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REVIEW

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

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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

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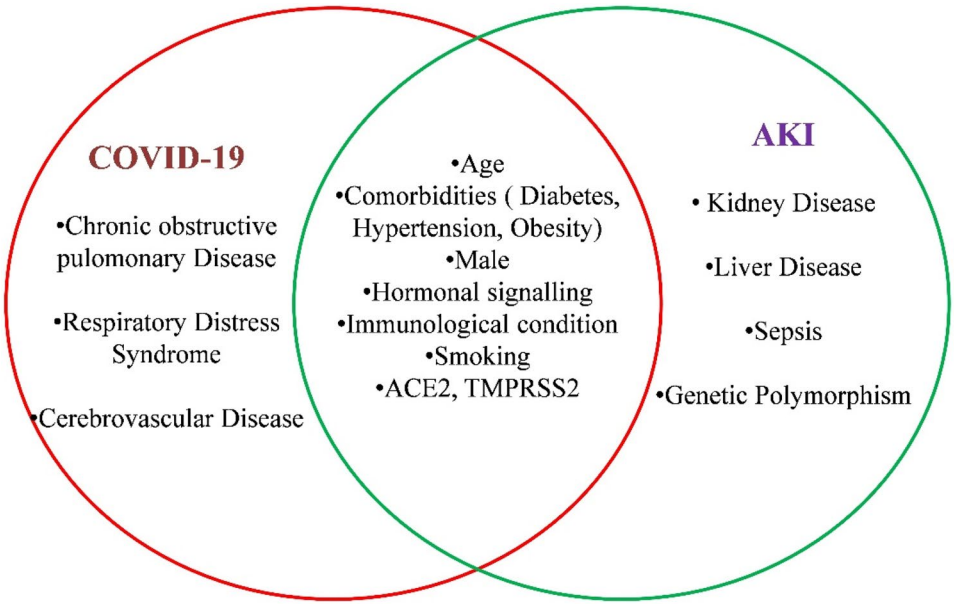

Fig. 1 Risk factors associated with acute kidney injury and COVID-19 in infected patients

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 mouse 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 patientsFemales 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, wereas 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 ACE-2 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

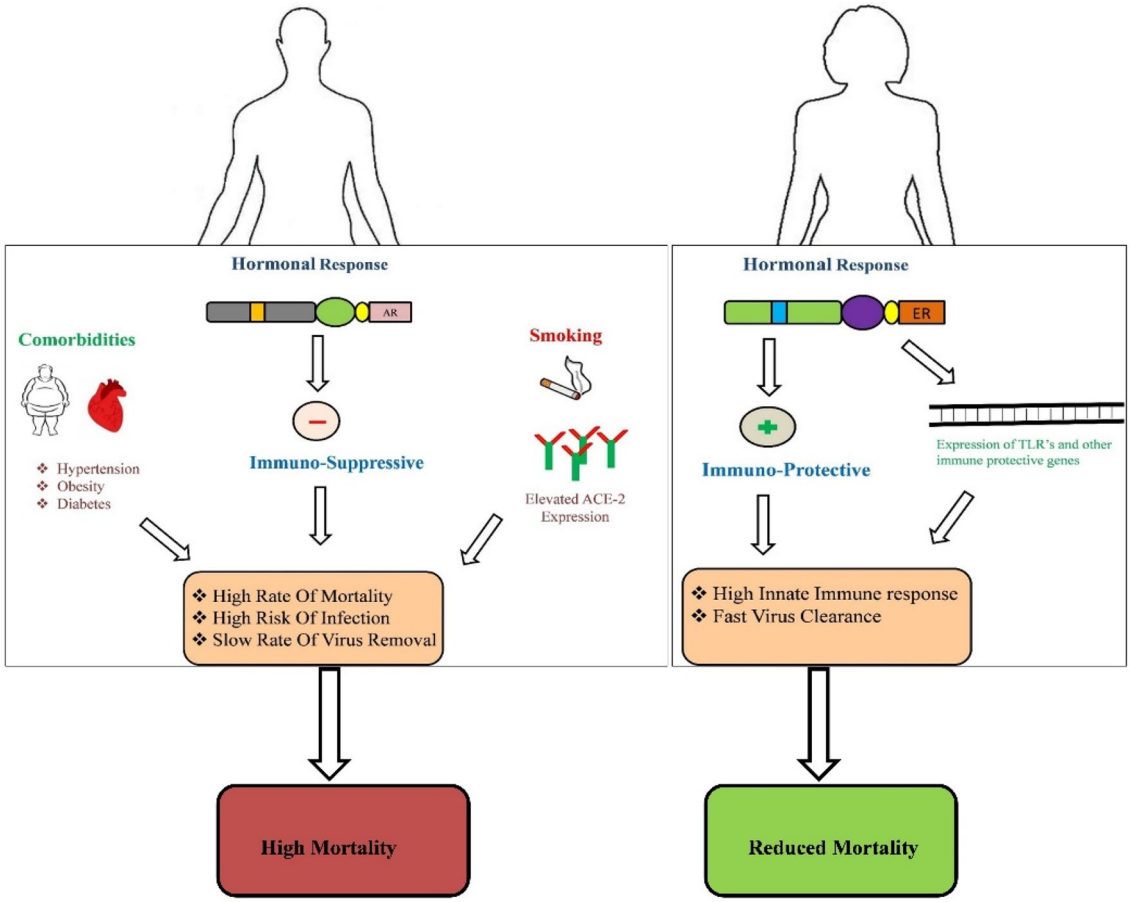

Fig. 2 Sex disparity in Covid-19 patients: the illustration demonstrates the regulation of Androgen with androgen receptor (AR) and shows immunosuppressive response followed by comorbidities. Whereas infected female has an immune protective role associated with estrogen receptor interaction and upregulates the immunoprotective genes

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 co-relate 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

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 invaded 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-ϒ, 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-ϒ) IFN-ϒ, 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, hyperinflammatory, 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% effectivity 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

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, Acellena 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 Vaxzevria 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 JNJ-78436735	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]

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.

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