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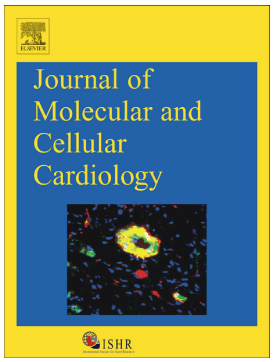

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Sex differences underlying preexisting cardiovascular disease and cardiovascular injury in COVID-19

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Abstract

The novel 2019 coronavirus disease (COVID-19), resulting from severe acute respiratory syndrome coronarvirus-2 (SARS-CoV-2) infection, typically leads to respiratory failure in severe cases; however, cardiovascular injury is reported to contribute to a substantial proportion of COVID-19 deaths. Preexisting cardiovascular disease (CVD) is among the most common risk factors for hospitalization and death in COVID-19 patients, and the pathogenic mechanisms of COVID-19 disease progression itself may promote the development of cardiovascular injury, increasing risk of in-hospital death. Sex differences in COVID-19 are becoming more apparent as mounting data indicate that males seem to be disproportionately at risk of severe COVID-19 outcome due to preexisting CVD and COVID-19-related cardiovascular injury. In this review, we will provide a basic science perspective on current clinical observations in this rapidly evolving field and discuss the interplay sex differences, preexisting CVD and COVID-19-related cardiac injury.

Keywords

Sex differences; cardiovascular; COVID-19; ACE2; arrhythmia; thrombosis

OUTLINE

1. Introduction

The novel 2019 coronavirus disease (COVID-19) results from severe acute respiratory syndrome coronarvirus-2 (SARS-CoV-2) infection and typically afflicts the lungs, with severe cases leading to acute respiratory distress syndrome[1]. Although the respiratory system is the major organ system affected by SARS-CoV-2, cardiovascular complications should not be overlooked by healthcare workers and basic scientists. In particular, acute myocardial injury, cardiac arrhythmias and microvascular dysfunction and thrombosis are reported to contribute to a large proportion of COVID-19 deaths[2–7].

Patients with pre-existing cardiovascular disease (CVD) do not appear to be more prone to SARS-CoV-2 infection since the prevalence of CVD in COVID-19 cases is consistent with the high prevalence in the general population[5,6,8,9]. However, pre-existing CVD is among the most common risk factors associated with hospitalizations, elevated cardiac injury biomarkers and death of COVID-19 patients[4,10,11]. As such, it is plausible that pre-existing CVD may exacerbate the course of disease and mortality in COVID-19 patients by promoting cardiovascular injury including myocardial damage, arrhythmias and microvascular dysfunction and thrombosis. Additionally, the pathogenic mechanisms of COVID-19 disease progression itself may be associated with the development of cardiovascular injury, which increases the risk of in-hospital death[12,13].

While there is a robust body of evidence elucidating sex differences in CVD, sex disparities in COVID-19 are becoming more apparent as well[14]. Interestingly, mounting data also indicate that individuals with higher risk of severe COVID-19 outcome due to preexisting CVD and COVID-19-related cardiovascular injury include a disproportionate number of males. In this review, we will discuss sex differences in the interplay between preexisting CVD, COVID-19 severity, and COVID-19-related cardiac injury by providing a basic science perspective based on the current literature in this rapidly evolving field.

2. Sex differences in preexisting cardiovascular disease, risk factors and COVID-19

As the clinical data surrounding COVID-19 infection and mortality rates continues to become more robust, a staggering trend is becoming apparent: COVID-19 positive males suffer worse disease progression and have a higher rate of mortality than females despite having a similar rate of infection[15]. The first published study investigating sex differences in the COVID-19 cases in China reports that men are more likely to experience serious illness and are 2.4 times more likely to die from COVID-19 while the average age of mortality and rate of infection remains the same for both sexes[15,16].

Sex differences in COVID-19 result from a complicated interplay between biological and societal influences, including preexisting CVD. Hypertension and history of CVD, both already known to increase COVID-19 severity and mortality[17], display strong sex differences with males exhibiting a higher prevalence of disease compared to age-matched women, prior to menopausal years[18,19]. On the other hand, women experience relatively worse outcomes of ischemic heart disease compared with men[20]. In HF, the overall lifetime risk is similar between men and women, there are marked sex differences in the variations of this condition, with males being predisposed to HF with reduced ejection fraction (HFrEF) and females to HF with preserved ejection fraction (HFpEF)[21]. In cardiac arrhythmias, the age-adjusted incidence of atrial fibrillation and Brugada syndrome is lower in women compared with that in men, whereas atrioventricular reentry tachycardia and cardiac events in long QT syndrome are more prevalent in adult females compared to males[22]. Lastly, male sex is an independent risk factor for various thrombotic events such as myocardial infarction, venous thromboembolism and thrombotic

stroke[23]. In this section, we highlight sex differences in preexisting CVD and how they may contribute to the striking sex differences found in COVID-19 mortality.

2.1. Sex hormones and chromosomes in CVD

Males exhibit increased risk of CVD compared to age-matched women, prior to menopausal years[18,19]. These data indicate that individuals more at risk of severe COVID-19 outcome due to pre-existing CVD include a disproportionate number of males.

The increased prevalence of CVD in males is multifactorial and well-studied with biological variables including sex hormones and their receptors as well as sex chromosomes. As detailed in a previous review from our group, the protective effects of estrogen have been well documented over the past few decades and may help explain why females of premenopausal age have lower incidence of CVD when compared to males[24,25]. Exerting its effects through both genomic and non-genomic pathways, estrogen has been shown to ward off CVD through its effects on vasculature, cardiomyocytes and cardiac fibroblasts to promote vasodilation, angiogenesis, and cardiomyocyte survival while reducing cardiac fibrosis and oxidative stress[24]. More recently, the role of sex chromosomes has been implicated in the sex differences found in CVD as well[26]. Sex chromosomes, which differ between males (XY) and females (XX), can impart sex differences in disease through altered expression of genes encoded by the X and Y chromosomes[27]. Strikingly, studies that examined the effects of sex chromosome complement (XX or XY) in the absence of sex hormones reveal that XX chromosome complement increases the risk of developing CV complications including hypertension, atherosclerosis and ischemic injury[26,28–30]. A handful of genes encoded by the X chromosome that escape inactivation on the second X chromosome in females are implicated as females have elevated expression of these genes compared to males, many of which are epigenetic modifiers. Taken together, premenopausal females seem to be protected against CVD when compared to males; however, with reduced levels of estrogen, post-menopausal women have an elevated risk of CVD complications. This increased risk could potentially prime older females with COVID-19 for more severe cardiac outcome, although more data is needed to parse apart the influence of menopause on COVID-19-related CVD complications.

2.2. ACE2 in CVD and COVID-19

Angiotensin-converting enzyme 2 (ACE2) is the functional receptor for SARS coronaviruses including the novel SARS-CoV-2 that causes COVID-19[31,32]. ACE-2, a carboxypeptidase transmembrane protein expressed in various cell types, regulates the activity of the renin-angiotensin system (RAS) by hydrolyzing angiotensin I (AngI) into Ang 1-9 and angiotensin II (AngII) into Ang 1-7[33]. While ACE2 is homologous to ACE, the enzyme that converts AngI to the vasoconstrictive, pro-inflammatory, pro-hypertrophic and pro-fibrotic AngII, ACE2 counterbalances the detrimental effects of ACE[34]. ACE2 confers cardioprotection by enhancing vasodilation and preventing cardiac hypertrophy, fibrosis and oxidative stress.[34] ACE2-deficient mice exhibit elevated AngII levels, increased cardiac hypertrophy and fibrosis, and severe diastolic and systolic dysfunction, which is rescued by recombinant human ACE2 therapy[35,36].

While animal models and analysis of human hearts at the whole tissue level do not provide conclusive results regarding the directionality of cardiac ACE2 expression in CVD[37–40], CVD does augment ACE2 expression in cardiomyocytes. ACE2 expression is increased in cardiomyocytes of patients suffering from dilated and hypertrophic cardiomyopathy, aortic stenosis and HFrEF compared to control donor hearts[37,41,42]. Interestingly, cardiac pericytes, fibroblasts and vascular smooth muscle cells from these patients exhibited lower ACE2 expression compared to control donor hearts[37,41]. Altered

cardiac ACE2 expression profiles in CVD have been proposed as a mechanism underlying the more severe course of disease in COVID-19 patients with pre-existing CVD, since elevated cardiac ACE2 could mediate SARS-CoV-2 infection.

2.3. Sex differences in ACE2

ACE2 is encoded by the X chromosome and is located in a region of the X chromosome that escapes X-inactivation in females[43]. Since females have two copies of the X chromosome compared to one copy in males, most X-escapee genes are found to have higher expression in females[44,45]. ACE2, however, displays an uncharacteristically heterogeneous pattern across various tissues exhibiting increased mRNA expression in certain male tissues[44]. It is hypothesized that gene-hormone interactions accounts for this uncharacteristic pattern of expression as ACE2 activity has been demonstrated to be sex hormone dependent[46,47].

In the left ventricle (LV), hypertensive male rats (both spontaneously hypertensive and mRen2 strains) experience higher levels of ACE2 activity and hypertrophy when compared to females.[48,49] Gonadectomy in males resulted in decreased ACE2 expression and reduced cardiac hypertrophy, whereas ovariectomy in females resulted in increased LV ACE2 activity and cardiac hypertrophy coupled with reduced hemodynamic function of the heart[49]. In contrast, studies using normotensive Lewis rats and MF1 mice did not demonstrate sexually dimorphic cardiac ACE2 activity[48,50]. These studies, however, demonstrated that estrogen altered the expression and activity of ACE2 in other tissues including plasma, adipose tissue, and kidneys, while the effect of estrogen was varied. A study investigating the role of sex chromosomes in ACE2 activity, revealed that while estrogen influenced ACE2 activity in the kidney of MF1 mice, sex chromosome complement (XX or XY) had no effect[50].

While ACE2 is encoded by the X chromosome, more highly expressed in certain male tissues than female tissues, and is influenced by estrogen, it is still unclear whether sexual dimorphisms in ACE2 directly contribute to the sex differences seen in COVID-19 severity and mortality. Even so, testing the use of short-term exogenous estrogen treatment as a therapy for COVID-19 patients is now underway in a Phase II clinical trial that includes both sexes (ID: NCT04359329)[51].

2.4. Sex differences, drugs and ACE2 in COVID-19

Since AngII plays a central role in CVD pathophysiology, drugs that inhibit the activity of ACE (ACEi) or block AngII receptors (ARBs) are commonly prescribed as a first-line treatment. Sex differences exist in the cardiovascular efficacy and outcome of ARB and ACEi use, indicating differences in drug absorption, distribution, metabolism, and excretion between males and females[52–54]. Various ACEi and ARB have been shown to enhance expression and activity of cardiac ACE2 in experimental animal models.[55,56] More recently, single-cell RNA sequencing (scRNAseq) revealed that hypertrophic cardiomyopathy patients taking ACEi trended towards elevated ACE2 expression in cardiomyocytes, fibroblasts, pericytes, and vascular smooth muscle cells[37]. Similarly, cardiomyocytes from ACEi-treated aortic stenosis and HFrEF patients exhibited enhanced ACE2 levels and unfavorable ACE/ACE2 ratios[41]. Since ACE2 is the main receptor of SARS-CoV-2, these studies led to initial concerns of enhanced susceptibility of SARS-CoV-2 infection; however, there is currently no proof that this outweighs their protective role in modulating RAS activity[41,57]. In two recent studies, including a large observational study of 8910 COVID-19 patients, no association was found between the use of ACEi and ARB and increased likelihood of a positive SARS-CoV-2 test nor with increased risk of COVID-19 complications when corrected for sex, amongst others[58]. As such, effects of sex-specific efficacy of ARB and ACEi on COVID-19 progression and outcome seem unlikely.

2.5. Sex differences in obesity

Obesity is a major risk factor for developing CVD and emerging evidence shows that obesity is also risk factor of developing severe COVID-19 outcome and mortality.[59–64] Sex differences in obesity are well established[65]. Obesity prevalence is significantly associated with sex and pathophysiological mechanisms of obesity are modulated by both sex hormones and chromosomes[65,66]. Whether sex differences exist in the prevalence of obesity in COVID-19 patients is thus far not fully elucidated, but allude to higher prevalence of obese male COVID-19 patients than female. A study of 200 COVID-19 patients in New York City found no difference in proportion of males and females when COVID-19 patients were stratified by BMI[60]. However, studies of 383 Chinese and 92 Italian COVID-19 patients reported that the proportion of men was significantly higher in the overweight and obese BMI groups[61,63].

Interestingly, it is hypothesized that RAS dysregulation may link obesity to COVID-19[67]. In line with this notion, an experimental mouse study reported that sex hormones contribute to tissue-specific ACE2 expression in the development of obesity-induced hypertension[47]. Here, high-fat diet fed females did not develop obesity-hypertension or elevated Ang 1-7 levels while males did. This effect was abolished upon ovariectomy and estrogen increased ACE2 levels. Considering the central role ACE2 and dysregulated RAS are thought to play in COVID-19, ACE2 may link sex differences, obesity, CVD and COVID-19.

2.6. Sex differences in smoking

In addition to biological factors, societal factors, including smoking, may also contribute to the sex differences present in COVID-19[68]. Reports from 2015 reveal 52.1% of Chinese males smoke compared to just 2.7% of females[69]. Sex differences in smoking prevalence also exist in other populations, although to a much lesser degree (*Italy*: 26% Males, 17.2% Females[70]; *United States*: 17.5% Males: 13.5% Females[71]). According to a meta-analysis, history of smoking is one of the most prevalent preexisting factors associated with patients hospitalized for COVID-19 infection[17]. Studies show smoking is also a risk factor for the development of chronic obstructive pulmonary disease, hypertension, and CVD[72], which are comorbidities positively associated with COVID-19 hospitalizations[17]. Single-cell RNAseq studies recently revealed an upregulation of the SARS-CoV-2 receptor, ACE2, in the lungs of smokers compared to never-smokers, which could influence the risk and severity of COVID-19 in smokers[73]. Taken together, the sex differences found among the smoking population may contribute to the sex differences in COVID-19 hospitalizations and morbidity. Smoking, which is largely more common in male populations, is associated with COVID hospitalization, can lead to cardio-pulmonary comorbidities, and upregulates the expression of ACE2 within the lung.

3. Sex differences in COVID-19-related cardiovascular injury

Cardiovascular injury in COVID-19 is mainly observed in the form of acute cardiac injury, microvascular injury and thrombosis. Various pathophysiological mechanisms may contribute to the development COVID-19-related cardiovascular injury including direct cardiotropic and endothelial viral infection, secondary systemic toxicity of the hyperinflammatory state, cardiovascular stress due to SARS-CoV-2-induced respiratory failure, or a combination of all three factors[74,75]. Sex disparities underlie some of these factors leading to COVID-19-related cardiovascular injury.

3.1. Sex differences in clinical cardiac injury in COVID-19

Cardiac involvement is a prominent feature in COVID-19 pathophysiology. Acute myocardial damage in COVID-19 patients may be inferred from elevated circulating biomarkers, electrocardiographic changes, and imaging studies revealing features of impaired cardiac function[76]. Acute cardiac injury, based on circulating biomarkers, is more frequent in severe compared to non-severe COVID-19 cases[10,77,78] and circulating biomarker concentration is associated with disease severity and fatality[10,78–80]. Altogether, up to 36% of COVID-19 patients were reported to suffer from acute cardiac injury based on elevated cardiac biomarkers[6,10,77,80].

While data is still emerging, some sex disparities seem to exist in COVID-19-related cardiac injury. A study of 112 Chinese COVID-19 patients has shown a trend towards more men being diagnosed with possible myocarditis than women[11]. Similarly, two studies of Chinese COVID-19 patients showed that women account for more of the mild cases which also exhibited lower levels of troponin I, creatine kinase–myocardial band fraction, myoglobin, and N-terminal B-type brain natriuretic peptide[79,81]. In a study of 1557 COVID-19-positive individuals in New Haven, more males presented with abnormally elevated troponin T[16]. A larger study of 2736 COVID-19 patients in New York City, however, reported no significant sex differences when COVID-19 patients were stratified by troponin T levels[80]. In a study of 1557 COVID-19-positive individuals in New Haven, more males presented with abnormally elevated troponin T than females[16]. Interestingly, in this patient population, a model of combined risk factors including, age, hypertension and body mass index, showed that prostatic disease increased the odds of COVID-19 patients having elevated troponin T levels, independently of the other risk factors[16]. Together these data indicate that individuals more at risk of severe COVID-19 progression and outcome due to cardiac injury may include a disproportionate number of males.

3.2. Sex differences in clinical cardiac arrhythmia in COVID-19

The clinical burden of cardiac arrhythmias in COVID-19 patients is becoming increasingly clear. Various forms of cardiac atrial and ventricular rhythm disorders have been reported in COVID-19 patients including atrial fibrillation, sinus tachycardia and bradycardia, complete conduction block and cardiac arrest[82]. Arrhythmia may associate with sudden cardiac death, which is a pathologic outcome also observed in COVID-19 patients[83–85]. Arrhythmia in COVID-19 patients is associated with myocardial injury and is thought to reflect the severity of illness[81,86,87]. Indeed, ICU admission is associated with arrhythmia, with up to 44% of COVID-19 patients in the ICU suffering from arrhythmia[5,88]. While the association of arrhythmias and in-hospital mortality in COVID-19 patients is inconclusive, it has been reported that the prevalence of arrhythmia is 60% in fatal COVID-19 cases[89].

Sex differences exist in cardiac electrophysiological characteristics as female sex is a known risk factor for drug-induced QT prolongation and torsade des pointes arrhythmia[90]. Whether sex differences exist in arrhythmia in COVID-19 patients remains under-reported. Since arrhythmia is associated with myocardial damage and elevated cardiac biomarkers are more prevalent in male COVID-19 patients, it is plausible that arrhythmia may also be more prevalent in male COVID-19 patients. However, a Chinese study of 234 COVID-19 patients shows no differences between the proportion of male and female COVID-19 patients with or without arrhythmia[86]. Future studies will be imperative to shed light on sex disparities in arrhythmia occurrence in COVID-19 patients.

3.3. Sex differences in clinical microvascular injury and thrombosis in COVID-19

Mounting reports on microvascular dysfunction and thrombosis in COVID-19 patients suggest that endothelial dysfunction and coagulation imbalances may contribute to COVID-19 pathophysiology. Elevated levels of fibrinogen and D-dimer levels have been reported in COVID-19 patients, indicating

elevated clot formation and fibrinolysis.[91] Elevated D-dimers were found to be associated with poor prognosis and increased risk of death.[4,92] Histology on post-mortem lungs and skin from COVID-19 patients revealed thrombogenic vasculopathy[93,94]. Moreover, thromboembolisms have been observed in several organs in COVID-19 patients[95–97]. Overall, 20-30% of COVID-19 patients in the ICU have been reported to suffer from thrombosis and major thromboembolic sequelae[7].

While data on sex differences in microvascular injury and thrombosis in COVID-19 is still sparse, sex disparities do not seem to be observed. A study of 248 Chinese COVID-19 patients shows that there is no significant difference in proportion of male and females in normal and high D-dimer groups.[98] Accordingly, a meta-analysis reported that elevated D-dimer in severe COVID-19 cases and non-survivors do not seem to associate with sex[99]. Interestingly however, an Italian study of 100 COVID-19 patients reported that fibrinogen levels in female COVID-19 patients were significantly higher compared to female controls, while this increase was not significant in males[100].

3.4. Sex differences in SARS-CoV-2 cardiotropic infection

Cardiac samples from patients who succumbed to the previous SARS coronavirus in 2003 provides insight into the cardiotropic potential of coronaviruses. SARS-CoV, which also binds to the ACE2 receptor, was detected in 35% of hearts[101] and present in cardiomyocytes that displayed vacuolar degeneration, atrophy and cytoplasmic lysis[102]. While SARS-CoV-2 has been detected in hearts of COVID-19 patients, no reports yet have shown conclusive evidence of direct SARS-CoV-2 infection in non-inflammatory myocardial cells in COVID-19 patients[103–106]. Several cell cardiac cell types express ACE2, including cardiomyocytes[107]. Recently, it was demonstrated that SARS-CoV-2 was able to infect human inducible pluripotent stem cell-derived cardiomyocytes *in vitro,* suggesting the potential for SARS-CoV-2 cardiotropic potential[108].

While data on sex differences in cardiotropic SARS-CoV-2 is yet unavailable, sex disparities do exist in the epidemiology and pathophysiology of viral myocarditis induced by various viruses, and this may also be the case for SARS-CoV-2[109–111]. Expression of the SARS-CoV-2 receptor ACE2 is regulated by sex hormones in opposite directions in male and female mice[49]. A recent study reported that androgen signaling may regulate ACE2 expression and subsequent SARS-CoV-2 infection in human cardiac cells since treatment with the 5 alpha reductase inhibitor dutasteride and androgen receptor modulator spironolactone augmented ACE2 levels and internalization of SARS-CoV-2 recombinant spike receptor binding domain in human embryonic stem cell-derived cardiac cells[16]. As such, sex hormones may underlie possible sex differences in cardiotropic SARS-CoV-2 infection by regulating ACE2 expression.

3.5 Sex differences in endothelial dysfunction

Microvascular injury and thrombosis in COVID-19 are thought to be caused by endothelial dysfunction since activated and injured endothelial cells recruit inflammatory cells and activate the coagulation cascade[112]. Histology on post-mortem from COVID-19 patients revealed that SARS-CoV-2 is able to directly infect endothelial cells concomitant with endothelialitis and apoptosis in several organs[113]. Accordingly, SARS-CoV-2 was shown to be able to directly infect human blood vessel organoids in vitro[114].

Sex differences in endothelial dysfunction are well-established[115]. For instance, estrogen promotes proper endothelial cell function by enhancing endothelial nitric oxide synthase (eNOS) expression while testosterone has opposite effects[24]. A hallmark of endothelial dysfunction is dampened eNOS expression with NO deficiency[116]. Decreased NO levels in injured endothelial cells contribute to thrombus formation[112]. Recently it was proposed that eNOS deficiency could be a pathophysiological

mechanism in COVID-19[116]. As such, sex hormones may affect endothelial dysfunction in COVID-19. However, also in the absence of sex hormones, sex differences exist in barrier integrity and survival between male XY and female XX microvascular endothelial cells[117,118]. Although sex-differences in COVID-19-related microvascular injury and thrombosis in the clinic do not seem apparent thus far, it is plausible that sex-differences play a pathophysiological role in COVID-19 endothelial dysfunction.

3.6 Sex differences in soluble ACE2

Upon binding to ACE2 on the cell surface, SARS-CoV-2 is endocytosed leading to downregulated ACE2 cell surface expression[119]. As such, the protective effects of ACE2 are likely blunted. Loss of membrane-bound ACE2 is hypothesized to be a critical step in the cardiac injury pathology in COVID-19. This notion is supported by experimental animal models wherein ACE2-deficient mice exhibit hypertrophy, fibrosis, HF and enhanced inflammation[35,36,120]. Autopsy material from the SARS epidemic revealed SARS-CoV infection in 35% of cardiac specimens concomitant with decreased membrane ACE2 levels, cardiac hypertrophy, inflammation, and fibrosis[120], indicating that loss of membrane-bound ACE2 indeed may be a pathogenic mechanism in SARS-CoV-induced cardiac injury. Similarly, ACE2 expression and activation in endothelial protects against endothelial dysfunction in atherosclerosis, hypertension and thrombosis[121–123]. It has been shown that ACE2 is released into the circulation which advances several CVD pathologies, and levels of soluble ACE2 in plasma correlate with worsened disease severity and prognosis in HF patients[34,124]. To date, no reports are available on levels of cardiac membrane-bound ACE2 or circulating levels of soluble ACE2 in COVID-19 patients. However, it seems that men, who are at increased risk of more severe COVID-19 progression, present with higher soluble ACE2 levels than women as was observed in both healthy subjects and two independent cohorts of HF patients[125,126].

3.7 Sex differences in systemic inflammation in COVID-19

SARS-CoV-2 infection is characterized by a robust cascade of inflammatory and immune events. In the early stages of infection, COVID-19 patients present progressive lymphocytopenia; however, patients were reported to eventually develop elevated white blood cell and neutrophil counts[2,5,127]. In the hyperinflammatory phase, driven by the host immune response, inflammatory markers become elevated and secondary organ damage may occur in what is deemed the cytokine storm. Systemic cytokine elevation is known to be cardiotoxic with the potential to induce profound myocardial injury, as reported in patients treated with chimeric antigen receptor T-cells who develop cytokine release syndrome[76,128,129]. Furthermore, cytokine storms may directly mediate ventricular electrical remodeling and significant QT interval prolongation, predisposing for ventricular arrhythmias[130]. Additionally, proinflammatory cytokines are known to promote coagulation and thrombosis by enhancing expression of tissue factor on endothelial cells, activating coagulation factors and inhibiting fibrinolysis, as is observed in severe cases of sepsis[131].

While the rate of SARS-CoV-2 infection seems to be similar between males and females[15], the ability to mount an immune response to protect against COVID-19 may contribute to sex differences seen in COVID-19 mortality and cardiac injury. Through a combination of sex biasing factors, females have a greater ability to detect virial infection and generally experience a more robust response to viral infection which could contribute to their protection against COVID-19 when compared to males[132–135]. Both sex hormones and sex chromosomes influence sex differences in immunity[134,136]. Sex hormones have been shown to bind to receptors on immune cell surfaces to alter their gene expression and activity[134]. Additionally, the X chromosome encodes a high density of immune-related genes and microRNAs which, despite inactivation of the second X chromosome in females, remain overly expressed in females compared to males, contributing to the heightened immune response in females[136–138].

The male-specific Y chromosome, which encodes substantially less genes than its X chromosome counterpart, has also been found to influence immune function as Y chromosome genes are expressed in various immune cell types and have been shown to alter immune function[139,140].

Notably, similar sex differences were also observed in the previous coronaviruses SARS and Middle East respiratory syndrome (MERS). In both SARS and MERS outbreaks, males had higher mortality rates than females[15,141,142]. Mouse studies investigating SARS, which also infects the airways and lungs through the ACE2 receptor, revealed that infected male and female mice had a unique immune signature compared to males, and estrogen protected against SARS severity partially through mediating this immune response[141]. While the data is still sparse, reports show a sex-specific immune signature may be present in SARS-CoV-2 infection as well. One study found male COVID-19 patients exhibit elevated circulating white blood cells and neutrophils when compared to female patients[15]. Another study revealed male COVID-19 patients exhibit a lower lymphocyte count and elevated levels of IL-10, TNF-α, and CRP compared to females[143]. It remains to be elucidated to which extent the sex differences observed in systemic inflammation in COVID-19 patients translate to differences in inflammation-induced cardiac injury, arrhythmia and microvascular dysfunction and thrombosis.

3.8 Sex differences in COVID-19 drug-induced cardiac arrhythmia

Arrhythmias in COVID-19 patients may result from biological factors in the pathophysiology of COVID-19 or may be induced by drugs used for treating COVID-19[144]. While the clinical efficacy of these drugs is still relatively unknown, the antimalarial drugs chloroquine and hydroxychloroquine were shown to have antiviral properties against SARS-CoV-2 *in vitro* by increasing endosomal pH and interfering with ACE2 glycosylation[145,146]. Administration of chloroquine and hydroxychloroquine with or without adjunctive azithromycin has been reported to significantly prolong the QT interval in COVID-19 patients[147–151]. The risk of developing torsade des pointes ventricular arrhythmia and arrhythmic death in COVID-19 patients treated with hydroxychloroquine/chloroquine/azithromycin however does not seem to increase[147–152].

Interestingly, an *in silico* modeling study using mathematical models of ion currents from human ventricular cardiomyocytes and clinically therapeutic drug doses has shown that females with preexisting cardiovascular disease may especially be susceptible to antimalarial drug-induced QT prolongation compared to males with cardiovascular disease or healthy individuals of either sex[153]. Indeed, sex differences in cardiovascular drug responses have been reported and female sex is a known risk factor for drug-induced QT prolongation and torsade des pointes which may be caused by female sex hormones affecting cardiomyocyte ion currents[90,154]. However, thus far no sex differences have been reported inthe prevalence of QT interval prolongation in COVID-19 patients treated with hydroxychloroquine/chloroquine with or without azithromycin[147,148,150].

4. Concluding remarks

Preexisting CVD and cardiovascular injury seem to be a prominent feature of COVID-19 severity and outcome. Research in the COVID-19 field is rapidly evolving; however, the thus-far observed sex disparities already emphasize the need to understand the pathophysiological role of sex hormones and chromosomes in COVID-19 disease progression and COVID-19-related cardiovascular injury. Clinically, studies show that males with preexisting CVD are particularly prone to more severe COVID-19 disease and COVID-19-related cardiovascular injury. As such, sex hormone and chromosome COVID-19 interactions will be a promising field of study to elucidate novel protective mechanisms and therapies for the treatment of COVID-19. Additionally, sex differences in ACE2 expression, inflammation and drug absorption, metabolism and tolerance make it imperative to study sex-specific disparities within COVID-

19 treatment efficacy.[155,156] Considering that sex differences in cardiovascular drug responses have been reported, sex differences will be of special interest for treating COVID-19-related cardiovascular injury[154,157,158]. Lastly, cardiac abnormalities including myocarditis, fibrosis, edema and left and right ventricular dysfunction have been reported in recovered COVID-19 patients[159–161]. Although as of yet no sex differences were found in recovered COVID-19 patients, it has been reported previously that males and females exhibit different functional outcome and long-term mortality after myocarditis, cardiac arrest and thrombotic events[109,159,162,163]. Longitudinal follow-up studies will therefore be imperative to gain more insight into the long-term cardiovascular effects and recovery in male and female COVID-19 patients.

Disclosures

None.

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Figure legend

Fig. 1. Factors underlying preexisting CVD, risk of COVID-19 severity, and COVID-19 related cardiovascular injury in males and females. Preexisting CVD is modulated by sex chromosomes and hormones, ACE2 expression, drug interactions, obesity and smoking, which may predispose males and females differently to COVID-19 severity. CVD, obesity and smoking are risk factors with a higher burden in male vs. female COVID-19 patients (shown with red icons in males). COVID-19 pathogenic mechanisms also contribute to cardiovascular injury. Males exhibit higher burden of cardiac injury than females, while no sex disparities in arrhythmia and microvascular injury and thrombosis have been reported thus far. COVID-19-induced cardiovascular injury is thought to be modulated by sex hormones, ACE2 expression and systemic inflammation, with the latter being more pronounced in males. Altogether, these factors may explain why male COVID-19 patients seem to be at higher risk for severe disease progression and cardiovascular injury compared to females. Red icons reflect sex differences in factors observed in COVID-19 patients, gray icons reflect factors wherein no sex difference has been found in COVID-19 patients or is yet unknown.

Highlights

- Cardiovascular complications are prominent in COVID-19
- Preexisting cardiovascular disease *is a risk factor for COVID-19 severity*
- Cardiovascular disease, smoking and obesity burden more male COVID-19 patients
- Cardiac injury and systemic inflammation are pronounced in male COVID-19 patients
- No sex disparities were observed in arrhythmia and thrombosis in COVID-19 patients

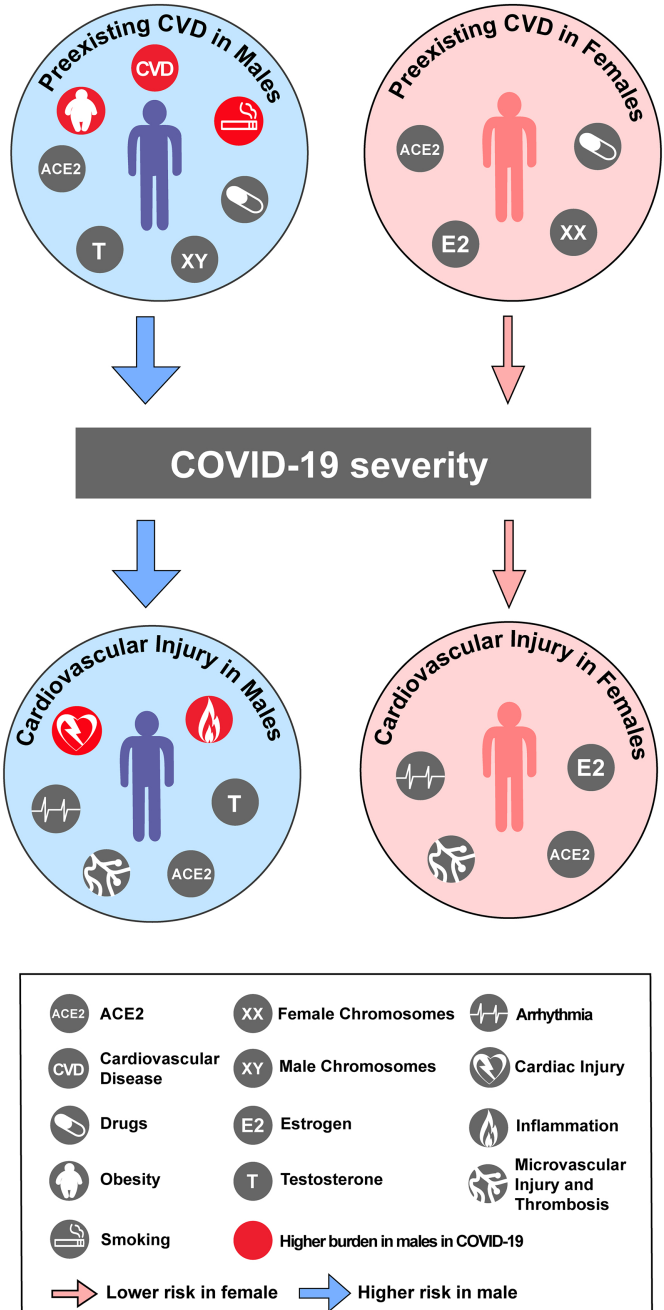
Preexisting CVD in Males
CVD
ACE2
T
XY
Preexisting CVD in Females
ACE2
E2
XX
COVID-19 severity
Cardiovascular Injury in Males
T
ACE2
Cardiovascular Injury in Females
E2
ACE2
ACE2 ACE2
CVD Cardiovascular Disease
Drugs
Obesity
Smoking
XX Female Chromosomes
XY Male Chromosomes
E2 Estrogen
T Testosterone
Higher burden in males in COVID-19
Arrhythmia
Cardiac Injury
Inflammation
Microvascular Injury and Thrombosis
Lower risk in female
Higher risk in male

Figure 1