Association of severity and mortality of Covid-19 cases among acute kidney injury and sexual dimorphism

Mukul Kumar Singh1 · Mayank Jain2 · Hari Shyam2 · Dinesh Kumar Sahu3 · Archana Mishra2 · Pratap Shankar4 · Shailendra Kumar2 · Vishwajeet Singh1

Received: 28 December 2021 / Accepted: 24 February 2022 / Published online: 6 March 2022 © The Author(s), under exclusive licence to Springer Nature B.V. 2022

Abstract

Introduction The outbreak of coronavirus disease 2019 (Covid-19) severely impacted global health and economic status. The native receptor-ligand interaction of Angiotensin-converting enzyme 2 (ACE2) and S protein induces host cell pathogenesis via immunosuppression.

Material and Methods The emerging evidence reports the sex disparity in Covid-19 induced mortality rate which affects abundantly men population. Although the biological interaction of Covid-19 with receptor upregulates the viral genome protein interactions and initiates the predictive multiorgan failure followed by acute kidney injury (AKI) in Covid-19 infected male population.

Conclusion Besides, the knowledge and lessons learned from the study depict that cellular and molecular links may explain the risk and severity of Covid-19 and AKI in the male population and lead to management of Covid-19 induced AKI. Therefore, this review explored the pathways associated with the pathogenesis of two diseased conditions with sex disparity.

Keywords AKI · Covid-19 · Sex-disparity · Immunosuppression · Pathogenesis

Introduction

In March 2020, the World Health Organization (WHO) declared SARS-CoV-2 a pandemic that impacted the lives of every human being. SARS-CoV-2 is a new coronavirus that outbreak emerged in Wuhan, China. And the disease caused by this virus is known as coronavirus disease 2019 (Covid-19). The identified risk factors associated with Covid-19 are asymptomatic respiratory infection to severe pneumonia and comorbidities like Obesity, Diabetes Mellitus, and Hypertension. These risk factors have also been reported during Acute Kidney Injury (AKI), which suggests that AKI might specifically contribute to the severity of Covid-19 (Fig. 1). Also, various studies have already been reported that the rate of Covid-19 infection is relatively similar in both males and females but the mortality rate quite higher (1.5 to 2.5 times) in males [1]. Studies suggested that the sex-biased difference in hormonal and immune response may be responsible for the higher mortality in the male population. Similarly, sexual dimorphism is also common in AKI. In the case of AKI, males were 2.19 times higher chance to develop AKI than females [2].

The co-relation among two diseased groups and the sternness of Covid-19 [3–5] and AKI progression are also higher in the male population [2, 6–10]. Chan et al., reported 46% of Covid-19 patients have a higher rate of AKI infection and shows patients with aging and comorbidities can become more critical for the Covid-19 and devastating for AKI [11, 12]. This review summarized scientific knowledge associated with recent progress and research updates in the context

1 Department of Urology, King George’s Medical University, Chowk, Lucknow, Uttar Pradesh 226003, India
2 Department of Thoracic Surgery, King George’s Medical University, Lucknow, UP 226003, India
3 Super Speciality Paediatric Hospital & Post Graduate Teaching Institute, Noida, UP 201301, India
4 Department of Centre for Advance Research, King George’s Medical University, Lucknow, UP 226003, India
of current understanding in a particular field: the cellular, Hormonal and immune system association and pieces of evidence for sex disparity between two diseased conditions Covid-19 and AKI; considerable therapeutic options available for Covid-19 and patients with Covid-19 induced AKI.

**Covid-19 and Cellular association with AKI crosstalk**

**Involvement of ACE2 receptor**

Angiotensin-converting enzyme 2 (ACE2) protein expression was observed in lung alveolar epithelial cells, small intestine epithelial cells, vascular endothelium coronary & intrarenal vessels, and in renal tubular epithelium. Whereas, in many organs, the ACE mRNA is abundant and exhibits expression in the testis, renal, cardiovascular, and gastrointestinal tissues[13]. There is a significant correlation in the pathogenesis of Covid-19 ACE2 to two biological functions. First is the catalytic conversion of Ang-I and Ang-II helps to protect organs and acts as the receptor for the entry of SARS-CoV-2 into cells [14]. Second is the ACE-2 induced Covid-19 entry through Spike protein encodes by S gene. The ligand-receptor interaction facilitates the acquisition of the ACE-2 expressing host cells. Since the mechanism of AKI in Covid-19 patients involved cellular damage associated with an invasion of ACE2 mediated Covid-19 entry and affected hemodynamic factor and cytokine storms [15, 16]. ACE is located on the X-chromosome, which shows its sex-biased expression and enables the Ang-I and Ang-II to be catalyzed. Anti-androgens were used to study pharmacological modulation of TMPRSS2 and ACE2 expression in human and animal lungs by Baratchian et al. There was no evidence of increased TMPRSS2 expression in male lungs in either human or mice. The expression of AR and ACE2 in mice and human lungs, on the other hand, differs by gender. ACE2 expression was higher in males smoker’s lungs than female smokers’ lungs [17]. In addition, one of Takahashi and colleague’s most noteworthy findings is that immune responses to SARS-CoV-2 differ between sexes. The viral loads, antibody titres, plasma cytokines, and blood cell phenotypes of patients with mild COVID-19 who had not received immunomodulatory medicines were compared by sex. Male patients have a higher induction of non-classical monocytes and higher plasma levels of innate immune cytokines. Females has more robust T cell activation than males during SARS-CoV-2 infection. Inadequate T cell responses in men led to worse disease outcomes than women [18]. Furthermore, in a study, males had higher mortality rate than females. Pro-inflammatory cytokines (IL-6, IL-8, MCP-1) were shown to be higher in serious male patients than females, but they were lower in moderate or control patients. Females had higher levels of the anti-inflammatory cytokine IL-10 than males in moderate group compared to the control group. Males exhibited much more circulating neutrophils and monocytes than females at 7 and 14 days, whereas females had significantly more B cells [19]. These manuscripts addressed the sex differences in Covid-19 in the context of the ACE2 gene and immunoresponse. Gagliardi et al., study reported an up-regulation of ACE2 influenced by estrogen and proposed the protective role in women with Covid-19 infection, stressing our view of the importance of ACE2 in sexually dimorphic behavior of Covid-19. Therefore, the
expression of ACE-2 in the kidney induces pathological alteration associated with Covid-19 which causes chronic kidney injury followed by acute kidney injury (AKI).

**Co-relation of the Transmembrane Protease Serine 2 (TMPRSS2) and CD147**

The expression of TMPRSS2 is another factor linked with Covid-19 and AKI in infected patients [20]. The fusion of SARS-CoV-2 and host cell membrane is associated with the cleavage activity of viral S-protein by serine protease-mediated TMPRSS2 activity [21]. The differential expression of TMPRSS2 was also found in various organs, which raises the susceptibility to infection with Covid-19. Also, TMPRSS2 is present in various organ tissues such as kidney, heart, liver, Intestinal epithelial cells, prostate, epididymis [22, 23].

The studies demonstrated pathological alteration coupled with Covid-19 expressed the glycosylated CD147 transmembrane on the basolateral and luminal surfaces of renal epithelial cells and identified as the primary binding site for S- protein followed by Covid-19 [24]. Besides, CD147 is associated as a ligand for E-selectin, thus neutrophil recruitment in the renal tubule indicates ischemic injury and renal fibrosis attributable to matrix metalloproteinase (MMP) and hyaluronan expression [25–27]. The co-relation between TMPRSS2 and CD147 was established in Covid-19 patients who were usually associated with Covid-19 entry in host cells [28]. These findings indicate that the expression of viral entry proteins poses a major risk to AKI in viral infected patients. However, chronic follow-up for patients with renal function failure should be needed for the management of Covid-19 infection and a particular treatment strategy for Covid-19.

**Gonadotropin hormone signaling**

**Androgen-induced immune dysregulation**

Androgen is the principal circulating hormone with a masculine character in male and androgen-induced signaling, which plays a pivotal role in the progression and proliferation of the prostate gland followed by prostate cancer (CaP) [29]. Androgen deprivation therapy (ADT) in CaP caused a hypogonadal syndrome that is critically destructive to renal function and contributes to AKI. ADT alleviation of testosterone leads to metabolic alteration, such as hyperglycemia, dyslipidemia, and elevated fat mass in the renal system results in obstruction in glomerular function. In addition, ADT neutralizes the vasodilation effect of testosterone on a renal vessel with a negative outcome and concluded androgen-induced acute kidney injury [30]. Studies have shown that prostate cancer patients who have undergone ADT have a lower risk of infection with SARS-CoV-2 compared to patients that have not receive ADT [31]. It is proposed that ADT may be helpful to Covid-19 and, as this disease progresses rapidly, ADT action may be beneficial at the initial stage of viral infection and not in later stages [32].

The studies demonstrate the immunosuppressive and affecting role of androgen in the immune system by influencing the expression of immune-associated genes against the infection (as shown in Fig. 2). The expression of androgen in the hematopoietic progenitor would cause the innate immunity of macrophages, neutrophils, monocytes, mast cells, and eosinophils to be affected. In addition, myeloid-derived suppressor cells (MDSCs) are regulated by neutrophils and monocytes with potent T cell-mediated testosterone suppression response in male population [33, 34]. Whereas the depletion of testosterone-induced MDSC in females is a beneficial result against the pathogenic infection of the immune system [35]. In vivo experiments indicate that androgen exposure downregulates the surface level of major histocompatibility complex (MHC) and human leukocyte antigen (HLA) and reduces the proliferation, differentiation, and activation of T Cells by inhibiting cytokine production in dendritic cells [36, 37].

Androgen has an immune suppressive effect and responds to renal dysfunction. This indicates that the aggregation of immunosuppressive agents could increase the AKI in the male population with Covid-19 and result in an increased mortality rate. In addition, androgen ablation in male mice shows increased immune cells efficiency for prostate cancer [38]. Sex mediated difference in innate and adaptive immunity was thus correlated with the severity and susceptibility of two diseases.

**Estrogen influenced immune system**

Estrogen is expressed differentially in reproductive and immune systems. The estrogen induced activity followed by estrogen receptor Estrogen receptor-α (Erα) and Erβ [39]. The expression of estrogen receptor subsequently present in human immune cells, including B & T lymphocytes, mast cells, macrophages, dendritic cells, monocytes, and natural killer cells [40]. Expression of ERs is cell-specific as the predominant form in CD4 T cells was found to be ERα, and ERβ was the predominant form in B cells [41]. Estrogen-induced signaling and upregulation affect the proliferation and progression of epithelial cells and become a major oncogenic driver for breast cancer. In addition, ER alpha has been reported in human monocytes with higher expression in postmenopausal women and males than in premenopausal females, sex and age-specific expression [41]. While in male and female T and B cells, there was no difference in ER expression, the
authors indicated that sex differences in immune response may not be a direct estrogen influence but may be indirect by gonadotropin-releasing hormones [41]. Though Males and females are under the influence of complex hormonal milieu. Estrogen has an immunoenhancing effect. However, the immune defense function of estrogen can be anticipated by altered the activity of immune cells in the adaptive immune system. Whereas the oncogenic role of androgen in males is correlate with estrogen. Since the innate response induced by dendritic cells, macrophages were functionally active in XX individuals. The estrogen hormone controls the function of cytokines by inhibiting pro-inflammatory and anti-inflammatory Interleukin-6 (IL-6), IL-4, (Tumor necrosis factor) TNF-α [42] and alteration of CD16 [43, 44]. In comparison, women over 70 years of age have a higher level of natural killer cells than males, which is the influence of estrogen in XX individuals. As a result, estrogen-induced signaling initiates a protective role against the sex-specific AKI [45]. In brief, females have strong innate and adaptive immune responses to AKI. Elevated transcriptional activation of immune response genes on X-chromosomes and sex-specific steroids such as estrogens, helps to facilitate to AKI in females [46].

**Testosterone-influenced immune system**

Testosterone has an immunosuppressive effect, [47] which suggests a decrease response to influenza vaccine [48]. Testosterone has been shown to inhibit T helper cell differentiation [49] and positively associated with the viral load of Venezuelan equine encephalitis virus in macaques [50]. The correlation between low testosterone and high B cells results in a positive response of vaccine in females rather than males who showed B lymphopoiesis [48]. Since the inhibitory influence of testosterone-induced B cells effect depends on bone marrow stromal cells where TGFβ upregulation inhibits interleukin (IL-6) expression and suppresses the B lymphopoiesis [51–53]. Although Covid-19 patients without immunomodulatory medicines and after study of Fig. 2 Sex disparity in Covid-19 patients: the illustration demonstrates the regulation of Androgen with androgen receptor (AR) and shows immunosuppressive response followed by comorbidities. Whereas infected female has an immune protective role associated with estrogen receptor interaction and upregulates the immunoprotective genes.
their SARS-CoV-2 (Immunoglobulin-G) IgG antibody, and plasma cytokines have been reported in both sex, the identification of robust T cells activation in infected females of Covid-19 and an increased rate of SARS-CoV-2 IgG antibody compared to males is reported [18, 54].

**Viral clearance and testis**

The testis is an immune-privileged organ since it cannot develop immune response both allo- and auto-antigenic. This function is essential to keep the immune response from immunogenic germ cells. The unregulated immune system can respond to sperm cells known as meiotic germ cell antigen (MGCA), and cause infertility with the surface antigen [55]. It can activate innate immunity when the organ is invade by microbial pathogens. It is known that viruses such as HIV, cytomegalovirus, and mumps infect the testicles and cause testicular disorders [56]. In addition, from semen samples, viruses like Zika, Ebola, and Marburg have been isolated and are believed to be sexually transmitted [57]. Shastri et. Al found that males in families required more time than other female family members to recover from Covid-19. The investigators observed that, at both mRNA and protein level 55, the testis had a high expression of ACE2 [58]. The authors indicated that it should be possible for the coronavirus to enter the testis and therefore lead to a higher viral load, requiring more time for viral clearance.

**Sex-biased expression of Toll-like receptors (TLR's)**

Male and female virus infection shows a different type of innate and adaptive immune response. In the case of acute HIV females have less viral RNA and higher mortality occurred by hepatitis in males [59]. X-chromosome contains several genes involved in pattern recognition receptors. Toll-like receptors TLR's express differently in males and females. TLR3, TLR7 is female-biased while TLR2 and TLR4 are male-biased [58]. TLR3, TLR7, and TLR9 recognize the viral RNA and DNA to protect against viral infections. TLR2 and TLR4 recognize the PAMPs on the cell wall to protect against bacterial infections [47]. The early antiviral response of the innate sensing of SARS-CoV-2 genetic material by the PRR including TLR7 may be a significant step [60]. Since TLR7 escapes X chromosome inactivation and is triggered by estrogen [59], females may have a better strategy to combat an early SARS-CoV-2 attack.

**Covid-19 and AKI induced inflammation**

Potential and stable change in gene expression including histone acetylation and deacetylation, chromosome compaction, DNA methylation, and non-coding sequence of RNA [61]. These modifications are associated with increased production of inflammatory markers like complement protein 3, Tumor growth factor-β (TGFβ), monocyte chemoattractant protein 1 (MCP-1) which ultimately induce epithelial to mesenchymal transition and cause renal fibrosis [62]. The AKI induces cellular and molecular damage and initiates a robust inflammatory response with susceptibility to oxidative stress [63]. The necrotic renal cells activate damage-associated molecular pattern (DAMP) and toll-like receptors (TLR) in epithelial and endothelial cells. The secretion of chemokines (CXCL1, CXCL8, CCL2, and CCL5) promote macrophage dependent inflammatory response in AKI patients [64]. Therefore, the change in expression of TNF-α, IFN-γ, IL-6, C3, C5a, IL-23, IL-4, IL-8 should be stabilized in systematic and renal inflammation for tissue repair and homeostatic status in existing two diseased conditions [64–67]. Though the significantly higher level of IL-6, IL-8 is linked with Covid-19 infection [68]. In addition, IL-6, IL-4, and MCP-1 contribute to the immune system initiated by the elevated TNF-α in infected patients [69, 70].

The high rate of morbidity and mortality of Covid-19 in the male population and the potential association of inflammation and AKI will substantially show the impact of inflammatory and anti-inflammatory cytokines TNF-α, (Interferon-γ) IFN-γ, IL-6, C3, C5a, IL-23, IL-4, IL-8 on AKI and helps to understand the pathways and impact of Covid-19 on AKI.

The current knowledge suggests that Covid-19 adversely affects the urinary system with special emphasis on the kidney [71]. The emerging evidence from autopsy studies shows the Covid-19 induced viral nephropathy induced by ACE-2 expression on proximal tubular cells of the podocyte, hyper-inflammatory, and cytokine storms induced at the primary site of Covid-19 infection [72, 73]. Therefore, Covid-19 inflammation at the adjacent organ may induce AKI, where inflammation is the driver of AKI.

It is important to note that ACE2 and TMPRSS2 are expressed by the kidney and may be a direct target of infection with Covid-19 that could result in inflammatory response [74, 75]. Conceptually, this can occur through the arteries that feed the kidney via systemic circulation, or viaducts responsible for glomerular filtration, which may have a deleterious effect on AKI. In addition, it is conceivable that the kidney could be a direct target of Covid-19-associated inflammation and adverse pathogenesis of Covid-19, based on a recent study showing that ACE2 and TMPRSS2 are expressed in the kidney.

Although these theories are less well known at present, in the sense of AKI, they suggest possible threats and routes of infection. They will need molecular validation and research
in-depth. The possible biological differences between males and females (hormone signaling, immunological) and behavioral differences that lead to sex divergence in response to Covid-19 and the inferred relation between Covid and AKI.

Therapeutics for COVID-19 and COVID-19 induced AKI in patients:

Therapeutic intervention

The current pandemic exemplified the twentieth century’s technological advantage. In the age of the pandemic, the focus has been on the development of potential vaccine, including the repurposing of existing drugs such as BCG, ACE2 Inhibitors Remdesivir, hydroxychloroquine, Tocilizumab, Sarilumab, Favilavir, and others. Despite this, over 1400 clinical trials for therapeutic interventions are now underway around the globe. More than 16 vaccines have been approved in various countries (Table 01), and over 100 vaccines are in clinical trials. These vaccines are derived using many technologies, such as adenovirus vaccine, adjuvanted protein subunit vaccine, inactivated vaccine, mRNA-based vaccine and so on. Whereas, apart from the above-cited vaccine, BNT162b2 is mRNA-based drug with 95% effectiveness against the Covid-19 in clinical trials (NCT04368728) [76]. Another vaccine CoronaVac (NCT04456595), (NCT04582344), (NCT04508075), [77, 78] BBIBP-CorV (NCT04560881), and Wuhan Institute of Biologicals (ChiCTR2000031809) had completed phase 3 trial with highly efficient protection against the Covid-19 by neutralizing the antibody response and demonstrated immunogenicity. The clinical trial study of SputnikV (NCT04530396) (NCT04564716) inside and outside of Russia shows a 91.4% effectiveness by the mechanism of a non-replicating viral factor in interim trials against Covid-19.

Furthermore, the long-term output of vaccine is unclear in younger aged and primarily targeted immune-compromised patients. Although, the vaccine response towards mutated stains could be attenuated and leads to propagating the outbreak [79]. Additionally, the time of exposure and their effect, availability, manufacturing, and storage of a vaccine are an issue in course of the pandemic[80]. Although, a drug with the potentiality to combat Covid-19 infection is listed in Table 1.

AKI treatment and Covid-19

The therapeutic approach of ACE2 inhibitor (ACEI) and angiotensin II receptor blocker (ARB) in AKI could inhibit the ACE2 pathways and avoid mitochondrial dysfunction associate with acute tubular necrosis, glomerulopathy, and protein exposure in bowman’s capsule of nephron [100]. Though the adjustment of body fluid coupled with ACE2 volume responsiveness will reduce the pulmonary edema and subsequently in AKI patients [101]. Therefore, the repurposed of ACEI/ARB as a potential therapeutic for the management of AKI in Covid-19 patients. The above treatment suggestion proposes that the severity of Covid-19 can be deprived by ACEI/ARB. Several studies showed the patients with Covid-19 on ACEI/ARB were having positive clinical outcomes [102]. Additionally, on the available scientific evidence, we hypothesized that the patients with AKI having ACEI/ARB therapy falls under the low-risk category of Covid-19 infection and attenuate the severity.

Conclusion

Based on the existing scientific evidence, we concluded that female have a strong immune system, which aids in the virus’s easy escape from the body, whereas males have lesser innate antiviral immune responses. As a result, females are more likely to develop an autoimmune disorder or have a poor response to immunization, as well as higher immunological pathogenesis. While the role of estrogen and protective effect is emphasized in an age-dependent manner. Because the vast majority of the severe ill and deceased women are postmenopausal, estrogen expression levels in them are expected to be comparable to men’s level. Furthermore, we hypothesize AKI patients on ACE inhibitor therapy have a lower risk of Covid-19-induced mortality. Though approximately 75% of the Covid-19 mortality rate occurs at the age of 65 years. Therefore, the trial of potential and repurposed drugs help to combat Covid-19 with a positive impact on induced AKI. Though, the clinical management of Covid-19 poses significant challenges in decision making and inhibits mitigating the risk of AKI in viral infected patients. This review concluded the knowledge about treatment and overlaps of Covid-19 with AKI. Additionally, the lack of standard AKI therapy in a set of Covid-19 is largely unclear and requires in-depth knowledge. Therefore, urologists and nephrologists need
an initiative for the research and preparedness during and post-pandemic era to consider the effect on the renal system in the surge of higher mortality and morbidity against Covid-19 induced AKI.

Acknowledgements The Author’s were thankful to the Vice Chancellor, King George’s Medical University, Lucknow, for their support and guidance. In addition Mr. Mayank Jain is grateful to the University Grant Commission (UGC) for providing him the Maulana Azad National Fellowship.

Table 1 List of authorized/approved vaccines for COVID-19

| S.No | Vaccine Name                  | Mechanism                  | Clinical Trial                     | Origin/ Sponsors                                                                 | References |
|------|------------------------------|----------------------------|------------------------------------|---------------------------------------------------------------------------------|------------|
| 1    | BNT162b2                     | mRNA-Based Vaccine         | NCT04368728                        | CanSino Biologics                                                               | [81]       |
| 2    | Covaxin (BBV152)             | Inactivated Vaccine        | NCT04471519                        | Bharat Biotech; National Institute of Virology                                | [82]       |
| 3    | Spikevax mRNA-1273           | mRNA Based Vaccine         | NCT04470427                        | Moderna, BARDA, NIAID                                                           | [83]       |
| 4    | Sputnik V                    | Non-replicating Viral vector | NCT04530396, NCT04564716         | Gamaleya Research Institute, Aceliena Contract Drug Research, and Development   | [84]       |
| 5    | CoronaVac                    | Inactivated Vaccine        | NCT04456595, NCT04582344          | Sinovac                                                                         | [85, 86]   |
| 6    | BBIBP-CorV                   | Inactivated Vaccine        | ChiCTR2000034780, NCT04560881     | Beijing Institute of Biologicals                                                | [87, 88]   |
| 7    | EpiVacCorona                 | Peptide Vaccine            | NCT04527575                        | Federal Budgetary Research Institution State Research Center of Virology and Biotechnology | [89]       |
| 8    | AZD1222 Vaxzevrina and Covishield | Replication Deficient viral Vector Vaccine | NCT04516746                      | The University of Oxford; AstraZeneca; IQVIA; Serum Institute of India          | [90]       |
| 9    | BCG                          | Live Attenuated Vaccine    | NCT04327206                        | University of Melbourne and Murdoch Children’s Research Institute; Radboud University Medical Center; Faustman Lab at Massachusetts General Hospital | [91, 92]   |
| 10   | COVID-19 Vaccine Janssen      | Non-Replicating Viral vector | NCT04505722                        | Johnson & Johnson                                                               | [93]       |
| 11   | BBIBP-CorV/NVSI-06-07        | Inactivated vaccine        | NCT04560881                        | Sinopharm and Beijing Institute of Biological Products                         | [94]       |
| 12   | WIBP-CorV                    | Inactivated vaccine        | ChiCTR2000031809                   | Sinopharm and the Wuhan Institute of Virology                                  | [87]       |
| 13   | Sputnik Light (rAd26)        | Recombinant adenovirus vaccine | NCT04741061                        | The Gamaleya Research Institute in Russia and the Health Ministry of the Russian Federation | [95, 96]   |
| 14   | NVX-CoV2373 (Nuvaxovid; Covovax in India) | Recombinant nanoparticle vaccine | NCT04611802                         | Novavax; CEPI, Serum Institute of India                                         | [97]       |
| 15   | ZF2001 (ZIFIVAX)             | Recombinant vaccine        | NCT04833101                        | China’s Anhui Zhifei Longcom Biopharmaceutical and the Institute of Microbiology of the Chinese Academy of Sciences | [98]       |
| 16   | Convidicea (PakVac, Ad5-nCoV) | Recombinant vaccine (adenovirus type 5 vector) | NCT04526990                         | China’s CanSino Biologics                                                      | [99]       |

Author Contributions Corresponding and First Author: Substantial contributions to the conception or design of the work and the acquisition; Drafting the work or revising it critically for important intellectual content. Co-Authors: Agreement related to the accuracy or integrity of any part of the work are appropriately investigated and resolved; Agreement to be accountable for all aspects of the work.

Funding Not applicable.

Data Availability Not applicable.
References

1. /50organization. TGH. The Sex, gender and COVID-19 project [updated 10 February 2022]. COVID-19 sex-disaggregated data tracker. https://globalhealth5050.org/the-sex-gender-and-covid-19-project/.
2. Neugarten J, Golestanian L, Kolhe NV (2018) Sex differences in acute kidney injury requiring dialysis. BMC Nephrol 19(1):131
3. Lim S, Bae JH, Kwon HS, Nauck MA (2021) COVID-19 and diabetes mellitus: from pathophysiology to clinical management. Nat Rev Endocrinol 17(1):11–30
4. Huang Y, Lu Y, Huang YM, Wang M, Ling W, Sui Y et al (2020) Obesity in patients with COVID-19: a systematic review and meta-analysis. Metab Clin Exp 113:154378
5. Pranata R, Lim MA, Huang I, Raharjo SB, Lukito AA. Hyper-tension is associated with increased mortality and severity of disease in COVID-19 pneumonia: A systematic review, meta-analysis and meta-regression. Journal of the renin-angiotensin-aldosterone system : JRAAS. 2020;21(2):147032032092699.
6. Szczek AC, Granger CB, Dasta JF, Amin A, Peacock WF, McCullough PA et al (2010) Acute kidney injury and cardiovascular outcomes in acute severe hypertension. Circulation 121(20):2183–2191
7. Patschan D, Muller GA (2016) Acute kidney injury in diabetes mellitus. Int J Nephrol 2016:6232909
8. Danziger J, Chen KP, Lee J, Feng M, Mark RG, Celi LA et al (2016) Obesity, acute kidney injury, and mortality in critical illness. Crit Care Med 44(2):328–334
9. Arany I, Grifoni S, Clark JS, Csongradi E, Marc C, Juncos LA (2011) Chronic nicotine exposure exacerbates acute renal ischemic injury. Am J Physiol Renal Physiol 301(1):F125–F133
10. Singh V, Singh MK (2021) Acute kidney injury in COVID-19: a brief review. Indian J Surg 23:1–5
11. Nuttall FQ (2015) Body mass index: obesity, BMI, and health: a critical review. Nutr Today 50(3):117–128
12. Chan L, Chaudhary K, Saha A, Chauhan K, Vaid A, Zhao S et al (2021) AKI in hospitalized patients with COVID-19. J Am Soc Nephrol 32(1):151–160
13. Hamming I, Timens W, Bulthuis ML, Lely AT, Navis G, van Goor H (2004) Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. J Pathol 203(2):631–7
14. Zhang H, Penninger JM, Li Y, Zhong N, Slutsky AS (2020) Angiotensin-converting enzyme 2 (ACE2) as a SARS-CoV-2 receptor: molecular mechanisms and potential therapeutic target. Intensive Care Med 46(4):586–590
15. Kudose S, Batal I, Santoriello D, Xu K, Barasch J, Peleg Y et al (2020) Kidney biopsy findings in patients with COVID-19. J Am Soc Nephrol 31(9):1959–1968
16. Akilesh S, Nast CC, Yamashita M, Henriksen K, Charu V, Troxell ML et al (2020) Multicenter clinicopathologic correlation of kidney biopsies performed in COVID-19 patients presenting with acute kidney injury or proteinuria. Am J Kidney Dis 77(1):82–93
17. Baratchian M, McManus JM, Berk MP, Nakamura F, Mukhopadhyay S, Xu W et al (2021) Androgen regulation of pulmonary AR, TMPRSS2 and ACE2 with implications for sex-discordant COVID-19 outcomes. Sci Rep 11(1):11130
18. Takahashi T, Ellington MK, Wong P, Israelow B, Lucas C, Klein J et al (2020) Sex differences in immune responses that underlie COVID-19 disease outcomes. Nature 588(7837):315–320
19. Qi S, Ngwa C, Morales Scheihing DA, Al Mamun A, Ahnstedt HW, Finger CE et al (2021) Sex differences in the immune response to acute COVID-19 respiratory tract infection. Biol Sex Differ 12(1):66
20. Pan XW, Xu D, Zhang H, Zhou W, Wang LH, Cui XG (2020) Identification of a potential mechanism of acute kidney injury during the COVID-19 outbreak: a study based on single-cell transcriptome analysis. Intensive Care Med 46(6):1114–1116
21. Brestle D, Heindl MR, Limburg H, Van Lam van T, Pilgram O, Moultouen H et al (2020) TMPRSS2 and furin are both essential for proteolytic activation of SARS-CoV-2 in human airway cells. Life Sci Alliance. https://doi.org/10.26508/lsa.202000786
22. Dong M, Zhang J, Ma X, Tan J, Chen L, Liu S et al (2020) ACE2, TMPRSS2 distribution and extrapulmonary organ injury in patients with COVID-19. Biomed Pharmacother 131:110678
23. Zhang H, Kang Z, Gong H, Xu D, Wang J, Li Z et al (2020) The digestive system is a potential route of 2019-nCov infection: a bioinformatics analysis based on single-cell transcriptomes. bioRxiv. 2020.2020.01.30.927806
24. Wang K, Chen W, Zhou Y-S, Lian J-Q, Zhang Z, Du P et al (2020) SARS-CoV-2 invades host cells via a novel route: CD147-spike protein. bioRxiv. 2020.2020.03.14.988345
25. Kato N, Yuzawa Y, Kosugi T, Hobo A, Sato W, Miwa Y et al (2009) The e-selectin ligand basigin/CD147 is responsible for neutralophil recruitment in renal ischemia/reperfusion. J Am Soc Nephrol 20(7):1565–1576
26. Kato N, Kosugi T, Sato W, Ishimoto T, Kojima H, Sato Y et al (2011) Basigin/CD147 promotes renal fibrosis after unilateral ureteral obstruction. Am J Pathol 178(2):572–579
27. Chueh TL, Zheng CM, Hou YC, Lu KC (2020) Novel evidence of acute kidney injury in COVID-19. J Clin Med 9(11):3547
28. Wang K, Chen W, Zhang Z, Deng Y, Lian JQ, Du P et al (2020) CD147-spike protein is a novel route for SARS-CoV-2 infection to host cells. Signal Transduct Target Ther 5(1):283
29. Dai C, Heemers H, Sharifi N (2017) Androgen signaling in prostate cancer. Cold Spring Harbor Perspect Med 7(9):a030452
30. Lapi F, Azoulay L, Niazi MT, Yin H, Benayoun S, Suisa S (2013) Androgen deprivation therapy and risk of acute kidney injury in patients with prostate cancer. Jama 310(3):289–296
31. Montopoli M, Zumerle S, Vettor R, Rugge M, Zorzi M, Cata-prano CV et al (2020) Androgen-deprivation therapies for prostate cancer and risk of infection by SARS-CoV-2, a population-based study (N = 4532). Ann Oncol 31(8):1040–5
32. Sharifi N, Ryan CJ (2020) Androgen hazards with COVID-19. Endocr Relat Cancer 27(6):E1–E3
33. Youn JI, Collazo M, Shalova IN, Biswas SK, Gabriovich DI (2012) Characterization of the nature of granulocytic myeloid-derived suppressor cells in tumor-bearing mice. J Leukocyte Biol 91(1):167–81
1. Tacke RS, Lee HC, Goh C, Courtney J, Polyaek SJ, Rosen HR et al (2012) Myeloid suppressor cells induced by hepatitis C virus suppress T-cell responses through the production of reactive oxygen species. Hepatology 55(2):343–353

2. Der E, Dimo J, Trigunaite A, Jones J, Jorgensen TN (2014) Gr1+ cells suppress T-dependent antibody responses in (NZB x NZW) F1 male mice through inhibition of T follicular helper cells and germinal center formation. J Immunol 192(4):1570–1576

3. Paharkova-Vatchkova V, Maldonado R, Kovats S (2004) Estrogens-Der E, Dimo J, Trigunaite A, Jones J, Jorgensen TN (2014) Gr1+ cells suppress T-dependent antibody responses in (NZB x NZW) F1 male mice through inhibition of T follicular helper cells and germinal center formation. J Immunol 192(4):1570–1576

4. Drake CG, Doody AD, Mihalyo MA, Huang CT, Kelleher E, Ravi S et al (2005) Androgen ablation mitigates tolerance to a prostate/prostate cancer-restricted antigen. Cancer Cell 7(3):239–249

5. Nilsson S, Makeka S, Treuter E, Tujague M, Thomsen J, Andersson G et al (2001) Mechanisms of estrogen action. Physiol Rev 81(4):1535–1565

6. Kovats S (2015) Estrogen receptors regulate innate immune cells and signaling pathways. Cell Immunol 294(2):63–69

7. Phiel KL, Henderson RA, Adelman SJ, Elloso MM (2005) Differential estrogen receptor gene expression in human peripheral blood mononuclear cells. ImmunoL Lett 97(1):107–113

8. Liu H, Liu K, Bodenner DL (2005) Estrogen receptor inhibits interleukin-6 gene expression by disruption of nuclear factor kappaB transactivation. Cytokine 31(4):251–257

9. Khan D, Ansar AS (2015) The immune system is a natural target for estrogen action: opposing effects of estrogen in two prototypical autoimmune diseases. Front Immunol 6:635

10. Liao ZH, Huang T, Xiao JW, Gu RC, Ouyang J, Wu G et al (2019) Estrogen signaling effects on muscle-specific immune responses through controlling the recruitment and function of macrophages and T cells. Skeletal Muscle 9(1):20

11. Meister I, Manilla-Munoz E, Leon-Cachon RBR, Paniagua-Rodriguez M, Garschagen S et al (2020) SexXY chromosomes and the immune system: reflections after a comparative study. Biol Sex Differ 11(1):3

12. Taneya V (2018) Sex hormones determine immune response. Front Immunol 9:1931

13. Furman D, Hejblum BP, Simon N, Jojic V, Dekker CL, Thiebaut R et al (2014) Systems analysis of sex differences reveals an immunosuppressive role for sex hormones in the response to influenza vaccination. Proc Natl Acad Sci USA 111(2):869–874

14. Kissick HT, Sanda MG, Dunn LK, Pellegrini KL, On ST, Noel JK et al (2014) Androgens alter T-cell immunity by inhibiting T-helper 1 differentiation. Proc Natl Acad Sci USA 111(27):9887–9892

15. Muclhenbein MP, Cogswell FB, James MA, Koterski J, Ludwig GV (2006) Testosterone correlates with Venezuelan equine encephalitis virus infection in macaques. Virol J 3(3):19

16. Olsen NJ, Gu X, Kovacs WJ (2001) Bone marrow stromal cells mediate androgenic suppression of B lymphocyte development. J Clin Invest 108(11):1697–1704

17. Tamayo E, Alvarez P, Merino R (2018) TGFbeta superfamily members as regulators of B cell development and function-implications for autoimmunity. Int J Mol Sci 19(12):3928

18. Gubbels Bupp MR, Jorgensen TN (2018) Androgen-induced immunosuppression. Front Immunol 9:794

19. Zeng F, Dai C, Cai P, Wang J, Xu L, Li J et al (2020) A comparison study of SARS-CoV-2 IgG antibody between male and female COVID-19 patients: a possible reason underlying different outcome between sex. J Med Virol 92(10):2050–2054

20. Zhao S, Zhu W, Xue S, Han D (2014) Testicular defense systems: immune privilege and innate immunity. Cell Mol Immunol. 11(5):428–37

21. Dejuq N, Jegou B (2001) Viruses in the mammalian male genital tract and their effects on the reproductive system. Microbiol Mol Biol Rev MMBR. 65(2):208–31

22. Salam AP, Horby PW (2017) The Breadth of Viruses in Human Encephalitis. Emerg Infect Dis 23(11):1922–1924

23. Pradhan A, Olsson PE (2020) Sex differences in severity and mortality from COVID-19: are males more vulnerable? Biol Sex Differ 11(1):53

24. Klein SL, Flanagan KL (2016) Sex differences in immune responses. Nat Rev Immunol 16(10):626–638

25. Scully EP, Haverfield J, Ursin RL, Tannenbaum C, Klein SL (2020) Considering how biological sex impacts immune responses and COVID-19 outcomes. Nat Rev Immunol 20(7):442–447

26. Goldberg AD, Allis CD, Bernstein E (2007) Epigenetics: a landscape takes shape. Cell 128(4):635–638

27. Rodriguez-Romo R, Berman N, Gomez A, Bobadilla NA (2015) Epigenetic regulation in the acute kidney injury to chronic kidney disease transition. Nephrology 20(10):736–743

28. Chen GY, Nunez G (2010) Sterile inflammation: sensing and reacting to damage. Nat Rev Immunol 10(8):826–837

29. Bolisetty S, Agarwal A (2009) Neutrophils in acute kidney injury: not neutral any more. Kidney Int 75(7):674–676

30. Kurt C, Panzer U, Anders HJ, Rees AJ (2013) The immune system and kidney disease: basic concepts and clinical implications. Nat Rev Immunol 13(10):738–753

31. Anders HJ, Schaefer L (2014) Beyond tissue injury-damage-associated molecular patterns, toll-like receptors, and inflammasomes also drive regeneration and fibrosis. J Am Soc Nephrol 25(7):1387–1400

32. Rabb H, Griffin MD, McKay DB, Swaminathan S, Pickers P, Rosner MH et al (2016) Inflammation in AKI: Current Understanding, Key Questions, and Knowledge Gaps. J Am Soc Nephrol 27(2):371–379

33. Ulhac ZS, Soraya GV (2020) Interleukin-6 as a potential biomarker of COVID-19 progression. Med Maladies Infect 50(4):382–383

34. Chen Y, Wang J, Liu C, Su L, Zhang D, Fan J et al (2020) IP-10 and MCP-1 as biomarkers associated with disease severity of COVID-19. Mol Med 26(1):97

35. Del Valle DM, Kim-Schulze S, Huang HH, Beckmann ND, Nirenberg S, Wang B et al (2020) An inflammatory cytokine signature predicts COVID-19 severity and survival. Nat Med 26(10):1636–1643

36. Ahmadian E, Hosseiniany Khatibi SM, Razi Soofiyani S, Abedi-Selter, Kokki H, Takala et al (2019) Sex differences in immune responses and COVID-19 outcomes. Nat Rev Immunol 20(7):442–447

37. Santoriello D, Khairellah P, Bomback AS, Xu K, Kudose S, Batal I et al (2020) Postmortem kidney pathology findings in patients with COVID-19. J Am Soc Nephrol 31(9):2159–2167

38. Sharma P, Uppal NN, Wancchoo R, Shah HH, Yang Y, Parikh R et al (2020) COVID-19-associated kidney injury: a case series of kidney biopsy findings. J Am Soc Nephrol 31(9):1948–1958

39. Maksimowski N, Williams VR, Scholey JW, Atkinson JM, Scholey JW, Williams VR (2020) Kidney injury: a case series of kidney biopsy findings. J Am Soc Nephrol 31(9):1948–1958

40. Wysocki J, Lores E, Ye M, Soler MJ, Battle D (2020) Kidney injury: a case series of kidney biopsy findings. J Am Soc Nephrol 31(9):1948–1958

41. Skeletal Muscle 9(1):20

42. Frausto GA, Carrion-Alvarez D, Ruiz-Rodriguez CO et al (2020) Androgen-induced immunosuppression. Front Immunol 9:794

43. Kotransky J, Lores E, Ye M, Soler MJ, Batelle D (2020) Kidney injury: a case series of kidney biopsy findings. J Am Soc Nephrol 31(9):1948–1958

44. Wysocki J, Lores E, Ye M, Soler MJ, Battle D (2020) Kidney injury: a case series of kidney biopsy findings. J Am Soc Nephrol 31(9):1948–1958
receptor blocker: implications for COVID-19. J Am Soc Nephrol 31(9):1941–1943
76. Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurman A, Lockhart S et al (2020) Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. N Engl J Med 383:2603–2615
77. Palacios R, Patino EG, de Oliveira PR, Conde M, Batista AP, Zeng G et al (2020) Double-Blind, Randomized, Placebo-Controller Phase III Clinical Trial to Evaluate the Efficacy and Safety of treating Healthcare Professionals with the Adsorbed COVID-19 (Inactivated) Vaccine Manufactured by Sinovac - PROFISCOV: a structured summary of a study protocol for a randomised controlled trial. Trials 21(1):853
78. Gao Q, Bao L, Mao H, Wang L, Xu K, Yang M et al (2020) Development of an inactivated vaccine candidate for SARS-CoV-2. Science (New York, NY) 369(6499):77–81
79. Tseng CT, Shrama E, Iwata-Yoshikawa N, Newman PC, Garron T, Atmar RL et al (2012) Immunization with SARS coronavirus vaccines leads to pulmonary immunopathology on challenge with the SARS virus. PLoS ONE 7(4):e35421
80. Lurie N, Saville M, Hatchett R, Halton J (2020) Developing Covid-19 vaccines at pandemic speed. N Engl J Med 382(21):1969–1973
81. Sahin U, Muik A, Derhovanessian E, Vogler I, Kranz LM, Vormehr M et al (2020) COVID-19 vaccine BNT162b1 elicits human antibody and TH1 T cell responses. Nature 586(7830):594–599
82. Ella R, Vadrevu KM, Jogdand H, Prasad S, Reddy S, Sarangi V et al (2021) Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine, BBV152: a double-blind, randomised, phase 1 trial. Lancet Infect Dis 21(5):637–646
83. Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R et al (2021) Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. N Engl J Med 384(5):403–416
84. Li YD, Chi WY, Su JH, Ferrall L, Hung CF, Wu TC (2020) Coronavirus vaccine development: from SARS and MERS to COVID-19. J Biomed Sci 27(1):104
85. Xia S, Zhang Y, Wang Y, Wang H, Yang Y, Gao GF et al (2021) Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine, BBIBP-CorV: a randomised, double-blind, placebo-controlled, phase 1/2 trial. Lancet Infect Dis 21(1):39–51
86. Tanriover MD, Doganay HL, Akova M, Guner HR, Azap A, Akhan S et al (2021) Efficacy and safety of an inactivated whole-virion SARS-CoV-2 vaccine (CoronaVac): interim results of a double-blind, randomised, placebo-controlled, phase 3 trial in Turkey. Lancet 398(10296):213–222
87. Al Kaabi N, Zhang Y, Xia S, Yang Y, Al Qahtani MM, Abdulrazzaq N et al (2021) Effect of 2 inactivated SARS-CoV-2 vaccines on symptomatic COVID-19 infection in adults: a randomized clinical trial. JAMA 326(1):35–45
88. Ahmed S, Khan S, Imran I, Al Mughairib F, Sheikh FS, Hussain J et al (2021) Vaccine development against COVID-19: study from pre-clinical phases to clinical trials and global use. Vaccines 9(8):836
89. Poland GA, Ovssyanikova IG, Kennedy RB (2020) SARS-CoV-2 immunity: review and applications to phase 3 vaccine candidates. Lancet 396(10262):1595–1606
90. Falsey AR, Sobieszczuk ME, Hirsch J, Sproule S, Robb ML, Corey L et al (2021) Phase 3 safety and efficacy of AZD1222 (ChAdOx1 nCoV-19) Covid-19 vaccine. N Engl J Med 385(25):2348–2360
91. Pittet LF, Messina NL, Gardiner K, Orsini F, Abruzzo V, Bankier S et al (2021) BCG vaccination to reduce the impact of COVID-19 in healthcare workers: Protocol for a randomised controlled trial (BRACE trial). BMJ Open 11(10):e052101
92. Singh MK, Jain M, Shyam H, Shankar P, Singh V (2021) Associated pathogenesis of bladder cancer and SARS-CoV-2 infection: a treatment strategy. Viruses 32(4):613–5
93. Sadoff J, Gray G, Vandebosch A, Cardenas V, Shukarev G, Grinsztejn B et al (2021) Safety and efficacy of single-dose Ad26.COV2.S vaccine against Covid-19. N Engl J Med 384(23):2187–201
94. Wang H, Zhang Y, Huang B, Deng W, Quan Y, Wang W et al (2020) Development of an inactivated vaccine candidate, BBIBP-CorV, with potent protection against SARS-CoV-2. Cell 182(3):713–21
95. González S, Olszewicki S, Salazar M, Calabria A, Regairaz L, Marín L et al (2021) Effectiveness of the first component of Gam-COVID-Vac (Sputnik V) on reduction of SARS-CoV-2 confirmed infections, hospitalisations and mortality in patients aged 60–79: a retrospective cohort study in Argentina. eClinicalMedicine 40:101126
96. Dolzhikova IV, Gushchin VA, Shehebyakov DV, Tsybin AN, Shchetinin AM, Pochtovy AA et al (2021) One-shot immunization with Sputnik Light (the first component of Sputnik V vaccine) is effective against SARS-CoV-2 Delta variant: efficacy data on the use of the vaccine in civil circulation in Moscow. medRxiv. 2021.2021.10.08.21264715
97. Dunkle LM, Kotloff KL, Gay CL, Añez G, Adelglass JM, Barrat Hernández AQ et al (2021) Efficacy and safety of NVX-CoV2373 in adults in the United States and Mexico. N Engl J Med 386(6):531–543
98. Zhao X, Zheng A, Li D, Zhang R, Sun H, Wang Q et al (2021) Neutralization of recombinant RBD-subunit vaccine ZF2001 elicited antisera to SARS-CoV-2 variants including Delta. bioRxiv. 2021.2021.07.15.452504
99. Halperin SA, Ye L, MacKinnon-Cameron D, Smith B, Cahn PE, Ruiz-Palacios GM et al (2022) Final efficacy analysis, interim safety analysis, and immunogenicity of a single dose of recombinant novel coronavirus vaccine (adenovirus type 5 vector) in adults 18 years and older: an international, multicentre, randomised, double-blind, placebo-controlled phase 3 trial. Lancet 399(10321):237–248
100. Larsen CP, Bourne TD, Wilson JD, Saqqa O, Sharshir MA (2020) Collapsing glomerulopathy in a patient with COVID-19. Kidney Int Rep 5(6):935–939
101. Matthy MA, Aldrich JM, Gotts JE (2020) Treatment for severe acute respiratory distress syndrome from COVID-19. Lancet Respir Med 8(5):433–434
102. Yehualashet AS, Belachew TF (2020) ACEIs and ARBs and their correlation with COVID-19 infection in adults: a randomized controlled phase III clinical trial. JAMA 326(1):35–45
103. Yehualashet AS, Belachew TF (2020) ACEIs and ARBs and their correlation with COVID-19: a review. Infect Drug Resist 13:3217–3224

Publisher’s Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.