Review Article

Sexual Dimorphism in Patients with COVID-19: Review

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ABSTRACT

The world is facing its biggest global crisis in the1 form of the nCoV-19 pandemic. Females have long been supposed to have stronger immunity against all diseases including the viruses and nCoV-19 seems to be part of a larger spectrum. The causes of less prevalence and mortality rates in females could range from a multitude of factors like stronger innate immunity to sex chromosomes to steroid hormones. Females under being diploid X chromosome undergo XCI which leads to varied manifestations of many immunomodulatory genes. The lower prevalence of COVID-19 in females could be attributable to lesser ACE2 receptors, biallelic expression of TLR7, Ddx3x, CD40L and CXCR3, higher IFN's, exaggerated expression of NEMO, IRAK1, JAK-STAT pathway, the higher number of macrophages, enhanced Th1 response and higher circulating antibodies in females. The major causes of death in a COVID-19 case has been reported to be ARDS, hypokalemia, respiratory failure, and multiorgan failure due to immune dysfunction. The increased expression of IL-6, CXCL-10, MCP-1, MIP-1α, CCL-14, and CCL-23 appear to tilt the balance in males towards an increased N/L Ratio leading to cytokine storm and ACE2 down-regulation progressing to hypokalemia, hypotensive shock and ARDS. Apart from the various protective effects existing in females in preventing the above complications, there is an upregulation of P53 and FOXP3 gene and a pro-apoptotic response which increases the Treg cells trying to bring back the female body to homeostasis.

Key Words: Coronavirus, COVID 19, Immunity, Interleukins, X chromosome inactivation

INTRODUCTION

COVID-19 is the biggest global crisis for decades. Gender may not be at the forefront of people's mind but it should not be ignored"[1]. From Influenza pandemic of 1918, SARS of 2003, MERS of 2012, Zika virus of 2015 to COVID-19 all have a higher infectivity and fatality rate in males than in females[2], even though females constitute roughly 70% of the workforce in health sector[3] and are heavily involved in taking care of the sick and elderly. The observed pattern could be a reflection of behavioural or physiological differences between a male and a female. Behavioural, as in more foraging[2], reluctance towards hand hygiene, the lesser inclination for timely medical care or higher rates of alcohol and smoking in males. But even Italy and United Kingdom where the difference between the male and female smokers seems thinner had a higher number of deaths of male COVID cases.[4] It could also be due to under-reporting or less access to health care in females. Physiologically, it could be a stronger immu-nity of females, sex chromosome or the steroid hormones.[2] This article gives an insight into the physiological causes of gender disparity for the rapidly evolving n-CoV-19.

GENDER BIAS IN COVID-19

University of Miami Miller School of Medicine says men across the globe are at 3 times risk of dying in a hospital from COVID-19 as females.[5] Chinese Centre for disease control and prevention found the male to female ratio of COVID-19 cases in China to be 1.06:1 and the fatality rate of 2.8% for males whereas 1.7% for females.[6] JAMA published an article saying of 1591 COVID-19 cases in ICU, 82% were males[7] and the case fatality ratio of male: female was 3:1.[8] Public health information from New York, world's largest outbreak shows deaths rate as 39/10000 in females whereas 71/10000 in males due to COVID-19.[9] In Spain twice the men died due to COVID-19 as compared to females.[10] Similar pattern is

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mirrored in France, Germany, Iran and a few states of India. Maharashtra, the biggest epicentre of COVID-19 in India reported 39% female and 61% male cases and the death rates were 35% and 65% respectively.[11] Contrary to the above data, Ministry of Health and Family Welfare, South Korea has revealed 41% of COVID-19 cases are males compared to 51% females.[10]

IMMUNITY AND GENDER BIAS

Sex, a biological factor not only exerts itself on physiological and anatomical differences but also to immune effector cells. Sex differences in frequency and severity for many diseases from meningococcal meningitis to tuberculosis to hepatitis-B have long been pointed out.[2] However, is COVID-19 a part of a larger pattern in which males lose out at every age or are there some characteristic differences making the prevalence, severity and mortality lesser in females?

EFFECT OF SEX HORMONES

Circulating sex hormones engage in intense physiological crosstalk with the immune effector cells (Table 1).[12] All the major immune cells like T-cell, B-cell, NK-cells, dendritic cells and macrophages express estrogen receptors ERα and ERβ indicating that immune cells are partly controlled by female sex steroid hormones.[13] Testosterone is immunoinhibitory through upregulation of anti-inflammatory cytokine Interleukin (IL)-10[14] while estrogen is immunostimulant by upregulating TNFα (Tumor necrosis factor-alpha)[15] which helps to inhibit viral replication. Hormones also influence the regulation and modulation of the immune response and immune signalling pathways.[16] Thus, the male bias becomes apparent only after sexual maturation and female disease predisposition changed with fluctuating hormones.[17] But it was observed that the sex bias exists in prepubertal boys and girls as well as postmenopausal women and elderly males indicating the role of factors other than steroid hormones.[18]

EFFECT OF X CHROMOSOME AND XCI

X-chromosome has approximately 1100 genes, the majority of which are innate and adaptive immune-related, as compared to roughly 100 genes on the Y chromosome.[19] XCI (X-chromosome inactivation) is the process by which 1 X-chromosome is inactivated to balance the gene expression in a diploid X female to a haploid X male. Thus, any damaging effect will have a pronounced impact on males producing the sex bias of a disease. On the other hand, females being functional mosaics, always express the beneficial X linked polymorphism and are less vulnerable to deleterious mutations.[20] Roughly 15% of the genes, mostly immunomodula-

tors, located at the edges of the X chromosome, escape XCI in a female, leading to their elevated expression.[21,22] XCI, escape from XCI and XCI skewing (non-random inactivation where a chromosome is silenced in more than 75% of the cells[23]) may account for immune differences between the sexes. Female T cells, B cells and lymphocytes have biallelic expression as they undergo XCI escape leading to overexpression of immune-related genes.[24] Further, X linked control mechanisms like noncoding micro-RNAs targeting 30-50% of protein-coding genes and either suppress or degrade mRNA translation account for immunological differences between genders.[25]

WHY MALES ARE MORE PRONE FOR COVID-19?

The characteristics of invading organism and the host interactions are important contributing factors in the final production of sex bias of a disease. Looking at the pathogenesis and immune response of the nCoV-19, some strong characteristics in favour of the sex bias are discussed.

Expression of ACE2 Receptors

The inhaled SARS-CoV-2 likely binds to nasal epithelial cells especially, goblet cells and alveolar type 2(AT2) cells to ACE2 (Angiotensin-converting enzyme 2), a functional receptor for the virus through its protruding spike protein.[26] For SARS-CoV-2 entry into a host cell, it's S protein needs to be further cleaved by host cellular proteases TMPRSS2 (Transmembrane protease, serine2).[27] A study across 11 European countries has shown that men have higher ACE2 receptors in their blood than women.[28] Xiyi Wei et al. through single-cell RNA sequencing of human lung tissue revealed higher expression of ACE2 in males than females. The various causes for the discrepancy could be the presence of ACE2 genes on X-chromosome, which due to XCI is expressed in only 50% of the female cells. It was also found that the androgen receptor (AR) is co-expressed with ACE2 and TMPRSS2 and both ACE2 and TMPRSS2 were found to be positively correlated with AR not to mention that androgen expression is significantly high in males. The AR gene, that inhibits antibody production is also coded on X-chromosome and undergoes skewed XCI implicating lesser expression in females.[29] Thus, the lesser the landing site for SARS-CoV-2 the lesser was the prevalence in females. Smoking, which was identified as a risk factor for COVID-19 is more prevalent in males as compared to females.[30] Researchers have shown that apart from over expression of ACE2 in AT2 cells, an additional receptor for SARS-CoV-2, L-SIGN was found to be higher in former smokers.[31,32] Studies have depicted 1.4 times higher chances in smokers to have severe symptoms of COVID-19 and 2.4 times more likely to have ICU admissions.[3]

Role of Pattern Recognition Receptors (PRRS)

The entry of SARS-CoV-2 into the host cell is first encountered by the antigen-presenting cells (APC) mainly macrophages and dendritic cells which identify the single-stranded mRNA by various PRRs mainly RLR (RIG like Receptors), TLR 3,4,7,8(Toll-like Receptors) and NLR (NOD-like Receptors). Each of the PRRs induces a different biological response to subsequent protein activation for eg.TLR-4 recognises the outer S protein component of nCoV.[33,34] Studies show that in-vitro treatment of macrophages with testosterone causes a significant decrease in TLR-4 expression thus making male mice more susceptible to SARS-CoV.[35-37] PRR engagement triggers the production of proinflammatory cytokines and chemokines along with IFN-1 (Interferon type 1) which is critical to the induction of antiviral immune response. TLR-7 gene which elicits strong IFN-1 production evades XCI and has a biallelic expression in female B lymphocytes, monocytes and dendritic cells[38] thus providing better protection to females.

Role of Interferons (INF)

IFNβ was found to be a potent inhibitor of coronavirus and SAR-CoV-2 is much more sensitive to IFN treatment than SARS-CoV.[39] Clinical data indicate a reduction of vascular leakage in ARDS (Acute Respiratory Distress Syndrome) patients with IFNβ1a treatment.[40] IFN related genes are upregulated in females as Ddx3x gene necessary for IFN-1 production is located on X-chromosome and casts a dose-dependent expression in females who are functional mosaics versus haploid males.[33] IFNs also upregulates CD 73 (Cluster of Differentiation) in pulmonary endothelial cells which secrete anti-inflammatory adenosine helping in the maintenance of endothelial barrier function hence preventing ARDS. Again, the female hormone estrogen increases the production of IFNγ while testosterone suppresses it.[35]

Signalling Pathway of TLRs

PRR engagement to viral protein and IFN-1 leads to activation of intracellular signalling pathway NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells), through IRAK-1 (Interleukin-1 Receptor associated Kinase-1) and Myd88 (Myeloid Differentiation primary response 88) proteins leading to the production of proinflammatory cytokines.[41]NEMO (NFκB Essential modulator) is a protein which activates NFκB. Both NEMO and IRAK-1 are X-linked causing a higher expression in females. Testosterone inhibits NFκB while estrogen activates it through MyD88 which has ERα receptors.[25] IFN-1 and various pro-inflammatory cytokines activate the JAK-STAT (Janus kinases-signal transducer and activator of transcription proteins) pathway to initiate transcription of IFN stimulated genes (ISG) leading to suppression of viral replication. Studies have depicted the upregulation of JAK-STAT in female mice.[35]

Role of Innate Immunity

Innate immune system of females is stronger due to increased resident macrophages, higher activation of macrophages by IFN and enhanced phagocytosis by the macrophages as compared to males.[35] Low levels of female hormone 17-β estradiol also increase the levels of Fc receptors on resident macrophages whereas testosterone reduces the macrophage activation by reducing the expression as well as the sensitivity of TLR-4 receptors. NADPH oxidase complex in macrophages encoded by CYBB gene is present on X-chromosome. A defective gene severely affects the respiratory burst of macrophages, so even if the female carries a defective gene, still the products are expressed but not in males.[25]

Role of Adaptive Immunity

APCs through CD4+ T-cells stimulate the Th_1 cells which further stimulate CD8+ T-cells leading to T-cell dependant antibody development.[42] CD8+T cells have a role in directly attacking and killing virus-infected cells, in contrast to which CD4+ T cells prime both CD8+ T cells and B cells. Estrogen enhances Th_1 cell differentiation through IL-12 and TNF-α for IFN-1 mediated activity against the virus as compared to testosterone which enhances the Th_2 cells through IL-4 and IL-10 which are ineffective against SARS-CoV-19.[19]All antiviral genes are upregulated to a greater degree in activated female cytotoxic T-cells than in male and half of these genes have estrogen-responsive elements in their promoter region.[35] TLR-7 which helps in T-cell dependant differentiation of naïve B-cell into immunoglobulin secreting cells and is an important component of antibody-mediated immune surveillance against reactivation of endogenous retroviruses undergoes XCI escape and thus has a higher expression in females, supposedly increasing the antibody response.[43] Based on marker gene expression it was proved that the plasma cells were enriched in female COVID-19 patients.[29] CD40L (CD40 Ligand) which is required for T cell dependant B cell activation has a biallelic expression in females due to XCI escape.[24] Previous researches have elucidated that PPARs (Peroxisome proliferator-activated receptor gamma) in T-cells represses NFκB activity and IL-2 production in lymphocytes and these PPARs are abundant in naïve and activated male T-cells due to androgens as compared to females. So PPAR deficient T cells in females produced increased levels of IFNγ, TNFα and NFκB.[35] The above-mentioned elements lucidly explain the likely factors behind the higher prevalence of SARS-CoV-19 in males as compared to females.

CAUSES OF DETERIORATION OF PATIENTS

For about 80% of the infected patients the disease is mild and restricted to upper airways. The recruited cells clear the infection, immune response recedes and patient recovers but in about 20%, the virus reaches the AT2 cells

developing pulmonary infiltrates, severe lung disease[44]and even progresses to systemic pathology. A case report in Wuhan from 99 COVID-19 patients reveals that there was an increase in the total number of neutrophils and IL-6 in about 38%, 52% respectively and a 35% decrease of total lymphocytes.[45] Another study showed the cause of death as respiratory failure, shock, and ARDS in 94%, 81%, and 74% of cases respectively[46] and the fatality rate in males was 2.8% as compared to 1.7% in females.[47] 39 studies comprising 77932 COVID-19 patients, in China showed 53.3% males and 46.7% females and men had higher odds of developing severe cases compared to women (OR=0.63, 95% CI=1.28-2.06).[39] Karlberg et al. analysed 1755 SARS-CoV-2 patients and found the mortality rate in males higher than females (p<0.0001).[48] Jian et al. study on COVID-19 concluded that men and women had same prevalence but men cases tended to be more serious than women (P=0.035) and the number of men who died was 2.4 times that of women (70.3 vs 29.7% P=0.016).[49] A meta-analysis of 206,128 confirmed cases of COVID-19 found that even though there was no difference in the proportion of male and female patients, male patients had double the odds of requiring ICU treatment on admission (OR=2.5) and higher odds of death (OR=1.60).[50]

WHY IS FATALITY RATE OF COVID-19 HIGHER IN MALES?

The probable causes are elucidated below:

Significance of N/L Ratio

Neutrophils being double-edged sword have to be regulated, otherwise can lead to tissue damage. The more severe condition patients were in, the higher were their levels of cytokines, especially IL-6 which leads to neutrophil-mediated viral clearance.[45] Elevation of IL-6 (p<0.0001) levels was a major predictor of fatality in 150 confirmed cases of COVID-19.[51]A study conducted on death cases of COVID-19 showed a reduction of blood lymphocyte percentage as a most significant and consistent trend.[52] Sustained and substantial peripheral lymphopenia due to destruction of T-cells, preferably CD8^{+}cells associated with an increase in the neutrophil count at the site of infection leads to high N/L Ratio, seen in 80% of severe COVID-19 patients.[53,54] Researchers have confirmed that TNFα, IL-6, and other pro-inflammatory cytokines could induce lymphocyte deficiency.[55] CXCL(chemokine C-X-C motif ligand)-10, a potent chemoattractant to monocytes, macrophages and activated T cells in response to IFNγ could also lead to lymphopenia.[56,24] IL-6,7 and IL6 receptor, IL-6 ST were all found to be higher in a severe male patient as estrogen reduces neutrophil recruitment whereas testosterone increases it.[57,29] The low neutrophil recruitment in females could also be due to inhibitory effects of high estradiol levels on production of CXCL-8,10 and

MCP (Monocyte Chemoattractant protein)-1.[56] A randomised controlled trial of IL-6 blocker has been approved in patients with severe COVID-19 pneumonia.[57] miRNA 223, located on the X chromosome which limits the recruitment of neutrophils by downregulating the CXCL-2 and MIP (Macrophage inflammatory protein)-1α genes is higher in females due to XCI escape[58] and thus reducing the severity of disease in females. Figure 1 depicts the causes of high N/L ratio. A study found that postmenopausal women showed a greater risk of hospitalisation than non-menopausal women (RR=1.91, 95% CI=1.06-3.46) proving estradiol showed a protective effect against disease severity. Increased levels of IL-6 and IL-8 were found in severe COVID-19 cases (p=0.040, p=0.033) and higher levels of IL2R,6,8,10 were observed in patients who had death as outcome and estradiol levels are negatively correlated with IL2R, 6 and IL8 in luteal phase.[59]

IMPACT OF CYTOKINE STORM

Although the cytokines released, help the body to evade negative effects of pathogen, excessive release due to a dysfunctional immune response causes hyper inflammation and alveolar damage progressing to ARDS[60]. ARDS is the leading cause of mortality of COVID-19 patients.[51] A common phenomenon present in almost all severe cases was increased levels of IL-2, IL-6, IL-7, IL-8, IL-12, IL-18, GCF, MCP-1, MIP-1α, TNFα, CXCL-8, CXCL-9, CXCL-10 and IFN.[53,44] release of the virus from airway epithelial cells causes pyroptosis and vascular leakage. IL-1β, an important cytokine released during pyroptosis is highly increased in SARS-CoV-2 infection.[61] A series of local inflammation starts with increased levels of IL6, IL-1β, TNF and MCP-1 which further attracts monocytes and neutrophils. These CD14^{+} and CD16^{+} expressing monocytes further produce chemoattractants like MIP-1α, TNFα and CXCL-10 leading to a positive feedback cytokine storm which progresses to ARDS and multiorgan failure.[62,63,64] The first autopsy of a COVID-19 patient highlighted the presence of monocytes in the lungs along with low levels of activated T cells in peripheral blood.[65] Whether direct virus-induced damage due to presence of ACE-2 receptors at various sites in the body or systemic cytokine storm or synergistic effects of both contributes to multiorgan dysfunction of severe COVID-19 patient needs to be addressed.[66] IL-6, the main proinflammatory factor to induce the cytokine storm inhibits Th1 and favours Th17, contributing to severe lung pathology and mortality from coronavirus.[67]Male COVID-19 patient exhibited a higher cytokine level of CCL (chemokine C-C motif ligand)-14, CCL-23 (monocyte, macrophage chemotactic factors) and IL-6, 7, 18 predisposing men to develop cytokine storm earlier.[29] CXCL-10, another important factor to develop cytokine storm was found to be higher in male patients and its receptor CXCR-3 has a biallelic expression in females due to XCI escape further protecting the females.[24,56]

Estrogen suppresses monocyte-macrophage recruitment by downregulating the MCP-1 expression during inflammation and inhibiting TLR-4 mediated NFκB activation in macrophages.[68] Gonadectomised male mice treated with estrogen exhibited reduced levels of TNFα and MCP-1.[37] Contrarily, a study revealed higher MCP-1 level in females which recruited inflammatory dendritic cells to the tracheal epithelium, conducive to virus control.[29,69] CCL-3,4 which inhibits HIV-1 from entering CD4+ T-cells and CXCL16 which maintains homeostasis of resident memory T-cells in the respiratory tract[70] were lower in male than female patients, which also could be the cause of differential outcome.[29,71]

DOWNREGULATION OF ACE-2 RECEPTORS

Attachment of the nCoV to the ACE2 receptor causes its downregulation leading to elevated levels of Angiotensin-2 and increase the stimulation of Angiotensin-2 type-1 receptor further progressing to RAS dysfunction, hypokalemia, hypotensive shock and lung and cardiovascular injuries.[72-75] A study on 109 severe COVID-19 patients illustrated that 80% had hypokalemia due to increase in angiotensin-2 levels[76]. Another study highlighted the positive correlation of severe COVID-19 cases with hypokalemia (95%CI=-0.18 to -0.07mmol/L).[77] Researchers have shown that estrogen helps in upregulating the ACE2 receptors and thus protecting female patients from progressing to ARDS or multiorgan failure. Studies have also shown that ACE2 has a cardioprotective and ARDS protective role.[78]

APOPTOSIS VERSUS NECROSIS

IFN-1, highly expressed in females, apart from combating the viral attack, upregulated the p53 gene leading to apoptosis of the virally infected cells. While necrotic cell death spreads viral particles, apoptosis limits the virus. Progesterone promotes pro-apoptotic prostaglandin (PGE_2) while testosterone inhibits PGE_2.[79,80] Testosterone also reduces the expression of FOXP-3 gene while estrogen, through its upregulation causes an increase in Treg cells thereby inhibiting the cytokine storm[81] and working towards maintenance of homeostasis. It was also found that the CD4+ T-cells and Treg cells within the total population of T-cells are higher in females whereas males had a higher proportion of CD8+ T-cells.[44] Another study suggested that estrogen signalling in females directly suppresses the SARS-CoV replication via effects on cellular metabolism.[37] Figure 2 shows the probable causes of reduced prevalence in a female COVID 19 patient.

CONCLUSION

Where almost all the discussions going around nCoV-19 epidemic are gender blind, the need of the hour is accurate and completely sex-disaggregated data to understand the nuances of infection, complications and death risks of COVID-19 affected males and females differently. Since this public health emergency is not gender-neutral its time that the policy decisions are made keeping gender bias in mind to fight the COVID-19 pandemic and in evaluation of effectiveness of vaccines.

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Table 1: Effect of sex steroid hormones on immune effector cells

| ESTROGEN	TESTOSTERONE
Increased Th1 response triggered by increased IL-12	Increased Th2 response triggered by increased IL- 4
Increased production of IFNγ and TNFα due to IL-12	Reduced type 1 IFN production due to IL-10
Supresses IL-10	Increases IL-10
Enhances macrophage activation	Downregulates macrophage activation by reduced expression of TLR-4
Reduced neutrophil recruitment	Increased neutrophil recruitment
Increased IgG and IgM production and remain longer in circulation	Decreased IgG and IgM production
Increased Treg cells due to upregulation of FOXP3 expression	Decreased Treg cells due to downregulation of FOXP3 expression
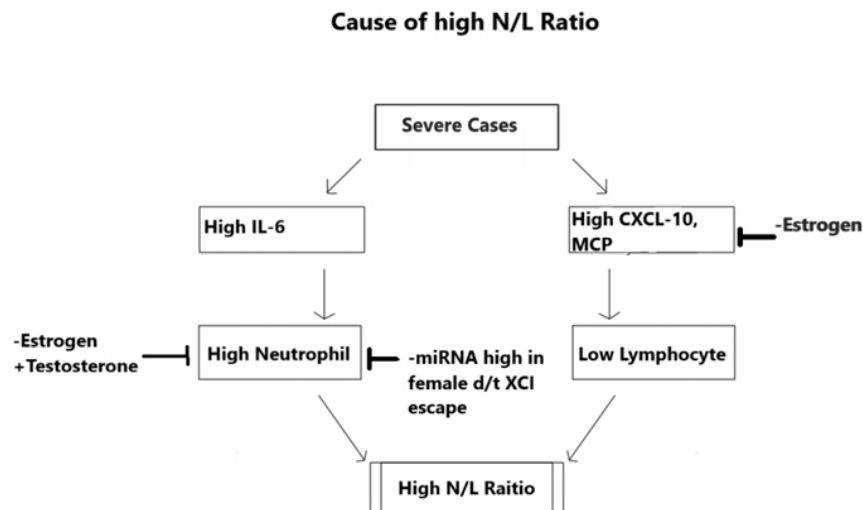
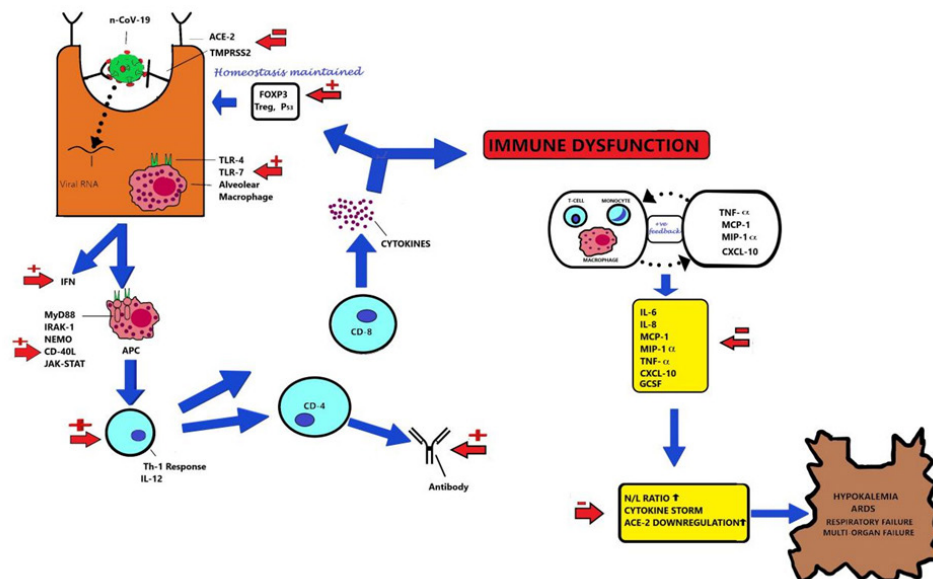**Figure 1:** Shows causes of high N/L Ratio in severe cases of COVID 19.

Figure 2: Summary of probable causes of reduced prevalence and severity in a female COVID-19 patient.