immune detection at the early stages of infection. Moreover, the virus induces inadequate types I, II and III IFN signatures in SARS-CoV-2 infected cell lines; primary bronchial cells and a ferret model, as revealed by [Blanco-Melo *et al.*, \(2020\)](#); [Chu *et al.*, \(2020\)](#). Similarly, severe COVID-19 patients have been shown to possess impaired IFN responses; dysregulated cytokines and chemokines profiles; thus exacerbate inflammatory responses, owing to low levels of IFN production or signaling ([Chen *et al.*, 2020b](#); [Hadjadj *et al.*, 2020](#); [Yang *et al.*, 2020c](#)). The low-level synthesis of type I and type III INFs with sufficient interferon-stimulated gene (ISG) expression, alongside with the elevated chemokines secretion during SARS-CoV-2 infection, result in the decreased antiviral genes transcription, which in turn drives the development of severe COVID-19 clinical features ([Blanco-Melo *et al.*, 2020](#); [Shah *et al.*, 2020](#)). In addition to their effects on the host IFN pathway, SARS-CoV-2 viral proteins such as nonstructural proteins and open reading frames are reported to impede several other innate immune signaling proteins resulting in the progression of COVID-19 infection ([Gordon *et al.*, 2020](#)).

Previous studies conducted by [Brandstadter and Yang, \(2011\)](#); [Schuster *et al.*, \(2016\)](#) revealed that the

natural killer (NK) cells play critical role in the defense against viral infections. Their activation results in targeted killing of infected/activated cells; cytotoxic degranulation and release of cytokines, and helps to modulate the host adaptive immune responses. Reduction in the numbers and blunted functions of the NK cells such as CD56^{dim}CD16⁺ and CD56^{bright}CD16^{+/-} cells, have been reported from several COVID-19 studies ([Market *et al.*, 2020](#); [van Eeden *et al.*, 2020](#); [Bao *et al.*, 2021](#)). According to [Song *et al.*, \(2020\)](#); [van Eeden *et al.*, \(2020\)](#); [Zheng *et al.*, \(2020\)](#), abridged count of these important NK cells is associated with decreased clearance of infected/activated cells; diminished cytotoxicity, impaired production of chemokines, IFN- γ and TNF- α , and unchecked elevation of the tissue-damaging inflammation markers leading to severe COVID-19 features. However, while lungs NK cells do not express ACE2; the entry receptor for SARS-CoV-2 ([Travaglini *et al.*, 2020](#)), the reduced NK cell counts and function have not been adequately linked to the direct effects of the virus. A recent study of [Vabret *et al.*, \(2020\)](#) added that impaired maturation of the NK compartment; or migration of the circulating NK cells into the lungs or to the other peripheral tissues of COVID-19 patients, have been hypothesized to be the possible reasons behind their reduced counts.

Furthermore, severe lymphopaenia in the CD4⁺ T-cell, CD8⁺ T-cell and B-cell previously observed in some cases of SARS and MERS ([Wong *et al.*, 2003](#); [Li *et al.*, 2004](#)), is another potent escape mechanism employed by SARS-CoV-2, to cause defects in the host antiviral and immune regulatory immunity, as reported by recent research works conducted by [Azkur *et al.*, \(2020\)](#); [Liu *et al.*, \(2020\)](#); [Tan *et al.*, \(2020b\)](#); [Wang *et al.*, \(2020a\)](#). Lymphopaenia in coronavirus infections is reported to occur via three main mechanisms mainly; impaired lymphopoiesis, redistribution of the circulating lymphocytes, and apoptosis or direct destruction of the lymphocytes ([Rokni *et al.*, 2020](#)). The exact mechanism by which SARS-CoV-2 causes lymphopaenia has not been fully elucidated. However, it is speculated that the virus

infects the T-lymphocytes through the receptor-dependent or the S protein-mediated membrane fusion thereby inducing the T-cell apoptosis and autophagic cell death of the peripheral blood mononuclear cells ([Wang *et al.*, 2020b](#); [Xiong *et al.*, 2020](#)). Besides reduction in the circulating T cells, SARS-CoV-2 equally directs the increased expression of the inhibitory receptors such as PD-1, TIM-3 and TIGIT on its surface, leading to exhaustion and loss in functions of the effector T cells, in order to overcome the host antiviral immune response ([Chiappelli *et al.*, 2020](#); [Qin *et al.*, 2020](#)).

Conversely, in addition to the influence of SARS-CoV-2, possible compounding elements of the environmental factors; genetics and age of the patient, co-morbidity of renal diseases, cancer and allergic conditions among others may modulate the severity of COVID-19. For instance, age-dependent factors such as differential expression of ACE2 are conceived to modulate the immune responses to SARS-CoV-2, because although COVID-19 adult patients mount more robust T cell response, higher serum neutralizing antibody titers and better antibody-dependent cellular phagocytosis, the children and youth infected with SARS-CoV-2 were established to develop milder disease and lower mortality rate ([Bunyavanich *et al.*, 2020](#); [Mortaz *et al.*, 2020](#); [Pierce *et al.*, 2020](#)).

Conclusion

The COVID-19 pandemic caused by SARS-CoV-2 is a multifactorial pathophysiological process involving pro-inflammatory cytokines; chemokines, blood cells, activated immune cells and residential tissue cells. The majorities of COVID-19 patients have mild to moderate illness, and normally recovers within one week developing protective T-cells and antibody immunity. However, the immunological dysregulations associated with lymphopaenia; eosinopaenia, extensive pneumonia and lung tissue damage, followed by ICS, ARDS, disseminated intravascular coagulation and multi organ failure are seen in severe diseases. The virus induced pro-inflammatory cytokine directed ARDS that is

consistently linked with severity and fatal COVID-19 outcomes, is evident following over-activation of some of the immune cells including; T cells, NK cells, B cells and antigen presenting cells.

Although the body of most COVID-19 patients recognizes the viral components such as the S and N proteins to mount an immune response leading to successful elimination of SARS-CoV-2; however, the virus has so far evolved several mechanisms especially in severe diseases to escape these immune responses. Notwithstanding, the majority of these evasion strategies have not been systematically delineated partly due to novelty of the virus. Thus, in spite of the growing immunological data about immunity to SARS-CoV-2 infection, there remain pressing unknowns, which necessitate further studies.

Acknowledgement

The authors wish to thank the management of Ahmadu Bello University, Zaria, Nigeria, for providing a conducive environment to undertake this study.

Funding source

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest

The authors have no conflicts of interest to declare that are relevant to the content of this article.

Ethical approval

Non-applicable.

4. References

Altmann, D.M. (2020). Adaptive immunity to SARS-CoV-2. *Oxford Open Immunology*. 1(1): 1-6. <https://doi.org/10.1093/oxfimm/iqaa003>

Azkur, A.K.; Akdis, M.; Azkur, D.; Sokolowska, M.; van de Veen, W.; Brügger, M.C.; O'Mahony, L.; Gao, Y.; Nadeau, K. and Akdis, C.A. (2020). Immune response to SARS-CoV-2 and mechanisms of immunopathological changes in COVID-19. *Allergy*. 75(7): 1564-1581. <https://doi.org/10.1111/all.14364>

Bahl, K.; Hübner, A.; Davis, R.J. and Welsh, R.M. (2010). Analysis of apoptosis of memory T cells and dendritic cells during the early stages of viral infection or exposure to toll-like receptor agonists. *Journal of Virology*. 84(10): 4866-4877. <https://doi.org/10.1128/JVI.02571-09>

Bao, C.; Tao, X.; Cui, W.; Hao, Y.; Zheng, S.; Yi, B.; Pan, T.; Young, K.H. and Qian, W. (2021). Natural killer cells associated with SARS-CoV-2 viral RNA shedding, antibody response and mortality in COVID-19 patients. *Experimental Hematology and Oncology*. 10(1): 1-4.

Bao, L.; Deng, W.; Gao, H.; Xiao, C.; Liu, J.; Xue, J.; Lv, Q.; Liu, J.; Yu, P.; Xu, Y. and Qi, F. (2020). Reinfection could not occur in SARS-CoV-2 infected rhesus macaques. *BioRxiv*. <https://doi.org/10.1101/2020.03.13.990226>

Blanco-Melo, D.; Nilsson-Payant, B.E.; Liu, W-C.; Uhl, S.; Hoagland, D.; Möller, R.; Jordan, T.X.; Oishi, K.; Panis, M. and Sachs, D. (2020). Imbalanced host response to SARS-CoV-2 drives development of COVID-19. *Cell*. 181: 1036-1045.e9. <https://doi.org/10.1016/j.cell.2020.04.026>

Bonam, S.R.; Kaveri, S.V.; Sakuntabhai, A.; Gilardin, L. and Bayry, J. (2020). Adjunct immunotherapies for the management of severely ill COVID-19 patients. *Cell Reports Medicine*. e100016. <https://doi.org/10.1016/j.xcrm.2020.100016>

Brandstadter, J.D. and Yang, Y. (2011). Natural killer cell responses to viral infection. *Journal of Innate Immunity*. 3(3): 274-279. <https://doi.org/10.1159/000324176>

- Bunyavanich, S.; Do, A. and Vicencio, A. (2020).** Nasal gene expression of angiotensin-converting enzyme 2 in children and adults. *Journal of the American Medical Association.* 323: 2427-9. <https://doi.org/10.1001/jama.2020.8707>
- Cai, Y.; Hao, Z.; Gao, Y.; Ping, W.; Wang, Q.; Peng, S.; Zhao, B.; Sun, W.; Zhu, M.; Li, K. and Han, Y. (2020).** Coronavirus disease 2019 in the perioperative period of lung resection: a brief report from a single thoracic surgery department in Wuhan, People's Republic of China. *Journal of Thoracic Oncology.* 15(6): 1065-1072.
- Cameron, M.J.; Kelvin, A.A.; Leon, A.J.; Cameron, C.M.; Ran, L.; Xu, L.; Chu, Y.K.; Danesh, A.; Fang, Y.; Li, Q. and Anderson, A. (2012).** Lack of innate interferon responses during SARS coronavirus infection in a vaccination and reinfection ferret model. *PLoS one.* 7(9): p.e45842.
- Chan, J.F.W.; Kok, K.H.; Zhu, Z.; Chu, H.; To, K.K.W.; Yuan, S. and Yuen, K.Y. (2020).** Genomic characterization of the 2019 novel human-pathogenic coronavirus isolated from a patient with atypical pneumonia after visiting Wuhan. *Emerging Microbes and Infections.* 9: 221-236. <https://doi.org/10.1080/22221751.2020.1719902>
- Chen, Y.; Liu, Q. and Guo, D. (2020a).** Coronaviruses: genome structure, replication, and pathogenesis. *Journal Medical Virology.* 92: 418-23. <https://doi.org/10.1002/jmv.25681>
- Chen, G.; Wu, D.; Guo, W.; Cao, Y.; Huang, D.; Wang, H.; Wang, T.; Zhang, X.; Chen, H.; Yu, H. and Zhang, X. (2020b).** Clinical and immunological features of severe and moderate coronavirus disease 2019. *Journal of Clinical Investigation.* 130: 2620-2629.
- Chiappelli, F.; Khakshooy, A. and Greenberg, G. (2020).** COVID-19 immunopathology & immunotherapy. *Bioinformatics.* 16: 219-22. <https://doi.org/10.6026/97320630016222>
- Chu, H.; Chan, J.F.W.; Wang, Y.; Yuen, T.T.T.; Chai, Y.; Hou, Y.; Shuai, H.; Yang, D.; Hu, B.; Huang, X. and Zhang, X. (2020).** Comparative replication and immune activation profiles of SARS-CoV-2 and SARS-CoV in human lungs: an *ex vivo* study with implications for the pathogenesis of COVID-19. *Clinical Infectious Diseases.* 71(6):1400-1409. <https://doi.org/10.1093/cid/ciaa410>
- Chu, H.; Zhou, J.; Wong, B.H.Y.; Li, C.; Chan, J.F.W.; Cheng, Z.S.; Yang, D.; Wang, D.; Lee, A.C.Y.; Li, C. and Yeung, M.L. (2015).** Middle east respiratory syndrome coronavirus efficiently infects human primary T lymphocytes and activates the extrinsic and intrinsic apoptosis pathways. *Journal of Infectious Diseases.* 213: 904-14. <https://doi.org/10.1093/infdis/jiv380>
- Clери, D.J.; Ricketti, A.J. and Vernaleo, J.R. (2010).** Severe acute respiratory syndrome (SARS). *Infectious Disease Clinics.* 24(1): 175-202. <https://doi.org/10.1016/j.idc.2009.10.005>
- Comar, C.E.; Goldstein, S.A.; Li, Y.; Yount, B.; Baric, R.S. and Weiss, S.R. (2019).** Antagonism of dsRNA-induced innate immune pathways by NS4a and NS4b accessory proteins during MERS coronavirus infection. *MBio.* 10(2): 1-7. <https://doi.org/10.1128/mBio.00319-19>
- Diao, B.; Wang, C. and Tan, Y. (2020).** Reduction and functional exhaustion of T cells in patients with Coronavirus disease 2019 (COVID-19). *Frontiers in Immunology.* 11. <https://doi.org/10.3389/fimmu.2020.00827>
- Gordon, D.E.; Jang, G.M.; Bouhaddou, M.; Xu, J.; Obernier, K.; White, K.M.; O'Meara, M.J.; Rezelj, V.V.; Guo, J.Z.; Swaney, D.L. and Tummino, T.A. (2020).** A SARS-CoV-2 protein interaction map reveals targets for drug repurposing. *Nature.* 583: 459-468.
- Gorse, G.J.; Donovan, M.M. and Patel, G.B. (2020).** Antibodies to coronaviruses are higher in older compared with younger adults and binding antibodies

are more sensitive than neutralizing antibodies in identifying coronavirus associated illnesses. *Journal of Medical Virology*. 92(5): 512-517. doi.org/10.1002/jmv.25715.

Grifoni, A.; Weiskopf, D.; Ramirez, S.I.; Mateus, J.; Dan, J.M.; Moderbacher, C.R.; Rawlings, S.A.; Sutherland, A.; Premkumar, L.; Jadi, R.S.; Marrama, D.; de Silva, M.A.; Frazier, A.; Carlin, F.A.; Greenbaum, A.J.; Peters, B.; Krammer, F.; Smith, M.D.; Crotty, S. and Sette, A. (2020). Targets of T cell responses to SARS-CoV-2 coronavirus in humans with COVID-19 disease and unexposed individuals. *Cell*. 181(7): 1489-1501. <https://doi.org/10.1016/j.cell.2020.05.015>

Hadjadj, J.; Yatim, N.; Barnabei, L.; Corneau, A.; Boussier, J.; Pere, H.; Charbit, B.; Bondet, V.; Chenevier-Gobeaux, C. and Breillat, P. et al. (2020). Impaired type I interferon activity and exacerbated inflammatory responses in severe COVID-19 patients. *medRxiv*. <https://doi.org/10.1101/2020.04.19.20068015>

Huang, C.; Wang, Y.; Li, X.; Ren, L.; Zhao, J.; Hu, Y.; Zhang, L.; Fan, G.; Xu, J.; Gu, X. and Cheng, Z. (2020). Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *The Lancet*. 395(10223): 497-506. [https://doi.org/10.1016/S0140-6736\(20\)30183-5](https://doi.org/10.1016/S0140-6736(20)30183-5)

Inandikhoglu, N. and Akkoc, T. (2020). Immune Responses to SARS-CoV, MERS-CoV and SARS-CoV-2. *Advances in Experimental Medicine and Biology - Cell Biology and Translational Medicine*. 9:5-12. <https://doi.org/10.1007/5584-2020-549>

Iwasaki, A. and Yang, Y. (2020). The potential danger of suboptimal antibody responses in COVID-19. *Nature Reviews Immunology*. 20: s339-341. <https://doi.org/10.1038/s41577-020-0321-6>

Jiang, H.W.; Li, Y.; Zhang, H.N.; Wang, W.; Yang, X.; Qi, H.; Li, H.; Men, D.; Zhou, J. and Tao, S.C. (2020). SARS-CoV-2 proteome microarray for global profiling of COVID-19 specific IgG and IgM

responses. *Nature Communications*. 11(1): 1-11. <https://doi.org/10.1038/s41467-020-17488-8>

Kikkert, M. (2020). Innate Immune Evasion by Human Respiratory RNA Viruses. *Journal of Innate Immunity*. 12: 4-20.

Kindler, E.; Thiel, V. and Weber, F. (2016). Interaction of SARS and MERS Coronaviruses with the Antiviral Interferon Response. *Advances in Virus Research*. 96: 219-43.

LeBert, N.; Tan, A.T.; Kunasegaran, K.; Tham, C.Y.; Hafezi, M.; Chia, A.; Chng, M.H.Y.; Lin, M.; Tan, N.; Linster, M. and Chia, W.N. (2020). SARS-CoV-2-specific T cell immunity in cases of COVID-19 and SARS, and uninfected controls. *Nature*. 584(7821): 457-462. <https://doi.org/10.1038/s41586-020-2550-z>

Li, T.; Qiu, Z.; Zhang, L.; Han, Y.; He, W.; Liu, Z.; Ma, X.; Fan, H.; Lu, W.; Xie, J. and Wang, H. (2004). Significant changes of peripheral T lymphocyte subsets in patients with severe acute respiratory syndrome. *The Journal of Infectious Diseases*. 189: 648-651. <https://doi.org/10.1086/381535>

Liang, Y.; Wang, M.L.; Chien, C.S.; Yarmishyn, A.A.; Yang, Y.P.; Lai, W.Y.; Luo, Y.H.; Lin, Y.T.; Chen, Y.J.; Chang, P.C. and Chiou, S.H. (2020). Highlight of Immune Pathogenic Response and Hematopathologic Effect in SARS-CoV, MERS-CoV, and SARS-Cov-2 Infection. *Frontiers in Immunology*. 11: 1022. <https://doi.org/10.3389/fimmu.2020.01022>

Liu, Y.; Yang, Y.; Zhang, C.; Huang, F.; Wang, F.; Yuan, J.; Wang, Z.; Li, J.; Li, J.; Feng, C. and Zhang, Z. (2020). Clinical and biochemical indexes from 2019-nCoV infected patients linked to viral loads and lung injury. *Science China Life Science*. 63(3): 364-374.

Lokugamage, K.G.; Hage, A.; Schindewolf, C.; Rajsbaum, R. and Menachery, V.D. (2020). SARS-

CoV-2 is sensitive to type I interferon pretreatment. *BioRxiv*. <https://doi.org/10.1101/2020.03.07.982264>

Long, Q.X.; Liu, B.Z.; Deng, H.J.; Wu, G.C.; Deng, K.; Chen, Y.K.; Liao, P.; Qiu, J.F.; Lin, Y.; Cai, X.F. and Wang, D.Q. (2020). Antibody responses to SARS-CoV-2 in patients with COVID-19. *Nature Medicine*. 26:1-4. <https://doi.org/10.1038/s41591-020-0965-6>

Market, M.; Angka, L.; Martel, A.B.; Bastin, D.; Olanubi, O.; Tennakoon, G.; Boucher, D.M.; Ng, J.; Ardolino, M. and Auer, R.C. (2020). Flattening the COVID-19 curve with natural killer cell-based immunotherapies. *Frontiers in Immunology*. 11: 1-23. doi.org/10.3389/fimmu.2020.01512

Mehta, P.; McAuley, D.F.; Brown, M.; Sanchez, E.; Tattersall, R.S.; Manson, J.J. and Collaboration, H.L.H. (2020). COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet London England*. 395(10229): 1033. [https://doi.org/10.1016/S0140-6736\(20\)30628-0](https://doi.org/10.1016/S0140-6736(20)30628-0)

Mortaz, E.; Tabarsi, P.; Varahram, M.; Folkerts, G. and Adcock, I.M. (2020). The immune response and immunopathology of COVID-19. *Frontiers in Immunology*. 11:e2037. <https://doi.org/10.3389/fimmu.2020.02037>

Naeem, Z. (2014). Middle East Respiratory Syndrome (MERS): An update. *International Journal of Health Sciences*. 7(3): 5-6. <https://doi.org/10.12816/0006053>

Orakpoghenor, O.; Markus, T.P.; Atata, J.A.; Erin, J.P.; Olaolu, O.S.; Udechukwu, C.C.; Ogbuagu, N.E.; Jolayemi, K.O.; Okoronkwo, M.O. and Umar, B.N. (2020). Pathologic basis of coronavirus disease 2019 (COVID-19) – An overview of cellular affinities, pathogenesis, clinical manifestations, autopsy findings and sequelae. *Annals of Cytology and Pathology*. 5(1): 078-083.

Pierce, C.A.; Preston-Hurlburt, P.; Dai, Y.; Aschner, C.B.; Cheshenko, N.; Galen, B.; Garforth, S.J.; Herrera, N.G.; Jangra, R.K.; Morano, N.C.

and Orner, E. (2020). Immune responses to SARS-CoV-2 infection in hospitalized pediatric and adult patients. *Science Translational Medicine*. 12(564): 1-10 eabd5487.

Prete, M.; Favoino, E.; Catacchio, G.; Racanelli, V. and Perosa, F. (2020). SARS-CoV-2 infection complicated by inflammatory syndrome. Could high-dose human immunoglobulin for intravenous use (IVIG) be beneficial? *Autoimmunity Reviews*. 19(7): 102559. <https://doi.org/10.1016/j.autrev.2020.102559>

Promptchara, E.; Ketloy, C. and Palaga, T. (2020). Immune responses in COVID-19 and potential vaccines: Lessons learned from SARS and MERS epidemic. *Asian Pacific Journal of Allergy and Immunology*. 38(1): 1-9. <https://doi.org/10.12932/AP-200220-0772>

Pyrc, K.; Dijkman, R.; Deng, L.; Jebbink, M.F.; Ross, H.A.; Berkhout, B. and Van der Hoek, L. (2006). Mosaic structure of human coronavirus NL63, one thousand years of evolution. *Journal of Molecular Biology*. 364: 964-973. <https://doi.org/10.1016/j.jmb.2006.09.074>

Qin, C.; Zhou, L.; Hu, Z.; Zhang, S.; Yang, S.; Tao, Y.; Xie, C.; Ma, K.; Shang, K. and Wang, W. (2020). Dysregulation of immune response in patients with COVID-19 in Wuhan, China. *Clinical Infectious Diseases*. 71: 762-8. <https://doi.org/10.1093/cid/ciaa248>

Rokni, M.; Ghasemi, V. and Tavakoli, Z. (2020). Immune responses and pathogenesis of SARS-CoV-2 during an outbreak in Iran: Comparison with SARS and MERS. *Reviews in Medical Virology*. 30(3): 1-6. <https://doi.org/10.1002/rmv.2107>

Sariol, A. and Perlman, S. (2020). Lessons for COVID-19 immunity from other coronavirus infections. *Immunity*. 53(2): 248-263. <https://doi.org/10.1016/j.immuni.2020.07.005>

Schuster, I.S.; Coudert, J.D.; Andoniou, C.E. and Degli-Esposti, M.A. (2016). “Natural Regulators”:

NK Cells as Modulators of T Cell Immunity. *Frontiers in Immunology*. 7:e235.

Seow, J.; Graham, C.; Merrick, B.; Acors, S.; Pickering, S.; Steel, K.J.; O'Bryne, A.; Kouphou, N.; Pickering, S.; Galao, R. and Betancor, G. (2020). Longitudinal observation and decline of neutralizing antibody responses in the three months following SARS-CoV-2 infection in humans. *Nature Microbiology*. 1-10. <https://doi.org/10.1038/s41564-020-00813-8>

Shah, V.K.; Firmal, P.; Alam, A.; Ganguly, D. and Chattopadhyay, S. (2020). Overview of Immune Response during SARS-CoV-2 Infection: Lessons From the Past. *Frontiers in Immunology*. 11: 1-17. <https://doi.org/10.3389/fimmu.2020.01949>

Shi, Y.; Wang, Y.; Shao, C.; Huang, J.; Gan, J.; Huang, X.; Bucci, E.; Piacentini, M.; Ippolito, G. and Melino, G. (2020). COVID-19 infection: the perspectives on immune responses. *Cell Death Differ.* 27(5): 1451-1454. <https://doi.org/10.1038/s41418-020-0530-3>

Shokri, S.; Mahmoudvand, S.; Taherkhani, R. and Farshadpour, F. (2019). Modulation of the immune response by Middle East respiratory syndrome coronavirus. *Journal of Cellular Physiology*. 234: 2143-51.

Shurin, M.R.; Morris, A.; Wells, A. and Wheeler, S.E. (2020). Assessing Immune Response to SARS-CoV-2 Infection. *Immuno Targets and Therapy*. 9: 111-114. <https://doi.org/10.2147/ITT.S264138>

Singh, N.; Suthar, B.; Mehta, A. and Pandey, A. (2020). Immune Response Towards COVID-19: A Review on Host Body. *Journal of Infectious Diseases and Diagnosis*. 5(1): e134. <https://doi.org/10.35248/2576-389X.5.134>

Song, C.Y.; Xu, J.; He, J.Q. and Lu, Y.Q. (2020). COVID-19 early warning score: a multi-parameter screening tool to identify highly suspected patients.

MedRxiv.

<https://doi.org/10.1101/2020.03.05.20031906>

Stephens, D.S. and McElrath, M.J. (2020). COVID-19 and the Path to Immunity. *The Journal of American Medical Association*. 324(13): 1279-1281. <https://doi.org/10.1001/jama.2020.16656>

Su, S.; Wong, G.; Shi, W.; Weifeng, S.; Jun, L.; Alexander, C.K.L.; Jiyong, Z.; Wenjun, L.Y. and Bi, G.F.G. (2016). Epidemiology, Genetic Recombination, and Pathogenesis of Coronaviruses. *Trends in Microbiology*. 24(6): 490-502.

Tan, W.; Lu, Y.; Zhang, J.; Wang, J.; Dan, Y.; Tan, Z.; He, X.; Qian, C.; Sun, Q.; Hu, Q. and Liu, H. (2020a). Viral kinetics and antibody responses in patients with COVID-19. MedRxiv. doi: <https://doi.org/10.1101/2020.03.24.20042382>

Tan, L.; Wang, Q.; Zhang, D.; Ding, J.; Huang, Q.; Tang, Y.Q.; Wang, Q. and Miao, H. (2020b). Lymphopenia predicts disease severity of COVID-19: a descriptive and predictive study. *Signal Transduction and Targeted Therapy*. 5: 1-3.

Tanaka, T.; Narazaki, M. and Kishimoto, T. (2016). Immunotherapeutic implications of IL-6 blockade for cytokine storm. *Immunotherapy*. <https://doi.org/10.2217/imt-2016-0020>

Tetro, J. (2020). Is COVID-19 receiving ADE from other coronaviruses? *Microbes and Infection*. 22:72-3. <https://doi.org/10.1016/j.micinf.2020.02.006>

Thevarajan, I.; Nguyen, T.H.O.; Koutsakos, M.; Thevarajan, I.; Druce, J.; Caly, L.; van de Sandt, C.E.; Jia, X.; Nicholson, S.; Catton, M.; Cowie, B. and SRL, S.Y.T. (2020). Breadth of concomitant immune responses prior to patient recovery: a case report of non-severe COVID-19. *Nature Medicine*. 26(4): 453-455. <https://doi.org/10.1038/s41591-020-0819-2>

Thornbrough, J.M.; Jha, B.K.; Yount, B.; Goldstein, S.A.; Li, Y.; Elliott, R.; Sims, A.C.; Baric, R.S.; Silverman, R.H. and Weiss, S.R.

- (2016). Middle East respiratory syndrome coronavirus NS4b protein inhibits host RNase L activation. *MBio* 7: e00258.
- To, K.K.W.; Tsang, O.T.Y.; Leung, W.S.; Tam, A.R.; Wu, T.C.; Lung, D.C.; Yip, C.C.Y.; Cai, J.P.; Chan, J.M.C.; Chik, T.S.H. and Lau, D.P.L. (2020).** Temporal profiles of viral load in posterior oropharyngeal saliva samples and serum antibody responses during infection by SARS-CoV-2: an observational cohort study. *The Lancet Infectious Diseases*. 20(5): 565-574.
- Travaglini, K.J.; Nabhan, A.N.; Penland, L.; Sinha, R.; Gillich, A.; Sit, R.V.; Chang, S.; Conley, S.D.; Mori, Y.; Seita, J.; Berry, G.J.; Shrager, J.B.; Metzger, R.J.; Kuo, S.C.; Neff, N.; Weissman, I.L.; Quake, S.R. and Krasnow, M.A. (2020).** A molecular cell atlas of the human lung from single-cell RNA sequencing. *Nature*. (587): 619-625. <https://doi.org/10.1038/s41586-020-2922-4>
- Vabret, N.; Britton, G.J.; Gruber, C.; Hegde, S.; Kim, J.; Kuksin, M.; Levantovsky, R.; Malle, L.; Moreira, A.; Park, M.D. and Pia, L. (2020).** Immunology of COVID-19: current state of the science. *Immunity*. 52: 910-941. <https://doi.org/10.1016/j.immuni.2020.05.002>
- Van Der Hoek, L. (2007).** Human coronaviruses: what do they cause?. *Antiviral Therapy*. 12(4b): 651-658
- van Eeden, C.; Khan, L.; Osman, M.S. and Tervaert, J.W.C. (2020).** Natural Killer Cell Dysfunction and Its Role in COVID-19. *International Journal of Molecular Sciences*. 21(17): e6351. <https://doi.org/10.3390/ijms21176351>
- Wan, S.; Yi, Q.; Fan, S.; Lv, J.; Zhang, X.; Guo, L.; Lang, C.; Xiao, Q.; Xiao, K.; Yi, Z. and Qiang, M. (2020).** Characteristics of lymphocyte subsets and cytokines in peripheral blood of 123 hospitalized patients with 2019 novel coronavirus pneumonia (NCP). *MedRxiv*. <https://doi.org/10.1101/2020.02.10.20021832>
- Wang, F.; Nie, J. and Wang, H. et al. (2020a).** Characteristics of peripheral lymphocyte subset alteration in COVID-19 pneumonia. *Journal of Infectious Diseases*. 221(11): 1762-1769.
- Wang, X.; Xu, W.; Hu, G.; Xia, S.; Sun, Z.; Liu, Z.; Xie, Y.; Zhang, R.; Jiang, S. and Lu, L. (2020b).** SARS-CoV-2 infects T lymphocytes through its spike protein-mediated membrane fusion. *Cellular and Molecular Immunology*. 1-3. <https://doi.org/10.1038/s41423-020-0424-9>
- Wong, R.S.M.; Wu, A.; To, K.F.; Lee, N.; Lam, C.W.K.; Wong, C.K.; Chan, P.K.; Ng, M.H.; Yu, L.M.; Hui, D.S. and Tam, J.S. (2003).** Haematological manifestations in patients with severe acute respiratory syndrome: Retrospective analysis. *BMJ*. 326:1358-62. <https://doi.org/10.1136/bmj.326.7403.1358>
- WHO (World Health Organization). (2021).** Coronavirus disease (COVID-19) Weekly Epidemiological Update and Weekly Operational Updates. www.who.int/publications/m/item/weekly-operational-update-on-covid-19--9-february-2021
- Wu, Z. and McGoogan, J.M. (2020).** Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. *Jama*. 323(13): 1239-1242.
- Wu, F.; Wang, A.; Liu, M.; Wang, Q.; Chen, J.; Xia, S.; Ling, Y.; Zhang, Y.; Xun, J.; Lu, L. and Jiang, S. (2020).** Neutralizing antibody responses to SARS-CoV-2 in a COVID-19 recovered patient cohort and their implications. *MedRxiv*, <https://doi.org/10.1101/2020.03.30.20047365>
- Xiong, Y.; Liu, Y.; Cao, L.; Wang, D.; Guo, M.; Guo, D.; Hu, W.; Yang, J.; Tang, Z. and Wu, H. (2020).** Transcriptomic characteristics of bronchoalveolar lavage fluid and peripheral blood mononuclear cells in COVID-19 patients. *Social*

Science Research Network Electronic Journal. 9:761-770. <https://doi.org/10.2139/ssrn.3549993>

Yang, X.; Yu, Y.; Xu, J.; Shu, H.; Xia, J.; Liu, H.; Wu, Y.; Zhang, L.; Yu, Z.; Fang, M.; Yu, T. and Wang, Y. (2020a). Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *The Lancet Respiratory Medicine*. 8(5): 475-481. [https://doi.org/10.1016/S2213-2600\(20\)30079-5](https://doi.org/10.1016/S2213-2600(20)30079-5)

Yang, L.; Tian, D. and Liu, W. (2020b). Strategies for vaccine development of COVID-19. *Chinese Journal of Biotechnology*. 36(4): 593-604. <https://doi.org/10.13345/j.cjb.200094>

Yang, Y.; Shen, C.; Li, J.; Yuan, J.; Wei, J.; Huang, F.; Wang, F.; Li, G.; Li, Y. and Xing, L. et al. (2020c). Plasma IP-10 and MCP-3 levels are highly associated with disease severity and predict the progression of COVID-19. *Journal of Allergy and Clinical Immunology*. 146:119–127. e4. <https://doi.org/10.1016/j.jaci.2020.04.027>

Yang, Y., Xiong, Z., Zhang, S., Yan, Y., Nguyen, J., Ng, B., Lu, H., Brendese, J., Yang, F., Wang, H. and Yang, X.F. (2005). Bcl-xL inhibits T-cell apoptosis induced by expression of SARS coronavirus E protein in the absence of growth factors. *Biochemical Journal*. 392(1): 135-143. <https://doi.org/10.1042/BJ20050698>

Zeng, Q.; Li, Y.; Huang, G.; Wu, W.; Dong, S. and Xu, Y. (2020). Mortality of COVID-19 is associated with cellular immune function compared to immune function in Chinese Han population. *Medrxiv*. <https://doi.org/10.1101/2020.03.08.20031229>

Zhang, Y.Y.; Li, B.R. and Ning, B.T. (2020a). The comparative immunological characteristics of SARS-CoV, MERS-CoV, and SARS-CoV-2 coronavirus infections. *Frontiers in Immunology*. 11: 1-21. <https://doi.org/10.3389/fimmu.2020.02033>

Zhao, J.; Yuan, Q.; Wang, H.; Liu, W.; Liao, X. and Su, Y. et al. (2020). Antibody responses to SARS-CoV-2 in patients of novel coronavirus disease 2019. *Clinical Infectious Diseases*. <https://doi.org/10.1101/2020.03.02.20030189>

Zheng, H.; Zhang, M.; Yang, C.X.; Zhang, N.; Wang, X.C.; Yang, X.P.; Dong, X.Q. and Zheng, Y.T. (2020). Elevated exhaustion levels and reduced functional diversity of T cells in peripheral blood may predict severe progression in COVID-19 patients. *Cellular and Molecular Immunology*. 17(7): 541-543. <https://doi.org/10.1038/s41423-020-0401-3>

Zhou, Y.; Fu, B.; Zheng, X.; Wang, D.; Zhao, C.; Qi, Y.; Sun, R.; Tian, Z.; Xu, X. and Wei, H. (2020). Aberrant pathogenic GM-CSF⁺ T cells and inflammatory CD14⁺CD16⁺ monocytes in severe pulmonary syndrome patients of a new coronavirus. *BioRxiv*. <https://doi.org/10.1101/2020.02.12.945576>