



RESEARCH ARTICLE

Why Individuals Respond To COVID-19 Differently: A Battle of Sexes?

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Abstract

Several factors including genetic variations, cytokine storm (CS), macrophage activated syndrome (MAS), and lymphopenia have been recently discovered to influence the severity of COVID-19. Many studies have exclusively studied the pathogenesis of this disease, which includes the entry of the virus into the body, multiplication and spread, the progression of tissue damage, and the production of an immune response. However, questions like what makes some people more vulnerable than others to SARS-CoV-2 - the causative agent of the coronavirus disease; the role of gene networks in determining or influencing the efficiency of infection or the severity of COVID-19 symptoms are still in the valley of obscurity. What makes some SARS-CoV-2 infected individuals extremely sensitive to the development of acute respiratory distress syndrome (ARDS) while others are asymptomatic remains to be understood. Herein, we review the impact of a genetic variant in susceptibility and severity among sex and gender disparities, the significance of this variation in cases of severity and immune responses. Furthermore, we address major characteristics in severe COVID-19 cases, such as biochemical and homeostatic effects. For example, lymphocyte count and concentrations of inflammatory mediators within patients. Also, this paper identifies key clinical indicators of severe infections in the presence of cytokine storm and lymphopenia. Moreover, it takes into account predisposing factors that induce the severity of symptoms and underline the differences between mild and severe infections. Lastly, we explained the benefits of using bioinformatics to accelerate the progress made in COVID-19 research and future perspective in this research area.

1 | INTRODUCTION:

Viral infection of higher organisms is known to be the overall result of all the processes of replication and gene expression, which

responses to viral infections.

Progress has been made among the scientific community in understanding and identification of specific human gene variants that contribute to enhanced susceptibility or resistance to viral diseases.

Amongst these viral diseases is the coronavirus disease (COVID-19) that becomes the cynosure of all eyes - the most notable epidemic in the history of mankind. However, our understanding of genetic susceptibility to this viral infection and its severity is still in its infancy.

Consistently, the evidence of sex difference trend in response to coronavirus diseases showed male predominance deaths, as observed in the prior SARS (3) and Middle East respiratory syndrome (MERS) epidemics (caused by SARS-CoV and MERS-CoV, respectively). (4). Although gender-related social factors, including smoking, health care-seeking behaviours and some co-morbid conditions, may impact the outcomes of COVID-19 (5) and contribute to male–female differences in disease severity. Thus, the cross-cultural emergence of increased risk of death for males points to biological risk determinants.

2 | GENETIC VARIATION: IMPACT OF SEX CHROMOSOMES ON INFECTION SUSCEPTIBILITY:

Different discoveries made with genome-wide or candidate gene approaches of genetic factors such as genes encoding virus receptors, receptor-modifying enzymes, and immunity-related proteins explained the virus-host interactions. More recently, the concept that genes on the X and Y chromosomes may influence sex differences is being increasingly reported by different researchers (6, 7) and it was recently suggested that the widely expressed ancestral single-copy chromosome Y genes may function as dosage-sensitive regulators of gene expression and translation as such may play essential roles in male

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viability, development, and sex differences in health and disease (8).

Males of many species are said to be more susceptible than females to parasitic, fungal, bacterial, and viral infections(9) because females are functional mosaics for X-linked genes due to X chromosome inactivation and this, combined with other X chromosome inactivation mechanisms such as genes that escape silencing and skewed inactivation, could contribute to an immunological advantage for females in many infections. The X chromosome was reported to express several genes which have an impact on immunological processes such as Toll-like receptors, multiple cytokine receptors, genes involved in T-cell and B-cell activity, transcriptional as well as translational regulatory factors (10), while in turn the Y chromosome encodes for a number of inflammatory pathway genes, which are exclusively expressed in men (11).

Moreover, since males are haploid for the X chromosome, it has been suggested that any damaging genetic variants on the X chromosome will have a more pronounced immunological consequence in males than in females, thereby introducing sex-based differences and influencing the sex bias of a disease (12).

One mechanism that has been proposed to account for this difference is the androgen receptor encoded on X chromosome which inhibits antibody production. These hormones involve in the immune response, and various immune-related cells which are partly controlled by the female sex steroid hormone estrogen (13). So, it is evident that females have increased resistance against microbial infections, higher antibody responses and more adverse reactions in response to a number of vaccines which suggests that females have a more vigorous immune defence against most invading pathogens. However, on the other hand, it was reported that the greater infectious disease burden in males is due to testosterone, which drives the development of secondary male sex characteristics at the expense of suppressing immunity. Testosterone possess an inhibitory effect on the immune system through upregulation of anti-inflammatory cytokines (IL-10), while estrogen enhances the immune system by upregulating pro-inflammatory cytokines (TNF α).

Adducing to this was an experimental study on mice done by (14) which revealed that male mice showed enhanced susceptibility to SARS-CoV including elevated viral titers and increased accumulation of inflammatory monocytes and neutrophils in the lungs. So, evident from humans and experimental rodent models has proved sex differences in immunity to respiratory viruses (15).

Having established the role of sex chromosome's impact in infection severity, angiotensin-converting enzyme 2 gene also plays an indispensable role in entry of SARS-CoV-2 and ultimately its severity amongst population. Recent study by (16) has shown that ACE2 expression was associated with multiple immune signatures such as markers of T cells, B cells, NK cells, and interferon response across various human tissues. These findings suggest that ACE2 not only acts as a receptor for SARS-CoV-2, but is also involved in mediating the post-infection processes including inflammatory responses. Also, genetic polymorphisms has been previously reported to exist in the ACE2 gene which encodes the cellular receptor for SARS-CoV-2; allelic variants of the ACE2 may influence the protein's binding with the virus and subsequent invasion of the cell. Additionally, the polymorphisms of cellular proteases was reported to facilitate the entry of SARS-CoV-2 into the cell, along with furin (14) and TMPRSS2 (17).

Furthermore, another risk factor that has been explored which could cause severity of SARS-CoV-2 amongst individuals is the human leukocyte antigens (HLA)- a critical components of the viral antigen presentation pathway. In particular, understanding how variation in HLA may affect the cause of COVID-19 could help identify individuals at higher risk from the disease. Austin Nguyen et al., (2020) explored the potential for cross-protective immunity conferred by prior exposure to four common human coronaviruses, which found that HLA-B*46:01 had the fewest predicted binding peptides for SARS-CoV-2, suggesting that individuals with this allele may be particularly vulnerable to COVID-19, which concur with a previous study done by M. Lin, et al., (2003) (18, 19).

3 | CYTOKINE STORM: THE HYPERACTIVITY OF CYTOKINES.:

Moreover, another factor that contributes to the severity of individuals, is the hyperactivity of cytokine. Cytokine storm arises in events of overproduction and hyperactivity of cytokines which could lead to a hyperinflammatory response and increase the migration of granulocytes such as macrophages, to the site of infection (29). As a result, it could exacerbate inflammatory damage of the epithelium tissue, which is referred to as the macrophage activated syndrome. (Tufan et al., 2020) study identified ferritin, IL-6, and NTF-alpha as the clinical indicators of severity in COVID-19 due to events of high physiological activity being correlated with elevated levels of inflammatory mediators such as MAS and CS.

There are several biochemical effects that would begin to manifest into COVID-19 in response to SARS-CoV-2 infections. Retrospective studies found patients who were hospitalised in the ICU were more likely to exhibit high concentrations of necrosis-activating factors, interleukin-7, interleukin-2, and macrophage inflammatory protein-1A (29). Similarly, a higher rate of viral replication is correlated with increased interleukin levels and interferons of class 2. Further reports suggest patients with severe clinical presentations of a dysregulated immune response have an increased rate of cytokine activity which is caused by the elevated concentrations of white blood cells such as neutrophils and lymphocytes (29). This stresses they are key targets for CS in the presence of lymphopenia. Lymphopenia refers to the reduced number of leukocytes associated with the adaptive immunity. For instance, CD3+ and CD8+ are below normal levels.

Researchers could assess the difference in interleukins and neutrophil:lymphocyte ratio between patients experiencing mild and severe symptoms of COVID-19. There are several studies which focus on the difference between severe and mild COVID-19 cases. For instance, studies show interleukin 2 and 6 are higher in severe cases (29). As well as, findings based on patients with severe COVID-19 who exhibited ARDS had tested positive for a higher concentration of IL-6 which was a key contributing

factor for MAS. Likewise, patient's exams displayed over half of their lungs were damaged. Moreover, the ratio of neutrophil to lymphocyte is higher than mild cases which could exacerbate the concentration of cytokines in severe cases. Research shows severe cases of COVID-19 in Wuhan were correlated with cytokine storm and ARDS (22).

Another factor to consider is whether the sex of the patient affects the level of inflammatory mediators such as cytokines in the body. Although a study illustrates there is a similar level of IL-8 and IL-18 between males and females who have severe SARS-CoV-2 infections, this is not concordant with other findings in the study (30). For example, the concentration of IFNA2 is higher in females, however levels of CCL5 are more elevated in males during the pathogenesis of the disease (30). This emphasises there should be a closer investigation in the variation of inflammatory mediator responses between males and females.

On the other hand, studies illustrate the non-homeostatic nature of the immune system arises in patients with less regulated pathways between memory and naive T cell. In this case, naive helper T cells count rose as the mature memory and cytotoxic suppressor T cells declined. Findings show severe infections are marked by exceptionally low concentrations of regulatory T cells and helper T cells (29). Homeostasis is important as it contributes towards an effective immune response. Therefore, because of the infection with SARS-CoV-2, it would lead to the impairment of negative and positive feedback and inhibit the maintenance of homeostasis (29). This event occurs due to the variation in the proportion of T and B lymphocyte subtypes which creates an environment that promotes a cytokine storm. However, not only dysregulation between white blood cell subtypes can promote a cytokine storm but upregulation of coagulation factors could have some impact on cytokine activity (29). The dysregulation of coagulation factors is another clinical presentation SARS-CoV-2 which can affect homeostasis. Thrombin is a coagulation factor that is regulated by anti-thrombin. Infection with SARS-CoV-2 triggers an inflammatory response which reduces anticoagulants such as anti-thrombin 3 and induces coagulation mechanisms (21). This results in a lack of homeostasis

between procoagulants and anticoagulants which is a characteristic seen in patients with severe COVID-19.

There should be considerations for the possible predispositions, which could be one of the plausible explanations for the variation in severity of COVID-19 between individuals. There are several mechanisms within an individual that forms a predisposing environment for a cytokine storm and MAS in response to viral infection (22). For example, lower level of interferon class 1 (INF-1) response, accumulation of neutrophil extracellular traps (NET), and viral defense strategies to evade the immune response, as well as the reduced expression of viral removal in the presence of genetic variation plays a role in the explanation for the differences in severity experienced by patients. An example of a defense strategy that SARS-CoV-2 virus displays; is the synthesis of vesicles to protect the virus from the immune response while it undergoes viral replication. As a result, this strategy could increase the severity of the infection. (Soy et al., 2020) identified lower plasma concentrations of INF-1 and MAD5 are associated with severe COVID-19. Moreover, during the immune response to the viral invasion of the host cell, the MAD5 receptor binds to viral RNA which generates INF-1 (22). Therefore an individual with an inherited lower expression of MAD5 is more susceptible to developing severe COVID-19.

4 | LYMPHOPENIA: THE REDUCED LYMPHOCYTE COUNT.:

(Zhao et al., 2020) studies illustrate a lymphocyte count lower than $1.5 \times 10^9/L$ indicates a positive diagnosis for lymphopenia. Lymphopenia is an important clinical marker to assess the severity of COVID-19 as it's less laborious and extremely cost-effective during the process of up-scaling the assessment for diagnostic procedures. It is suggested that there is a lack of knowledge to assess the severity of disease during the early pathogenesis of the disease. Consequently, it could reduce the effective management of resources, the treatment strategy for COVID-19, and lead to a higher risk of mortality. Lymphopenia occurs early and is prognostic, which is potentially

associated with reduction of the CD4+ and some CD8+ T cells. This leads to imbalance of the innate/acquired immune response, delayed viral clearance, as well as hyperstimulation of macrophages and neutrophils.

Studies highlight patients with severe COVID-19 had a lower lymphocyte level than patients with mild symptoms (23). Additionally, patients with severe cases are usually associated with a higher risk of pneumonia and ARDS which is supported by (Huang and Pranata 2020) as they identified individuals showing severe COVID-19 symptoms had lower lymphocyte plasma levels and diagnosed with ARDS (26). Also, a study which compared the concentrations of lymphocytes between severe and non-severe cases, revealed that plasma lymphocyte level decreased more significantly in severe cases as opposed to non-severe cases (24). This highlights levels failed to decline as a result of an infection in mild cases. Additionally, lymphocyte levels of patients released from the hospital rose by 10% in severe cases (24). Conversely, lymphocyte levels increased more than 20% within patients suffering from more severe COVID-19. This reveals lymphocyte levels are more effected in severe occurrences which leads to the manifestation of lymphopenia.

Furthermore, clinical evidence showed factors such as high inflammatory mediators and lactic acid can influence the lymphocyte count upon infection of SARS-CoV-2. The process of infection by SARS-CoV-2 infects lymphocytes by binding to ACE2 receptors, which provides entry into the host lymphocyte and leads to apoptosis (24). Also, SARS-CoV-2 can infect organs responsible for the production of lymphocytes such as bone marrow. In events of cytokine storm, concentrations of interleukin-6 and TNF-alpha rise and induces cell death of lymphocytes. Additionally, high severity of infection is associated with abnormally elevated lactic acid concentration, which can prevent cytokinesis of lymphocytes in patients with underlying hyperlactic acid syndrome. Overall, upon infection of the SARS virus, it results in a lower lymphocyte count and lymphopenia.

Lymphopenia (having reduced numbers of lymphocytes in the blood) has been reported in severe cases

of COVID-19 in multiple studies, including drastic declines in CD4+ and CD8+ T cells as well as NK and B cells. A recent study by Takehiro et al., 2020 which examines immune response in covid-19 patients revealed that lymphocytes subsets such as T cells are abundant and terminally differentiated in female than male patients. Although, detailed phenotyping of T cells for naive T cells, central/effector memory T cell, follicular T cells, and regulatory T cells revealed no remarkable differences in the frequency of these subsets between sexes. However, it was observed that higher levels of CD38 and HLA-DR-positive activated T cells in female patients compared to male patients. Moreover, PD-1 and TIM-3 positive terminally differentiated T cells were more prevalent among female patients compared to male patients. Interestingly, these findings were seen in both CD4 and CD8 T cells, but the differences were more significant in CD8 T cells. Together, these findings suggests why male response are more severe to covid-19 than females.

However, studies that provide support for the association of lymphopenia with severe COVID-19 are based on large meta-analyses and retrospective studies which largely originate from China and poses some limitations. Disadvantages in COVID-19 research are due to studies being based on patients in a different stage of pathogenesis, the literature is not peer-reviewed and there is a lack of agreement in the cut-off point for lymphopenia (23). Although sample size considers changes in lymphocyte plasma levels during the pathogenesis of COVID-19, further investigations should use a larger sample. As a result, these factors could affect the objectivity of the findings. Equally, the current field also has a lack of sufficient evidence to support lymphopenia as a marker to assess severity. Therefore, results that form the basis of clinical management should be used with caution. To improve the investigation there should be more prospective results. On the other hand, more studies should investigate the length of time between the diagnosis of lymphopenia and the development of ARDS exhibited by patients. This would increase the understanding of the pathological changes that occur in severe infections (23).

5 | BIOINFORMATIC APPLICATIONS: ADVANCEMENT OF RESEARCH:

Bioinformatic tools can be used to facilitate COVID-19 research projects surrounding vaccine discovery and investigation of components responsible for an effective immune response to vaccines. It is crucial to uncover this mechanism as the components can be transferred to vulnerable individuals. Tools such as AI, machine learning, and large data collection software can be used to store and access big data for analysis and advance the understanding of the immune response during the pathogenesis of COVID-19 and the patient's recovery. Bioinformatic studies found white blood cells such as lymphocytes could be crucial for recovery and has applications in treating SARS-CoV-2. Recovery is associated with a change in antibodies that can be used to formulate vaccines and immunoglobulins to manage the infection (28). This finding was achieved through the use of RNA single-cell sequencing to observe changes in the translation of lymphocytes in the body during the recovery stage (28). Therefore, illustrates software can be used to monitor and analyse the immune response to identify patterns that can be manipulated to make vaccines.

So far through the applications of bioinformatics, there is critical evidence to show predisposing factors for cytokine storm being present in some individuals. This could imply variation in the immune response between individuals could be a major contributing factor for patients presenting a different level of severity. Thus, AI can aid in the exploration of this challenge which is supported by (Koff et al., 2020), who explained tools such as AI can assess the variation in the effectiveness of the immune response to vaccines in the elderly. Findings from this study can identify biomarkers and model the immune system of immunocompromised groups. Nevertheless, there would need to be a collaborative effort between experts within the field of math, computer science, and immunology. Ultimately, bioinformatics has many advantages as it can be used to improve the immune response in immunosuppressed individuals which could increase their survival rate from COVID-19, as these groups would have a higher vaccination rate. Moreover, AI algorithms can uncover a

range of immune responses to vaccines, target mechanisms behind the most effective immune reactions, and support the understanding of immune response to pathogens. On one hand, the data collected could help form a computer model of clinical trials which would lower the cost of research projects, increase the effectiveness of managing resources, and save time. This exemplifies how the application of AI and informatics have the potential to rapidly control COVID-19 transmission, treatment, mortality rates, and prepare society for another potential outbreak.

6 | CONCLUSION:

To conclude, the main characteristic of severe COVID-19 cases is identified to include cytokine storm and lymphopenia, angiotensin-converting enzyme 2 gene, as well as sex chromosomes. CS arises in environments consisting of accumulated interleukins and a dysregulated immune response which results in an abnormal low lymphocyte count and MAD-5 counts. Therefore, there will be hyper inflammation at the site of infection, on the epithelium which could lead to a manifestation of pneumonia and ARDS. These conditions are associated with severe COVID-19 cases of patients hospitalised in the ICU. Additionally, there is an absence of agreement in the lymphocyte count which would indicate lymphopenia.

Moreover, leveraging bioinformatics in COVID-19 research provides many benefits for the scientific community such as increasing data accessibility with cloud technology. Also, investigating immune responses to vaccines and treatments by utilizing computational modeling of the immune system during clinical trials.

Lastly, our study demonstrated novel information on various immune response in covid-19 patients that informed information on caused of severity in different sexes. Thus, researches should be channeled integrate sex as a biological variable in all stages, from fundamental research to preclinical drug development, clinical trials and epidemiological analyses. This will uncover novel features of the host immune response to SARS-CoV-2 thereby enhancing early

screening of critical illness, diagnosis and treatment of covid-19 and ultimately result in more equitable health outcomes.

7 | REFERENCES:

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