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Review

Sex-tailored pharmacology and COVID-19: Next steps towards appropriateness and health equity☆

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ABSTRACT

Making gender bias visible allows to fill the gaps in knowledge and understand health records and risks of women and men. The coronavirus disease 2019 (COVID-19) pandemic has shown a clear gender difference in health outcomes. The more severe symptoms and higher mortality in men as compared to women are likely due to sex and age differences in immune responses. Age-associated decline in sex steroid hormone levels may mediate proinflammatory reactions in older adults, thereby increasing their risk of adverse outcomes, whereas sex hormones and/or sex hormone receptor modulators may attenuate the inflammatory response and provide benefit to COVID-19 patients. While multiple pharmacological options including anticoagulants, glucocorticoids, antivirals, anti-inflammatory agents and traditional Chinese medicine preparations have been tested to treat COVID-19 patients with varied levels of evidence in terms of efficacy and safety, information on sex-targeted treatment strategies is currently limited. Women may have more benefit from COVID-19 vaccines than men, despite the occurrence of more frequent adverse effects, and long-term safety data with newly developed vectors are eagerly awaited. The prevalent inclusion of men in randomized clinical trials (RCTs) with subsequent extrapolation of results to women needs to be addressed, as reinforcing sex-neutral claims into COVID-19 research may insidiously lead to increased inequities in health care. The huge worldwide effort with over 3000 ongoing RCTs of

Abbreviations: ACE2, Angiotensin-converting enzyme 2; ACE-Is, ACE inhibitors; AF, Atrial fibrillation; AIFA, Italian Medicines Agency; AnxA1/FPR2, Annexin A1/formyl-peptide receptor 2; ARBs, Angiotensin-II receptor blockers; ARDS, Acute respiratory distress syndrome; AT1R, Angiotensin receptor type-1; BLAZE-1, Blocking Viral Attachment and Cell Entry with SARS-CoV-2 Neutralizing Antibodies; CDC, Centers for Disease Control and Prevention; CI, Confidence Interval; COVID-19, Coronavirus Disease 2019; CYP, Cytochrome P; DHT, Dihydrotestosterone; DMARDs, Disease-modifying anti-rheumatic drugs; DOAC, Direct oral anticoagulant; E2, 17β-estradiol; E4, Estetrol; EMA, European Medicines Agency; ER, Estrogen receptor; FAERS, FDA Adverse Events Reporting Monitoring System; FcRn, Neonatal Fc receptor; FDA, Food & Drug Administration; GC, Glucocorticoids; GM-CSF, Granulocyte macrophage-colony stimulating factor; H_2S, Hydrogen sulfide; HCV, Hepatitis C virus; HR, Hazard ratio; ICU, Intensive care unit; IgG1, Immunoglobulin subclass 1; IL, Interleukin; IL-6R, IL-6 receptor; JAK, Janus Kinase; JAKi, JAK inhibitors; LMWH, Low-molecular-weight heparin; mAbs, Monoclonal antibodies; MERS, Middle-East Respiratory Syndrome; mTOR, Mammalian target of rapamycin; NIH, National Institutes of Health; PEG, Polyethylene glycol; PF4, Platelet factor 4; PG, Progesterone; RAAS, Renin-angiotensin-aldosterone system; RBD, Receptor binding domain; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; SERMs, Selective estrogen receptor modulators; SETH, Spanish Society of Liver Transplantation; T, Testosterone; TCM, Traditional Chinese Medicine; TCZ, Tocilizumab; Th1, T helper 1 cells; TIV, Trivalent influenza vaccination; TMPRSS2, Transmembrane protease serine 2; TNF-α, Tumor Necrosis Factor alpha; VTE, Venous thromboembolism.

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pharmacological agents should focus on improving knowledge on sex, gender and age as pillars of individual variation in drug responses and enforce appropriateness.

1. Introduction

The influence of sex and gender on human health and diseases continues nowadays to be underestimated and underinvestigated in medical intervention. In particular, the lack of accurate sex and gender consideration to evaluate disparities in drug safety and efficacy hurts both women and men. This is particularly evident in clinical trials, where sex and gender inequality in subjects' enrollment remains a substantial challenge.

The current global health emergency, COVID-19, whose etiological agent has been identified to be SARS-CoV-2, has changed the world in an unprecedented way. While the society is facing this extraordinary catastrophe, scientist and clinicians need to recognize the phenotypical differences between men, women, and people with non-binary identities as a fundamental key to deeply understand the effects of this health crisis on different individuals, as well as to identify unbiased clinical protocols.

Global Health 50/50, an independent, evidence-driven initiative to advance action and accountability for gender equality in global health, provided an overview of open-access sex-disaggregated data from official national sources through the COVID-19 Data Tracker. This is the world's largest database of sex-disaggregated data on COVID-19 health outcomes. The tracker currently collects sex-disaggregated data on vaccinations, testing, confirmed cases, hospitalizations, intensive care unit (ICU) admissions and deaths. Data are constantly collected from the ministry of health websites, national statistics sites, death registers and government social media accounts. As the disease has spread worldwide, the May 2021 Update Report tracked the availability of data for 198 countries – which together accounted for 99.9% of COVID-19 confirmed cases and reported deaths globally. As of May 2021, 51% (101) of the 198 countries being tracked reported sex-disaggregated case data and 37% (73) reported sex-disaggregated death data, which was consistent with the proportion reporting in April. Across all available global data, slightly more women than men got vaccinated for COVID-19 and more women were tested for COVID-19. Men and women account for similar numbers of confirmed cases, but the gender gap grows further along the pathway, with men accounting for a higher proportion of hospitalizations (53%), ICU admissions (64%) and deaths (57%) [1].

Furthermore, sex-disaggregated COVID-19 data did not account for gender identity. Therefore, data on the impact of COVID-19 on transgender and non-binary people are lacking, although some efforts are in place to address this issue.

Despite clear gender differences in COVID-19 health outcomes, no information on gender-targeted treatment strategies is currently available. Without this evidence, gender-specific health care needs can neither be identified nor adequately addressed, and treatment appropriateness is not warranted. Thus, in current and future clinical trials for COVID-19, variables of paramount importance such as sex and gender should be taken into serious consideration, not only in relation to disease features, but to tailor the appropriate therapies in order to eliminate gender blindness in medical research. Thus, as prophylactic and therapeutic treatment studies begin, sex and gender analyses should be included in the protocols.

At the time of writing, the analysis of the clinicaltrials.gov database reported 3517 items when searched for "COVID-19 and therapy". The analysis also included synonyms, as "treatment (3181 studies), therapeutic (460 studies), therapeutics (158 studies), disease management (5 studies), COVID (3449 studies), SARS-CoV-2 (1132 studies), Coronavirus disease 2019 (191 studies), severe acute respiratory syndrome coronavirus 2 (128 studies), Novel Coronavirus (101 studies), 2019-nCoV (35 studies), Coronavirus Disease 19 (22 studies), SARS Coronavirus 2 (14 studies), Wuhan coronavirus (1 study)".

Despite the huge amount of clinical protocols, and although both male and female individuals were considered eligible for the studies, no specific gender-analysis were foreseen in terms of differences in drug safety or efficacy. In this light, the present review will try to shed light on available treatments currently tested for COVID-19. The study focused on literature reports and ongoing clinical trials in the time frame March 2020-June 2021.

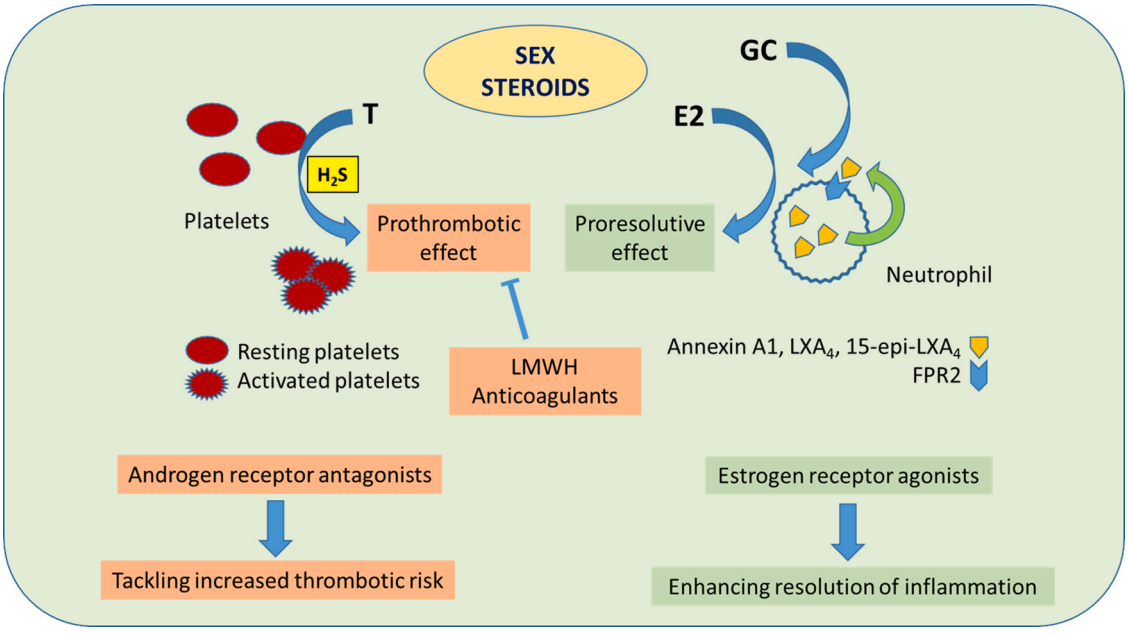

Fig. 1. Androgens and estrogens actions, effects and mechanisms: a possible role in contrasting severe COVID-19 outcomes. (T, Testosterone; E2, estradiol; PG, progesterone; GC, glucocorticoid; H_2S, hydrogen sulfide; LXA_4, lipoxin A_4; 15-epi-LXA_4, epi-lipoxin A_4 or aspirin-triggered lipoxin; FPR2, formyl peptide receptor 2).

2. Sex hormones and COVID-19

2.1. Estrogen and progesterone

Estrogens, in particular the main female sex hormone 17β-estradiol (E2), have been suggested to play a protective role in COVID-19. This seems to occur through different pathways including suppression of inflammatory storm, induction of anti-viral immune responses and enhancement of virus degradation within endolysosomes, resulting in endosomes and lysosomes fusion [2]. E2 affects the activity or expression of different components of the renin-angiotensin-aldosterone system by upregulating the expression of ACE2, which appears to be higher in females than in males [3]. Binding of the SARS-CoV-2 spike protein to ACE2 induces its down-regulation, leading to reduced angiotensin (1–7) production in the lung and igniting acute respiratory failure [4,5]. Hence, E2-mediated ACE2 over-expression in female patients could contribute to the better outcome and lower death rate observed in female COVID-19 patients in comparison to males [6].

The active role of estrogens in accelerating resolution of inflammation suggests that estrogens and/or selective estrogen receptor modulators (SERMs) attenuates the inflammatory response and its exacerbation [7–9]. The Annexin A1/formyl-peptide receptor 2 (Anx-A1/FPR2) axis is one of the pathways involved in this interplay, which is also shared by glucocorticoids (GC), and could represent a mechanistic/pharmacological base for the potential protective action by estrogens in COVID-19 outcomes (Fig. 1). Besides estrogens, progesterone (PG) also confers protection from severe lung injury by dampening the exaggerated inflammatory immune cascade, or "cytokine storm". In a mouse model of influenza A, PG administration has been shown to decrease pulmonary inflammation, reduce protein leakage into airways, and promote faster recovery by enhancing repair of pulmonary epithelial cells [10].

In accordance with the protective role of female sex hormones, data from the Italian Surveillance System [11] highlight how the lethality rate for COVID-19 is reduced in women of reproductive age (20–39 years of age) and sensibly lower than in men. Afterwards, it steadily increases from 0.2% within the age range 40–49 to over 20% at 80–89, but an imbalance between women and men still remains. Supporting these hypotheses, a positive association between COVID-19 and menopausal status and a negative association with combined oral contraceptive pill use have been observed in large-scale self-reported data analysis in UK [12]. Moreover, a retrospective study of hormone therapy in female COVID-19 patients showed that the fatality risk for women $>$ 50 years receiving E2 therapy was reduced by over 50%. For younger, pre-menopausal women (15–49 years), the risk of COVID-19 fatality is the same irrespectively of E2 treatment, probably because of higher endogenous E2 levels [13]. Intriguingly, when women with COVID-19 were stratified by menstrual status, pre-menopausal women had lower rates and short duration of hospitalization together with less requirement for respiratory support compared to post-menopausal women (see relevant Summary Box) [14].

2.1.1. Clinical trials on estrogen and progesterone in COVID-19 patients

Based on the aforementioned evidence, gender-based clinical trials studying effects of estrogen therapy to attenuate severe complications of COVID-19 are required and could represent a successful approach (Fig. 1). Administration of exogenous hormones could therefore represent a therapeutic/prophylactic approach or a treatment adjunct to reduce COVID-19 disease severity. Several clinical trials testing the effect of E2 and PG on clinical response and mortality of COVID-19 are underway at the time of writing (June 2021) and are listed below.

In Mexico, a recruiting trial will investigate the effect of a combined E2 and PG patch (NCT04539626) in male $\geq$ 18 years and female $\geq$ 55 years' patients with non-severe COVID-19. The study will evaluate the progression of clinical signs and symptoms (fever, dyspnea, cough, fatigue daily score) and any adverse outcome in comparison to placebo for 30 days.

In the USA, a phase 2 clinical trial (recruiting) is investigating whether symptom severity can be reduced with E2 administered by transdermal patch (NCT04359329), in adult men $\geq$ 18 years and older women with COVID-19 $\geq$ 55 years. A further USA phase 2 trial (active, not recruiting) is assessing whether E4 is safe and effective at protecting participants from the more severe symptoms of COVID-19 (NCT04801836). The study will monitor the progression to more severe disease in men and post-menopausal women hospitalized with COVID-19 not yet needing breathing help.

In Qatar, a phase 2 clinical trial (not yet recruiting) will investigate whether a transdermal E2 gel will protect adult men and post-menopausal women with confirmed COVID-19 against progression to more severe disease (NCT04853069).

In the USA, a pilot trial testing whether symptoms severity can be reduced with oral PG in men (NCT04365127) has been completed and showed very encouraging data. Indeed, results suggested that administration of PG at a dose of 100 mg twice daily by subcutaneous injection represents a safe and effective approach to treat COVID-19 by improving clinical status among men with moderate to severe illness [15].

Another phase 2 (not yet recruiting) clinical trial in the USA (NCT04865029) will analyze whether a short systemic steroid therapy with E2 and PG, administered early to hospitalized and confirmed COVID-19 positive patients of both sexes in addition to standard of care, can reduce the severity of symptoms and improve outcomes.

Other clinical trials are ongoing regarding the efficacy of SERMs. Tamoxifen is a nonsteroidal triphenylethylene derivative that binds to the estrogen receptor (ER) and acts as an antagonist in breast tissue while acting as an agonist or a partial agonist in the uterus, bone and heart. Therefore, tamoxifen is an effective treatment for ER+ breast cancer and postmenopausal osteoporosis, but it increases risk of endometrial cancer and cardiovascular disease [16]. Tamoxifen has shown potential for drug repurposing in COVID-19 [17]. This agent decreases the rate of vesicular transport through the recycling and secretory pathways and inhibits phagocytosis [18].

In Egypt, two distinct clinical trials (not yet recruiting) will analyze the effects of a combined therapy with isotretinoin (down-regulator of ACE2) and tamoxifen in the protection against SARS-CoV2 in adult female and male patients (Phase 2, NCT04389580) and of the combination of all-trans retinoic acid (for its anti-inflammatory, anti-platelet and fibrinolytic activities) with tamoxifen as potential treatment for the lung complication of COVID-19 (Phase 2, NCT04568096). Estrogens and tamoxifen are not the only drugs showing a potential utility in COVID-19 management. Raloxifene, a benzothiophene-derived SERM [16], has been recently demonstrated to be effective in treating viral infections for its action on ER, suggesting its potential for drug repurposing [19]. Raloxifene acts as an agonist in the bone, cardiovascular system and liver, but shows antagonistic effects in human breast and uterus. Of note, a specific mechanism of inhibition of Ebola virus infection by raloxifene has been suggested [20]. This agent interferes with viral replication within host cells by reducing the expression of sphingosine and the related accumulation of calcium ions within endolysosomes preventing viral escape. Raloxifene decreases the influenza A virus titer in nasal epithelial cells isolated from female but not male patients [21], and inhibits RNA replication of HCV [22]. Of note, raloxifene has also been demonstrated to antagonize interleukin (IL)-6 signaling in severe COVID-19 patients protecting against acute respiratory distress syndrome [23]. These findings strongly recommend raloxifene as a potential therapeutic strategy for COVID-19, and its sexually dimorphic antiviral efficacy warrants further investigation.

2.2. Androgens and anti-androgens

The higher death rate observed in men compared with women put androgens (i.e. testosterone, T) under the spotlight as possible players in the exacerbation of COVID-19 symptoms. Plasma T levels decrease in

elderly men and in the presence of highly prevalent comorbidities in COVID-19 such as obesity and diabetes [24]. Recent data report that the gradual decline in total and free testosterone levels correlates with serious pulmonary complications requiring advanced care [25]. T has been linked to thromboembolic events following its exogenous administration to treat a number of diseases, including hypogonadism [26–28]. The majority of cases described are not linked to hypogonadism, where T therapy displays beneficial actions well beyond adverse effects [29,30]. Unregulated testosterone activity or excessive levels may conceivably trigger detrimental pathways, leading to an unbalanced coagulative physiology, thus facilitating thrombi formation as observed in men affected by COVID-19. A number of reports suggest monitoring homocysteine levels before and during therapy, as thromboembolic events have been consistently described after 6–12 months of treatment, despite anticoagulation therapy [26,31]. Homocysteine is a widely accepted risk factor for cardiovascular disease, and has been linked to hyperactive platelet aggregation mediated by H_2S (Fig. 1) [32]. Testosterone has also been associated with the generation of H_2S, whose plasma levels are higher in males than in females [33]. Therefore, T (and male gender) per se might be a risk factor for vascular thrombosis (see relevant Summary Box).

Studies in animal models and humans documented that hypogonadism is associated with increased pro-inflammatory cytokines, while increased testosterone levels following exogenous treatment suppress the release of IL-1β, IL-6, IL-1, tumor necrosis factor (TNF)-α and leukotrienes [29,30,34]. In elderly men, the decline of testosterone correlated with the onset of a proinflammatory condition [35]. The increased death rate in aged male patients with COVID-19 suggests that testosterone plays a protective role in the progression of COVID-19 infection due to the cytokine storm [36]. However, T has been reported to enhance neutrophil recruitment in a bacterial model of prostate inflammation, generating an inefficient inflammatory response associated with a neutrophil N2-like phenotype [37]. Neutrophils play a key role in innate immunity and in inflammation as they also drive the resolution pathway by triggering mechanisms based on different cell mediators/receptors [38].

2.2.1. Clinical trials on androgens or anti-androgens

As for estrogens, several clinical trials testing the effect of T on the clinical response and mortality of COVID-19 patients are underway at the time of preparation of this review and are discussed below.

Interestingly, T increases ACE-2 expression, whereas dihydrotestosterone (DHT) significantly induces the expression of transmembrane protease serine 2 (TMPRSS2), thereby increasing viral entry [39]. A randomized interventional comparative phase 4 clinical trial in Egypt (NCT04623385, not yet recruiting) in adult male and female patients will test the effect of 13-cis-retinoic acid (isotretinoin, a potent inhibitor of DHT) plus testosterone, which could up-regulate pulmonary protective pathways and at the same time protect against thrombosis. Other Egyptian trials in both female and male adult patients will test isotretinoin alone (NCT04577378, Phase 2, not yet recruiting) or in combination with the ACE inhibitor captopril (NCT04578236, Phase 2, not yet recruiting).

Trials exploring anti-androgen therapies aiming to reduce disease severity by inhibiting TMPRSS2 are also underway in different countries including Sweden (enzalutamide, in both sex adult patients, Phase 2, recruiting, NCT04475601 [40]), USA (bicalutamide in male patients, NCT04509999, Phase 3, recruiting, and camostat + bicalutamide in all sex elderly patients, NCT04652765, phase 1 recruiting) and Brazil (proxalutamide in male patients, NCT04446429, completed and now extended to female patients, phase 3, NCT04853134 active not recruiting; proxalutamide in hospitalized COVID-19 male and female patients, not yet recruiting phase 3 NCT04728802; proxalutamide in male and female patients in Intensive Care Unit, recruiting phase 3 NCT04853927; dutasteride in adult male patients, NCT04729491, completed).

Summary Box

- **Highlights**

17β-estradiol (E2) and progesterone (PG) have been suggested to play a protective role in COVID-19
A negative association has been highlighted between COVID19 and hormonal contraceptive or replacement therapy
Testosterone (T) has a direct correlation with serious pulmonary complications and thromboembolic events

- **Strength**

Several clinical trial underway testing the effect of E2, SERMs, PG, T or anti-androgen on clinical response and mortality of COVID-19

- **Limitations**

It is far to be understood whether molecular mechanisms physiologically operating in females could still be effective in male individuals (and viceversa) when triggered with exogenous molecule
Similarly, it is unclear whether young or elderly women and young or elderly men could display different responses to sex steroids

Summary of highlights, strength and limitations of sex hormones in COVID-19 patients.

3. Coagulative disorders therapy and COVID-19

A systematic review estimated that 17.3% of critically ill patients with COVID-19 had venous thromboembolism (VTE) [41]. SARS-CoV2 induces a thrombo-inflammatory phenotype, characterized by endotheliopathy, hypercoagulability and coagulation activation resulting in increased risk of thromboembolic events [42]. Endothelial dysfunction as measured by markers of endothelial cell and platelet activation such as von Willebrand factor and soluble P-selectin is a key feature of COVID-19-associated coagulation disorder, and may be associated with critical illness and death. In a cross-sectional study of 68 adult patients hospitalized with a confirmed diagnosis of COVID-19, among all patient characteristics analyzed, only sex showed a significant difference in distribution between intensive care unit (ICU) and non-ICU subgroups, with fewer females requiring ICU admission [43]. Regrettably, no sex stratification was performed for treatment outcomes (see relevant Summary Box).

3.1. Clinical trials on anticoagulants

A meta-analysis from direct oral anticoagulant (DOAC) trials found a sexual dimorphism in outcomes, with male patients being more protected from stroke/systemic embolic events and female patients more protected from major bleeding events [44]. It has been suggested that underestimation of kidney function via standard equations in women possibly leads to suboptimal dosing and low efficacy of DOACs, which are excreted by the kidneys to a variable extent [45,46].

While evidence largely comes from real-world studies, large international prospective clinical trials are ongoing to confirm benefit of antithrombotic therapy in COVID-19 patients. Regrettably, focus on sex differences is limited despite clearly distinct clinical presentation and response to treatment in males vs. females [47]. For instance, landmark clinical trials in the '90s showed remarkable sexual dimorphism in the response to low-dose aspirin in primary prevention [48,49].

A retrospective observational study carried out in 24 centers in France reported a beneficial effect of oral anticoagulant prior to hospitalization for COVID-19 on disease outcomes. Out of nearly 3000 study subjects, about 60% patients were males. Among other factors, male sex was significantly associated with ICU admission and in-hospital mortality. Of note, in patients not on anticoagulants prior to hospitalization, parenteral heparin or LMWH treatment started during hospitalization was not associated with a better prognosis (Fig. 1). A smaller retrospective, single-institution study from the U.S. including patients who received therapeutic anticoagulation for at least 1 month before COVID diagnosis yielded consistent findings. While the majority of patients were females with a median age of 78, 69% of patients who died were male [50].

In contrast, a register-based cohort study in Sweden including over 400,000 subjects with a recorded diagnosis of heart disease showed that ongoing DOAC use in patients with AF was not associated with lower risk of severe COVID-19 compared with patients with AF or those with major cardiovascular disease not on DOACs [51]. While male patients comprised over 60% in each group, DOAC users were older and, more often, female compared with AF patients with no DOAC use. Regrettably, study outcomes were not stratified by sex (see relative Summary Box).

Recently, retrospective [52] and cohort studies [53] from Italian research groups reported that prophylactic doses of low-molecular-weight heparin (LMWH: enoxaparin 4000 IU, once daily) efficaciously reduced the mortality in hospitalized COVID-19 patients with mild/moderate disease. Conversely, a recent systematic review and meta-analysis of eight retrospective observational studies of nearly 3000 patients did not highlight any significant variations in mortality rate in patients receiving prophylactic doses of heparin [54]; however, the analysis was reported regardless of age and sex.

While outpatients with mild COVID-19 are encouraged to increase mobility, hospitalized patients with COVID-19 should undergo risk stratification for venous thromboembolic event prophylaxis [55]. Three international trials spanning four continents (NCT02735707; NCT04372589; NCT04505774) are assessing the benefit of full doses of anticoagulants to treat moderately ill or critically ill adults hospitalized for COVID-19, compared to a lower dose often used to prevent blood clots in hospitalized patients. Enrollment, however, was paused among critically ill COVID-19 patients requiring ICU support, as therapeutic anticoagulation drugs did not reduce the need for organ support and potentially induced harm. In the multicenter, randomized INSPIRATION trial [56], intermediate-dose compared with standard-dose prophylactic anticoagulation did not improve the primary composite efficacy outcome or its major components, including all-cause mortality and VTE. Similarly, in an open-label, multicenter, randomized, controlled trial including 615 patients hospitalized with confirmed COVID-19 and elevated D-dimer concentration, a 30-day course of therapeutic anticoagulation with rivaroxaban 20 mg daily (and enoxaparin 1 mg/kg twice daily for clinically unstable patients) did not result in better clinical outcomes when compared with in-hospital prophylactic anticoagulation with heparin. However, therapeutic anticoagulation for 30 days with rivaroxaban or enoxaparin led to a higher incidence of major or clinically relevant non-major bleeding than did in-hospital prophylactic anticoagulation [57].

A prospective multihospital registry of nearly 5000 adult hospitalized COVID-19 patients (53% males) with a mean follow-up of 3 months found that VTE, arterial thromboembolism and all-cause mortality occurred with a higher frequency (7.3%) during the post-discharge period than previously reported [58]. Age $>$ 75 years was among key predictors of post-discharge thromboembolic events and death. Post-discharge thromboprophylaxis consisting of prophylactic dose rivaroxaban, apixaban or enoxaparin was prescribed in 12.7% of the population. The use of post-discharge anticoagulants, mostly at prophylactic doses, was associated with a striking 46% reduction of major thromboembolic events and death risk.

Summary Box

- **Highlights**

COVID-19 predisposes patients to arterial and venous thrombosis
Anticoagulants at discharge, mostly in prophylactic doses, are associated with a 46% decrease in the composite endpoint of major TE or all-cause mortality

- **Strengths**

Heparin prophylaxis reduces mortality in the patient subgroup with moderate symptoms
Standard-dose thromboprophylaxis rather than dose escalation appears to be beneficial in critically ill patients with COVID-19
Real-world evidence of benefit from oral anticoagulants prior to hospitalization for COVID-19 on disease outcomes

- **Limitations**

Uncertainty in optimal prophylactic anticoagulant regimen
Unclear benefit of routine empirical use of intermediate-dose prophylactic anticoagulation in unselected patients with COVID-19 admitted to the ICU
No evidence for sex-tailored antithrombotic treatment and prophylaxis

Table 1
RAAS system.

Drugs	Approval (EMA)	Mechanism of action	Potential mechanism of action on COVID-19	Advice (EMA)	Sex perspective
ACEIs	First-line treatment for patients under 55 years with hypertension and second-line treatment for patients over 55 years with hypertension.	Inhibition of the activity of angiotensin-converting enzyme, component of the RAAS system, which converts angiotensin I to angiotensin II, a vasoconstrictor, and hydrolyzes bradykinin, a vasodilator.	Increasing of ACE2 expression, facilitating SARS-CoV-2 entry into cells.	Increasing risk of contracting SARS-CoV-2 is still to be demonstrated. EMA confirms that hypertensive patients COVID-19 positive must continue to use ACE inhibitors as advised by their doctors.	**No information in relation to sex**
ARBs	Treatment of patients with hypertension and heart or kidney diseases.	Binding and inhibition the AT_1 and thereby blocking the arteriolar contraction and sodium retention secondary to RAAS system activation.	Increasing of ACE2 expression, facilitating SARS-CoV-2 entry into cells.	Increasing risk of contracting SARS-CoV-2 is still to be demonstrated. EMA confirms that hypertensive patients COVID-19 positive must continue to use ARBs as advised by their doctors.	**No information in relation to sex**

Summary of highlights, strength and limitations of coagulative disorders therapy in COVID-19 patients.

4. The RAAS and COVID-19

ACEIs and ARBs are recommended as first-line treatments for patients under 55 years with hypertension and second-line treatment for those over 55. ACEIs are also widely used to treat congestive cardiac failure. There are several controversial hypotheses on the potentially harmful or beneficial effects of antihypertensive drugs acting on the renin-angiotensin-aldosterone system (RAAS) in COVID-19 [59,60]. SARS-CoV-2 interfaces with the RAAS through ACE2. It is now understood that SARS-CoV-2 utilizes the ACE2 receptor as its main entry portal in the target cell and possibly as a route of secondary "metastatic" end-organ disease [61]. The interaction between the virus and ACE2 may be one determinant of its infectivity, and there are concerns that RAAS inhibitors may change ACE2 expression and hence COVID-19 virulence. *In vitro* and in vivo studies have demonstrated that ACEIs as well as ARBs can significantly increase ACE2 expression, thereby facilitating SARS-CoV-2 entry into cells [62,63]. Mechanistically, it is possible that ACE2 tissue level changes in response to ACEIs/ARBs in humans, but large clinical studies have not yet confirmed this. However, it has also been described that viral binding to ACE2 decreases its surface expression and prevents angiotensin-II cleavage by ACE to generate angiotensin$_{1–7}$, which counterbalances the effect of angiotensin-II signaling through AT_1R. Hence, binding of angiotensin-II to AT_1R leads to increased pulmonary vascular permeability, resulting in lung injury [64,65]. By blocking AT1R-mediated angiotensin-II adverse effects and increasing ACE2-mediated production of angiotensin$_{1–7}$ production, ARBs may counteract this effect and reduce lung damage [4].

4.1. ACE inhibitors and angiotensin-II receptor blockers use in COVID-19 patients

A literature search for ACE2 updated to June 2021 returned more than 30,000 articles, largely classified as reviews. A big push to publish data on ACE2 comes from the current pandemic event, marking a gender difference in disease evolution. Indeed, women seem to be more protected than men from disease progression, and this evidence has been linked to higher ACE2 levels in female subjects. However, ACE2 identification goes back to more than 20 years ago, and research continued for years in this field because ACE2 is strongly engaged in blood pressure regulation and cleaves a range of substrates involved in different physiological processes. Estrogens are believed to inhibit the activity or expression of different components of the RAAS system. E2 upregulates ACE2 expression [3], which is accordingly higher in females than in males. Binding of SARS-CoV-2 spike protein to ACE2 induces ACE2 down-regulation, which in turn leads to decreased angiotensin$_{1–7}$ production in the lung, resulting in acute respiratory injury. Therefore, higher estrogen levels leading to ACE2 over-expression could account for better outcomes and improved survival in female patients [66]. The X-linked nature of the ACE2 gene, with females showing a wide range of phenotypes, may have a greater role than that defined so far in the

Table 2
Antiviral therapies overview.

Drugs	Approval (EMA)	Mechanism of action	Efficacy	Safety
Remdesivir	Yes Patients with pneumonia under oxygen therapy who do not require high-flow oxygen or mechanical ventilation or ECMO and with onset of symptoms for less than 10 days	Inhibit RNA polymerase activity	Still to be demonstrated **No difference in recovery rate ratio between male and female (One clinical trial)**	Safe **Reported different AE in relation to sex (One pharmacovigilance study)**
Lopinavir/ ritonavir	No	Lopinavir: protease inhibitor. Ritonavir: enhances pharmacological exposure	Not effective **No information in relation to sex**	Higher than umifenovir [84] **No information in relation to sex**
Umifenovir	No	Inhibit several stages of the viral life cycle	Under investigation **No information in relation to sex**	Safe [85] **No information in relation to sex**
Favipiravir	No	Inhibit RNA polymerase activity	Under investigation **No information in relation to sex**	Favipiravir vs control groups: less odds for adverse effects in the Favipiravir arm but of no statistical significance [86] **No information in relation to sex**

ECMO: Extracorporeal Membrane oxygenation.

gender differences observed in COVID-19 pathogenesis.

Estrogens influence the vascular system by inducing vasodilatation, inhibiting vascular remodeling processes, and modulating both the RAAS and the sympathetic system. This leads to a protective effect on arterial stiffness during reproductive age that is dramatically reversed after menopause. Having established that it is essential not to suspend antihypertensive therapies even in case of coronavirus infection, it is important to underline this also in terms of sex differences. Men and women differ in prevalence, awareness, and control rate of hypertension in an age-dependent manner. Studies suggest that sex hormones changes play a pivotal role in the pathophysiology of hypertension in post-menopausal women. Data on the efficacy of antihypertensive therapy between genders are conflicting, and the underrepresentation of aged women in large clinical trials could influence the results. An interesting review by Ramirez and Sullivan, entitled *Sex Differences in Hypertension: Where We Have Been and Where We Are Going* [67], highlights that while men have long been known to display greater increases in blood pressure compared with women, only recently intense efforts have been made to enhance the awareness that women show similar risks to develop hypertension. Due to a) the uncertainty around harmful or beneficial effects of ACEIs and ARBs in COVID-19 patients, b) the need not to suspend antihypertensive therapies even in case of COVID-19 infection, and c) the evidence that antihypertensive therapy has been profiled mainly in men, it seems appropriate to stress the importance of sex differences also in this context (Table 1).

Summary Box

- **Highlights**

SARS-CoV-2 interfaces with the RAAS through ACE2: *in vitro* and *in vivo* studies demonstrated that ACEIs and ARBs can significantly increase ACE2 expression

- **Strengths**

Cardiovascular Societies published position statements strongly advising continued use of ACEIs and ARBs given a lack of evidence that RAAS drugs are unsafe

- **Limitations**

Uncertainty around possible associations of ACEIs and ARBs with COVID-19
Very few evidence on gender and sex differences for ACEIs and ARBs in COVID-19 management

Summary of highlights, strength and limitations of RAAS in COVID-19 patients.

4.2. Clinical trials of ACE inhibitors and angiotensin-II receptor blockers in COVID-19 patients

Based on several observational studies, there is accumulating evidence that ACEIs and ARBs do not increase the risk of contracting SARS-CoV-2 infection. Specifically, there is no evidence of harm due to anti-RAAS medications in COVID-19 [68–70]. On the other hand, conflicting findings regarding the role of ACEIs and ARBs as prognosis modifiers in COVID-19 hospitalized patients have been reported [66,71–73]. Published studies on this research question generally suffer from small sample size, which prevents extensive analyses. Furthermore, the identification of all covariates related to prior use of chronic medications may not be accurately evaluated in the setting of a healthcare emergency, when data are collected prospectively. The mixed quality of studies investigating whether ACEIs and ARBs use can modify the prognosis of COVID-19 is due to the fact that two meta-analyses of observational studies reported contrasting results. One meta-analysis suggested a protective effect of RAAS inhibitors regarding all-cause mortality and critical illness [74], while the other one found no significant association with all-cause mortality [75]. In addition to contradictory results, these meta-analyses are problematic because they included an observational study that has since been retracted [76]. This highlights the need for large-scale studies using appropriate methods to investigate whether prior ACEIs and ARBs use among COVID-19 patients improves or worsens outcomes. Analysis of ongoing trials from clinical trials.gov reports encouragingly studies testing the effect of angiotensin modulators on clinical outcomes in COVID-19 patients at high-risk for cardiovascular disease recruiting all sexes (NCT04591210, NCT04364893, NCT04364984, NCT04331574).

5. Antiviral therapy

Antiviral drugs (i.e. remdesivir, lopinavir/ritonavir, favipiravir, umifenovir) developed for viruses other than SARS-CoV-2 have been among the first drugs proposed for the treatment of COVID-19 (Table 2). These drugs can inhibit either viral entry (via the ACE2 receptor and TMRSS2), viral membrane fusion and endocytosis, or the activity of the SARS-CoV-2 3-chymotrypsin-like protease and the RNA-dependent RNA polymerase [77]. Remdesivir is an antiviral drug of the nucleotide analog class developed for the treatment of Ebola virus disease and also used for the treatment of SARS-CoV-2 infections [78]. The association of two antiviral drugs such as lopinavir and ritonavir, used for the treatment of HIV, were also proposed for SARS-CoV-2 infection in the first phase of the pandemic. Lopinavir is a protease inhibitor, while ritonavir enhances its pharmacological exposure by inhibiting the cytochrome P450 (CYP) isoenzyme 3A4. [79] In a recent published meta-analysis, remdesivir did not demonstrate efficacy for hospitalized COVID-19 patients [80]. Although its efficacy has still to be demonstrated [81,82], remdesivir is approved in clinical practice for treatment of hospitalized patients with pneumonia under oxygen therapy not requiring high-flow oxygen or mechanical ventilation or extracorporeal oxygenation and with onset of symptoms for less than 10 days. Another systematic review and meta-analysis assessing the efficacy and safety of lopinavir/ritonavir in COVID-19 patients reported no significant advantage and more adverse events in the use of these drugs over standard of care (supplemental oxygen, ventilation, antibiotic agents, vasopressor support, renal replacement therapy, and extracorporeal membrane oxygenation), or over other antiviral agents [83]. Thus, the lopinavir/ritonavir association is not used for the treatment of COVID-19 in clinical practice and its off-label use has been suspended by EMA.

Two broad-spectrum antiviral agents, favipiravir and umifenovir, are being tested for the treatment of SARS-CoV-2 infection. Umifenovir is approved in Russia and China for prophylaxis and treatment of

influenza, and it exerts its antiviral effects via a direct-acting viricidal activity and by inhibiting several stages of the viral life cycle [87]. Favipiravir is used to manage influenza and has the potential to treat RNA virus infections by inhibiting RNA polymerase activity [88]. Both favipiravir and umifenovir are now under investigation in many clinical trials but are not approved in Europe and USA due to limited clinical evidence. Preliminary results suggest a potential activity of favipiravir in the treatment of the patients in mild-to-moderate COVID-19, in particular with regard to the time of clinical cure [89].

As for viruses other than SARS-CoV-2-19, published evidence shows that the efficacy and safety of antiviral drugs differs between sexes [90] and the adverse reactions to antiviral drugs are typically more serious in females than males. The beneficial effects of antiviral treatments for viral disease might differ by gender likely due to two main reasons: the first one involves the pharmacokinetics profile of men and women, and the second one refers to sex hormone status that could influence the outcomes of the antiviral therapy [90]. Treatment of the infection caused by *Herpes simplex* or influenza A viruses seems to induce better clinical and virologic outcomes in males [90]. As for COVID-19, two observational studies on drug utilization by gender of antiviral drugs reported higher use of antiviral drugs among men (see relevant Summary Box). The first study by Rivera et al. performed in the United States on 2186 adults with invasive cancer and confirmed diagnosis of COVID-19 analyzed a subcohort of patients receiving remdesivir [91]. The study shows that the probability to receive remdesivir tended to be higher in males (1.24 – CI: 0.84–1.85). The second study by Vernaz et al. was conducted in Switzerland and analyzed a cohort of patients receiving lopinavir/ritonavir (83 patients) versus standard of care [92]. The authors reported that the probability of receiving lopinavir/ritonavir was also higher in men ($p = 0.05$). As discussed by Rivera et al., a possible explanation of this higher use among men might be that male patients, who are more vulnerable to COVID-19 such as obese patients and patients with hypertension, are more likely to receive any anti-COVID-19 therapy. A randomized, double-blinded, placebo-controlled, clinical trial by Beigel et al. analyzed 541 patients (352 males; 189 females) in treatment with remdesivir and 521 in treatment with placebo (332 male, 189 female) [93]. While reporting a benefit in the use of remdesivir for both sexes, the authors showed no difference between male and female in the recovery rate ratio (males: 1.30 (1.09–1.56); females: 1.31 (1.03–1.66)). Anyway, no specific outcome for mortality and safety was shown in relation to sex. As for safety, a recent meta-analysis reported that remdesivir could be safely administered to hospitalized patients [94]. A pharmacovigilance study published in preprint by Zhang and colleagues analyzing data from the FAERS reported a network association of remdesivir with cardiac arrest in both males and females. The authors also reported that, while women are at increased risk for hypoxia, hypotension and renal impairment, remdesivir treatment in male patients is associated with respiratory failure [95].

5.1. Clinical trials on antiviral drugs and COVID-19 in relation to gender

Two studies in clinicaltrials.gov, assessing the use of antiviral agents for COVID-19, reported in the summary schedule a stratification of results by sex: NCT0468443 (completed) and NCT04569851 (enrolling). Unfortunately, none of the studies has reported outcomes yet. Moreover, although antiviral agents were reported as intervention in these studies, no information about the reporting of the results by specific treatment and gender/age was shown in the summary schedule, nor was found information about a possible stratification of pre- and post-menopausal women (see relevant Summary Box).

Summary Box

- **Highlights**

As for viral infection other than SARS-CoV-2, females suffer greater adverse effects then men following antiviral agents administration, while men undergoing the same therapy display beneficial effects
Antiviral agents are used more in men than in women with COVID-19
No difference in recovery rate ratio between male and female with COVID-19 (results form one RCT)

- **Strengths**

Remdesivir can be safely administered in COVID-1 hospitalized patients

- **Limitations**

Poor evidence on the efficacy of antiviral drugs from recently published meta-analysis
No information on efficacy and safety of antiviral agents with respect to age and very limited informations in relation to sex

Summary of highlights, strength and limitations of antiviral therapy in COVID-19 patients.

6. Monoclonal neutralizing anti-SARS-CoV-2 antibodies

Monoclonal antibodies (mAbs) represent a novel therapeutic approach for the treatment of non-hospitalized COVID-19 patients. These drugs have been approved by FDA and EMA, and have been recently added to the therapeutic offer for recently diagnosed (3 days) COVID-19 patients above age 12 who do not require supplemental oxygen and are at high risk of progressing to severe COVID-19. The neutralizing mAbs against SARS-CoV2 are bamlanivimab, bamlanivimab associated with etesevimab, and the combination casirivimab and imdevimab.

With regard to bamlanivimab and etesevimab, these drugs are potent antispike neutralizing mAbs originating from two different patients recovered from COVID-19 in North America and China, respectively. The rationale of combining these two compounds comes from preclinical data indicating that etesevimab can interact with a different epitope with respect to bamlanivimab. Thus, the association should neutralize resistant variants with mutations in the epitope normally bound by bamlanivimab. These drugs have been approved in confirmed COVID-19 patients according to the BLAZE-1 study. This study is a still recruiting randomized phase 2/3 multicentric trial composed by 9 arms. Indications that such combination may represent an effective treatment emerged also from the reduced number of hospitalizations, emergency room access or death within 28 days after treatment. Similar results were found in the at-risk population also including pregnant and pediatric populations (12–17 years) with one or more predisposing factors

for severe disease progression.

Another mAb combination is REGN-COV2, i.e. the association of casirivimab and imdevimab. Such combination is made of two recombinant human IgG1 against SARS-CoV-2 mAbs unmodified in their Fc regions. Casirivimab and imdevimab bind to non-overlapping epitopes of the spike protein RBD. This combination has been provisionally approved in adult and pediatric (above 12 years of age) outpatients. However, the efficacy, safety and tolerability of REGN-COV2 is still under evaluation in a randomized, quadruple-blind, placebo-controlled clinical trial (still recruiting, NCT04425629).

Anti-COVID-19 mAbs can be routinely used in the clinical context; however, these drugs could be randomly assigned considering that these EMA/FDA approved drugs can be prescribed and requested with a therapeutic interchange approach. An observational study has just been registered with the aim of evaluating in a pragmatic way the therapeutic exchange policy for these drugs and will include adult and old patients, both males and females. There will be three treatment arms (bamlanivimab, casirivimab + imdevimab, and bamlanivimab + etesevimab). This study will help compare the effectiveness of different mAbs that has not been directly tested yet.

sub-concentrations of Ab or non-neutralizing Ab has been associated with enhancement of viral entry, replication in target cells and cytokine release [96].

After vaccination, complete immunization may take several weeks, thus passive immunization post-prophylaxis, as the one proposed in the above study, might represent an immediate long-term protection since modifications of Fc regions would prolong their half-life for weeks or even months [97]. The intramuscular use of this mAb is under evaluation and might help to simplify their use.

Studies are still ongoing and may offer the advantage to highlight gender differences in recruited subjects. Unfortunately, results and ad interim analyses are not available yet. We expect that the data deriving from the use of these drugs in mild COVID-19 patients stratified by sex or age could represent a great advance in the knowledge of their efficacy and safety in specific populations allowing specific tailoring of the therapeutic strategy. Therefore, based upon the above evidence, we expect that these sex-driven differences in mAb disposition may also occur in COVID-19 patients, thus more gender-focused research would help optimize mAb use in clinical settings.

Summary Box

- **Highlights**

mAbs represent a novel therapeutic approach for the treatment of non-hospitalized COVID-19 patients

- **Strengths**

These drugs can also be administered in pediatric population (from 12 years) and are under evaluation also in pregnant women

- **Limitations**

These drugs needs to be administered in a correct timeframe in hospitalized setting. The presence of sub-concentrations of Ab or non-neutralizing Ab has been associated with enhancement of viral entry and replication in target cells and increased cytokine release

Regdanvimab, another mAb directed against the Spike protein, is provisionally approved by EMA for reducing risk of hospitalization in mild COVID-19 patients at high risk of progressing to severe form of the disease. Regdanvimab is currently evaluated in a phase 2/3 (still recruiting) randomized, parallel-group, placebo-controlled, double-blind clinical trial conducted in both sexes in SARS-CoV-2 patients over 18 years of age.

Biochemical modification in the Fc portion of the Ab, along with other modifications such as PEGylation, are additional approaches to improve properties of this type of treatment for severe patients. AZD7442 is a combination of two mAbs (AZD8895 and AZD1061) for intramuscular administration under phase III trial (still recruiting, NCT04723394) characterized by substitutions in amino acid composition in their F_c fraction with the aim of extending their half-lives. The modification reduces F_c effector function and decreases the potential risk of antibody-dependent enhancement of disease. The presence of

Summary of highlights, strength and limitations of neutralizing antibodies therapy in COVID-19 patients.

7. Immunosuppressive and immunomodulatory drugs

Physiologic gender-related differences in immune responses contribute to the gender gap in COVID-19 outcomes, as females most likely experience a mild disease compared to males [98]. The immune system hyperactivation in response to SARS-CoV-2 infection justifies the use of immunomodulatory and immunosuppressive drugs routinely used for treatment of autoimmune diseases or after solid-organ or hematopoietic stem cell transplantation [99]. SARS-CoV-2 deeply alters the immune balance in males by causing hyperactivation of kinin, complement, and coagulation cascades and enhancing macrophage-mediated phagocytosis, massive pro-inflammatory cytokine release (cytokine

storm), and amplification of inflammation and immune responses, ultimately leading to pulmonary edema, thrombotic microangiopathy and acute respiratory distress syndrome (ARDS) [100]. Sex hormones can deeply influence composition and functions of the immune system favoring T helper 1 (Th1) and B cell-mediated responses, also in SARS-CoV-2 infection [101,102]. For example, males show augmented circulating levels of innate response-related pro-inflammatory cytokines, such as IL-8 and IL-18, and of non-classical monocytes, while females have an enhanced T cell-mediated immune response and lower cytokine levels [103]. Therefore, based on gender differences in SARS-CoV-2 epidemiology and immune responses during infections, gender-related variations in responsiveness to immunomodulatory and immunosuppressive drugs repurposed for treatment of COVID-19 can be foreseen.

7.1. Immunosuppressive therapies

Few prospective studies with immunosuppressive or immunomodulatory drugs have been conducted for Covid-19 treatment, while most of available data come from observational studies of incidence and outcomes of solid organ or hematological transplanted patients under immunosuppressive treatment, or subjects with autoimmune disorders [104]. Two large nationwide studies on liver transplant patients under immunosuppressive therapies have been conducted in Europe; however, both studies started with the bias that more than 70% of recruited subjects were males. Incidence of COVID-19 in these subjects is reported to be low probably because of self-isolation [105]. Calcineurin and mTOR inhibitors have a protective role in liver transplant patients as drug continuation is associated with a mild-moderate disease, while immunosuppression discontinuation right after COVID-19 diagnosis or mycophenolate therapy are related to worse outcomes [106]. Mycophenolate, a reversible non-competitive inhibitor of purine and DNA synthesis essential in lymphocytes, might synergistically deplete T lymphocytes during SARS-CoV-2 infection, which impair viral clearance and contribute to poor prognosis [106,107]. In the SETH study, a similar number of liver transplant females develop either mild/moderate or severe disease (19% vs 13%; $p = 0.189$) [108]. However, gender-based statistical analysis was not performed, and some female-related pharmacokinetics differences in cyclosporine or tacrolimus concentrations might have been diluted within the large number of males (71.2%) enrolled in the study [109,110]. Based on the beneficial effects of cyclosporine, tacrolimus, and everolimus in Covid-19 transplanted patients, the pragmatical, randomized (1:1), open-label, single-center, phase II TACROVID clinical trial has been designed to evaluate the efficacy and safety of methylprednisolone pulses, tacrolimus, and standard of care in severe COVID-19 patients [111]. TACROVID is still recruiting (NCT04341038), and patients are randomly assigned 1:1 to the experimental arm receiving methylprednisolone pulses of 120 mg/day for three consecutive days and tacrolimus twice daily to achieve a trough concentration of 8–10 ng/mL.

In a retrospective, single-center, observational study conducted on 607 Spanish patients, gender was not reported as a risk factor for death in a multivariate analysis, while cyclosporine at accumulated dose of 300 mg significantly decreased mortality of COVID-19 patients [112]. The investigators also considered gender-based differences in cyclosporine pharmacokinetics. This high efficiency of cyclosporine in reducing 4-fold the mortality among COVID-19 patients might be related to the ability to modulate immune responses avoiding hyperactivation of immune cells and tissue damage, and to inhibit viral replication likely by interfering with cyclophilin, which is important in the SARS-CoV-2 life cycle [113]. An Italian study confirms these data, supporting the gender-independent protective role of calcineurin inhibitors from developing severe COVID-19, especially among transplanted patients [114].

7.2. DMARDs

Drugs for treatment of rheumatoid arthritis and other autoimmune diseases have shown similar efficacy in reducing hospitalization and death rates compared to the general population [115–118]. Compared to transplanted patients, subjects with autoimmune disorders enrolled in these studies were mostly females [119]. Results from a US study showed similar hospitalization rates between patients with or without rheumatic disease, and similar mortality; however, multivariate analysis was not adjusted for type of immunosuppressive therapy, and management of immunosuppressive medications during SARS-CoV-2 infection was not known in over 60% of study subjects, thus making difficult a generalization of these results [120].

Patients with rheumatic diseases under immunosuppressive agents or DMARDs are not at increased risk of severe COVID-19 with incidence of positivity for SARS-CoV-2 infection ranging from 0.22% to 1.25% in three Italian surveys [121–123]. In addition, older males with rheumatoid arthritis treated with methotrexate are more likely to require hospitalization for Covid-19 compared to females with other rheumatologic diseases [124]. Similarly, Gianfrancesco et al. confirmed increased hospitalization rate of males with rheumatic disorders and under steroid treatment (> 10 mg/day prednisone-equivalent glucocorticoids) [125].

Overall, DMARDs have shown a protective role against severe COVID-19 in patients with autoimmune and rheumatologic disorders in both sexes, except for methotrexate that seems to be linked to a higher risk of hospitalization especially in older males.

7.3. JAKi

JAKi, such as ruxolitinib and baricitinib, have been used for treatment of COVID-19 patients because of their ability to modulate cellular and humoral immune responses [126,127]. JAKi can reduce viral replication, as described for ruxolitinib in HIV inhibition in in vitro and mouse models, and for baricitinib in SARS-CoV-2 inhibition of host proteins (numb associated kinases) involved in viral entry and replication [128–130]. A total of 12 studies using JAKi for Covid-19 treatment are reported (ruxolitinib, $n = 3$; baricitinib, $n = 8$; and tofacitinib, $n = 1$), showing a clinical benefit of this drug class in reducing invasive mechanical ventilation needs in severe COVID-19 patients presumably more likely in females, while not influencing hospitalization length [131–133]. However, these studies have several limitations: recruited patients were mostly males, and JAKi therapy was likely confounded by other concomitant interventions, such as the anti-complement C5 monoclonal antibody eculizumab or the antiviral agent remdesivir [131,132,134,135].

Summary Box

- **Highlights**

Calcineurin and mTOR inhibitors and JAK inhibitors can reduce immune system hyperactivation and subsequent tissue damage, and inhibit viral replication
Methotrexate and mycophenolate increase the risk of severe Covid-19 likely by synergistically depleting T lymphocytes and impairing viral clearance

- **Strengths**

Calcineurin, mTOR, and JAK inhibitors have a protective role against severe Covid-19 in both sexes

- **Limitations**

Only retrospective observational studies with several confounding, such as use of several drugs simultaneously and gender-prevalence in study enrollment (e.g. male prevalence)

Summary of highlights, strength and limitations of immunosuppressive therapy in COVID-19 patients.

8. Glucocorticoids

After an initial stage of viral replication, SARS-CoV-2 infection can be followed by a second stage characterized by a hyperinflammatory response that dysregulates cytokine secretory patterns [136]. This condition drives lung epithelial cells and vascular endothelial cells injury leading to lung infiltration of neutrophils and macrophages. Recent studies show that the pro-inflammatory pattern has been driven by IL-6 as well as other cytokines/chemokines [137]. Male patients are reported to have higher plasma levels of IL-8 and IL-18, while females show T cell activation more consistently than males during SARS-CoV-2 infection [103]. Given the hyperinflammatory response to SARS-CoV-2 virus, the rationale of glucocorticoid (GC) use in treating COVID-19 is to decrease the inflammatory responses in the lungs and control the acute lung injury and acute respiratory distress syndrome [77]. GCs are used in clinical practice in patients with severe COVID-19 disease who require oxygen supplementation with or without an invasive or non-invasive mechanical ventilation. A recent systematic review and meta-analysis shows that GCs are associated with decreased all-cause mortality in severe COVID-19 patients with no increase in the incidence of serious adverse events [138]. Given that GCs are the primary physiological anti-inflammatory hormones, and that sex hormones may also have immune-modulatory functions, a link between GCs and sex hormones emerges from several studies (see relevant Summary Box) [139].

A WHO prospective meta-analysis reported the association between systemic GC use and mortality among critically ill patients with COVID-19. In the specific subgroup analysis, they found no evidence that the effect of GCs on 28-days mortality varied with age ($<=$ 60 vs 60+) or gender [140]. With a large number of clinical trials assessing the use of corticosteroids in patients with COVID-19, two observational studies analyzed gender differences in relation to corticosteroid use. The first study by Wu et al., conducted in China in 382 patients, of which 226 on treatment with GCs (150 males, 76 females), reported that GCs were used significantly more frequently in men ($p = 0.0135$) and in younger patients ($p = 0.0077$) [141]. The other observational study by Monedero et al. conducted in Spain and Andorra evaluated 882 patients, of which 691 received GCs [142]. Patients were stratified into those who received early (before or within the first 48 h in the ICU) or delayed GCs ($>$ 48 h after admission to the ICU) and those who did not receive GCs. Females receiving early- and delayed GCs were 153/485 and 72/206, respectively (no statistical difference between groups was found). No statistical difference in patient age was observed between groups ($p = 0.06$). The Authors also compared mortality for early vs non-early GC patients: in the sensitivity analysis of the study, use of early GCs was not as effective in women and patients with age $<$ 60 years, while a statistical difference was seen among male patients (hazard ratio: 0.68; CI 0.51–0.90; $p = 0.006$) and patients $\geq$ 60 years (hazard ratio: 0.69; CI 0.54–0.89; $p = 0.004$).

8.1. Clinical trials on glucocorticoids

Two studies assessing the use of GCs for COVID-19 and reporting stratification of results by sex or outcomes for pregnant women in the summary schedule were found in clinicaltrials.gov. Only one study (NCT04462367: recruiting) reported gender as an outcome measure. None of the above studies has reported outcomes yet. Moreover, although GCs are mentioned in the intervention section, information about neither results by specific treatment and gender nor stratification of pre- and post-menopausal women was found in the summary schedule.

Summary Box

- **Highlights**

Potential link between corticosteroids and sex hormones in the regulation of immune response that can differentiate the response to corticosteroids based on gender and/or age (pre- or post-menopausal)
Results from meta-analysis report no evidence that the effects of corticosteroid on 28-days mortality may vary with age or gender in COVID-19 patients
Early use of corticosteroids (before or within 48 hours from admission in ICU) was not consistently effective in female and younger COVID-19 patients as shown in one observational study

- **Strengths**

Use of corticosteroids is associated wit a decreased all-cause mortality in COVID-19 patients and did not enhance the incidence of serious adverse events

- **Limitations**

Poor evidence with respect to gender and age

Summary of highlights, strength and limitations of antiviral corticosteroid therapy in COVID-19 patients.

9. Monoclonal antibodies directed towards the cytokine storm

Multiple viral pathogens are known to induce a hyperinflammatory state, the so-called "cytokine storm". This has been considered as a prognostic factor for more severe clinical course of COVID-19. Based upon this evidence, the use of mAbs against ILs or IL receptors has been proposed as a useful therapeutic strategy to prevent clinical worsening and death. In this regard, drugs able to block inflammatory pathway such as TCZ, a humanized IgG1 mAb directed against IL-6R, have been commonly used for most severe cases. TCZ binds IL-6 receptors and blocks intracellular signal transduction. This action has effects on both the immune system, considering that it inhibits the action of inflammatory mediators involving B and T lymphocytes and inflammation, because it inhibits the production of acute phase proteins [143]. Several clinical trials investigated the beneficial role of TCZ in severe COVID-19 patients. Clinical improvement has been evidenced in open-label studies in COVID-19 patients [144–146]. However, the usefulness of this treatment has been questioned by negative results [147,148], and some Authors remained critical [145].

Sarilumab, a fully IgG1 mAb against IL-6R, was reported not to be effective in a recent publication (highlighting the need for adequately powered trials involving biological immunomodulatory therapies for severe COVID-19) [149]. During the cytokine storm $CD4^+$ T lymphocytes rapidly convert into pathogenic Th1 cells with production of GM-CSF also in the lungs. Therefore, strategies to reduce GM-CSF levels have been proposed as possible mechanisms for reversing such pathologic conditions. In this light, drugs acting in synergism with antiviral agents that block GM-CSF, such as the mAb gimsilumab, have been tested for lung injury or Acute Respiratory Distress Syndrome (ARDS) due to COVID-19 in a phase 2 clinical trial (NCT04351243). This trial enrolled severe COVID-19 patients who were either male or non-pregnant females 18 or older. Another experimental strategy that is being pursued is blocking of IL-1 cascade. However, the anti-IL-1β mAb canakinumab, under investigation in phase 3 randomized double-blind trials in hospitalized COVID-19 with pneumonia and cytokine release syndrome in patients of both sexes, failed to meet primary and secondary endpoints according to a statement from Novartis (NCT04362813-CANCOVID). On the other hand, intramuscular anakinra was shown to prevent respiratory failure in a subclass of COVID-19 patients [150] and an observational retrospective study, part of the COVID-19 Biobank study (NCT04318366), comparing anakinra at low or high dose in severe COVID-19 patients, evidenced a possible efficacy and safety of the higher dose when given in the right time frame [151].

9.1. Sexual dimorphism of mAb disposition and efficacy

Fluctuations in hormonal status due to pharmacological intervention (hormone replacement/contraception) or life conditions (pregnancy, lactation, or menopause) may affect disposition of drugs, including biological agents [152]. mAbs are metabolized by several mechanisms, one of which is the interaction with macrophage FcR or Fcγ receptor that bind the tail of antibodies, while the FcRn protects IgG from intracellular catabolism. Thus, the clinical outcome of mAb therapy may be improved by increasing FcR avidity. This could be a future perspective for improving mAb-based COVID-19 therapy, considering that lung disposition may represent a limitation for these treatments. Interestingly, mAb can cross the placental barrier through FcRn-mediated transport ending up with passing maternal Ab in the fetal circulation [153,154]. Therefore, mAbs holding the Fc portion can cross the placenta during the third trimester since such portion is recognized by FcRn. However, limited data are available in regard to mAb in pregnancy and even less so in females affected by COVID-19, thus it is very difficult to gain sex-driven information in the efficacy and safety profile of mAbs used in this context.

Interestingly, FcR expression and function are under control of several hormones, including sexual hormones. Indeed, it has been reported that estrogens augment IgG clearance by enhancing macrophage action mediated through Fc receptor interaction [155], while PG may reduce Fcγ expression leading to higher macrophage-mediated Ab clearance [156]. Furthermore, other conditions that are more prevalent in women, such as alteration in thyroid function or increased immune response to infectious disease, might modulate mAb disposition and efficacy.

Although evidence comes mainly from preclinical data, human studies have indicated sex differences in mAb pharmacology [157]. In this regard, TCZ displayed a lower clearance rate in females compared to males in patients with rheumatoid arthritis [158]. Sex differences clearly exist in antibody-mediated effector functions across women and men, tuned by sex-dependent differences in response to antibody effector function. However, it should be noted that different reactions to the same biological agent might depend not only on sex differences but also on pathogenic conditions. Indeed, the anti-CD20 antibody rituximab is more effective in females when used as an anticancer agent [159], while it is more effective in males when used as an immunosuppressant in autoimmune disease [160].

10. Sex differences in response to COVID-19 vaccines

Clinical data [161,162] have shown that male and female individuals have different immune responses to infections and vaccines: women

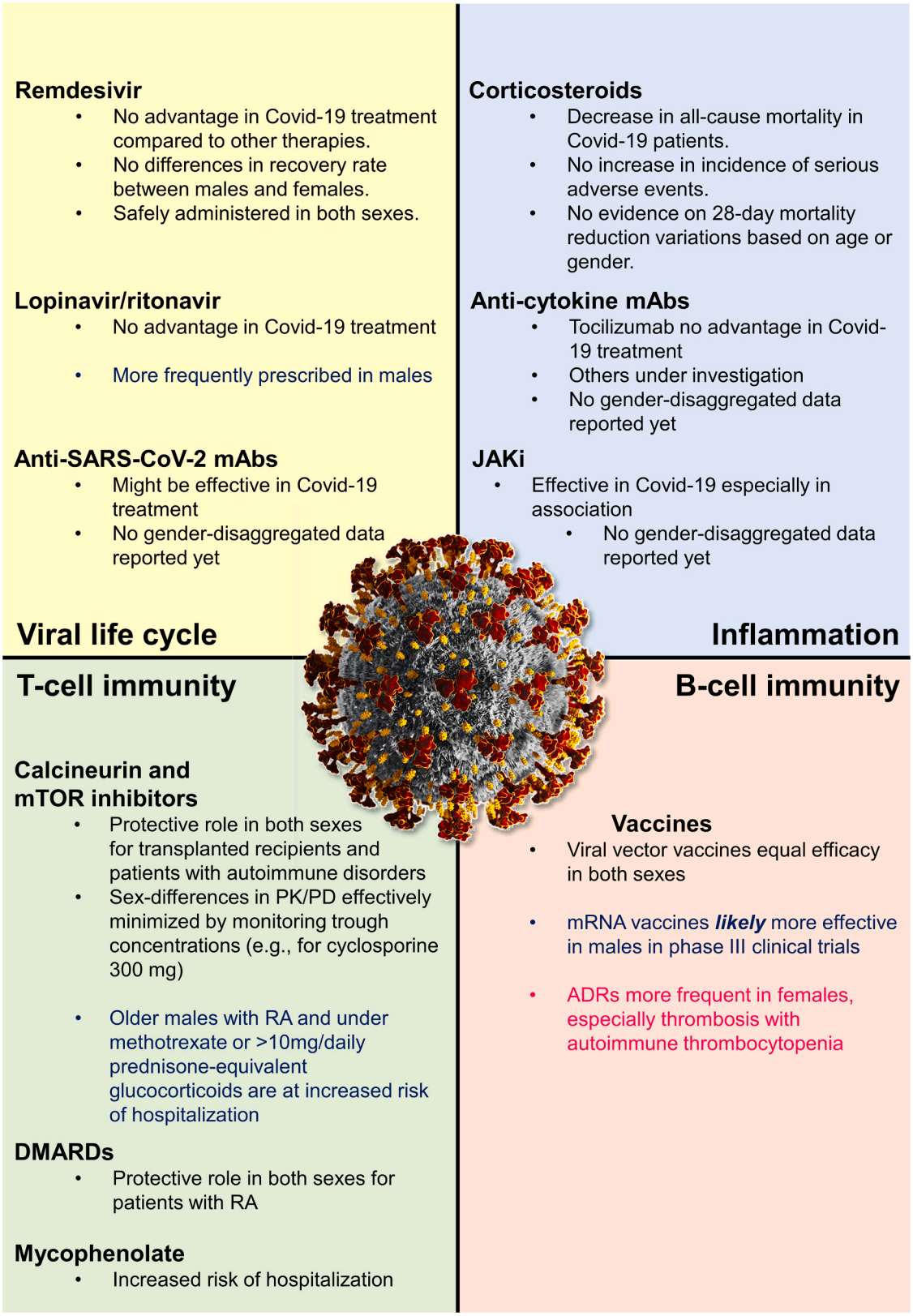

Fig. 2. Classes of drugs and vaccines used to treat or prevent SARS-CoV-2 infection and development of COVID-19. Blue color highlights prevalence in male vs. female sex. Pink color highlights prevalence in female vs. male sex. Black color indicates no significant differences between male and female sex.

usually mount a more intense immune response with antibody titers even twice as high as those reached in men (see relevant Summary Box). The biological mechanisms underpinning the sex bias in vaccine immune response are mainly based on sex hormones and genetic/epigenetic mechanisms that can modulate immune responses. However, these differences are not considered in dosage and schedule of

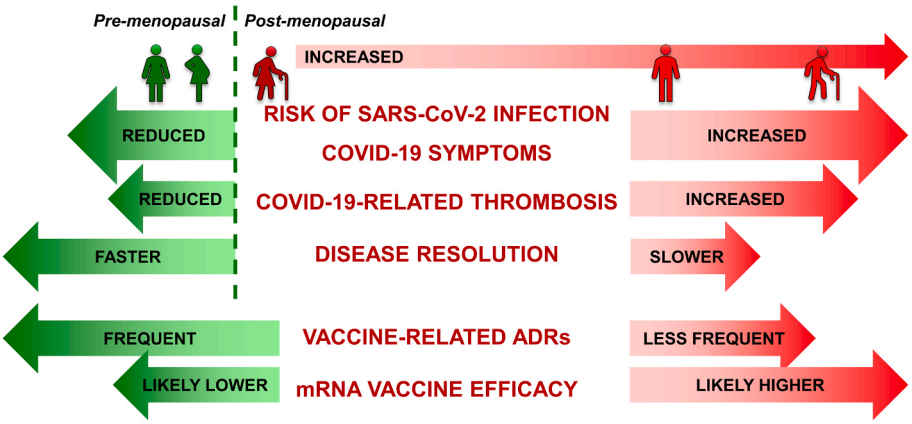

Fig. 3. COVID-19-related effects attributable to sex steroid action/sexual differentiation/gender. Differences have been depicted following comparison between male and female individuals according to age, and with respect to pregnancy, premenopausal or post-menopausal condition. Disease outcomes (e.g. infection and symptoms severity, inflammatory state, risk of thrombosis) are shown in green for young and pregnant females, indicating a protective condition. Detrimental conditions exacerbating COVID-19 (young and elderly males, post-menopausal females) are shown in red.

vaccination. In this context, Engler et al. [163] showed that seasonal TIV with half dose of vaccine in women induced protective HI antibody titers at levels similar to those induced in men with the full dose. With regard to COVID-19 vaccines, these have only recently been distributed and become available for widespread use. Therefore, data from sex comparison of anti-S antibody titers following vaccination are just starting to be available [164]. The phase 2/3 clinical trials of all the new COVID-19 vaccine platforms (Pfizer/Biontech, Moderna, Astra Zeneca, Johnson&Johnson and Sputnik vaccines) included men and women. Sex-disaggregated data published so far suggest an inverse trend of the response between men and women compared to conventional vaccines [165–168]. In fact, higher efficacy has been observed in men for the two genomic vaccines (Pfizer, 96.4% in males vs. 93.7% in females; and Moderna, 95.4% in males vs. 93.1% in females, respectively) [165,166] as well as for the adenoviral vector-based vaccine (Sputnik, 94.2% in males vs. 87.5% in females, respectively) [168]. In the case of AstraZeneca adenoviral-based vaccine, similar humoral and cell mediated immune responses were shown in men and women [167]. These results are only preliminary and derived from trials on limited number of selected volunteers, thus they await to be confirmed after follow-up of widespread mass vaccination campaign.

Generally, the greater women immune responsiveness to vaccines is associated with more frequent and severe adverse effects of vaccination, duly reported in the AIFA annual report of vaccine post-marketing surveillance [169]. With regard to currently administered COVID-19 vaccines, distribution by gender of the reporting rates entered in the Italian National Surveillance Network, published in the AIFA report updated to March 26 [170], shows that the adverse effects were significantly more frequent in females (76%) than in males (23%), although the number of vaccinated females at the time of data analysis outnumbered that of men. Similarly, the data released in February by the US CDC on adverse effects during the first month of the COVID-19 vaccine showed that, while women received 61% of vaccine doses, 78.7% of side effects reported to the agency were from women [171]. Considering the rare and severe adverse effects to vaccines, such as allergic reactions, a 2019 study looking at vaccine adverse events reported to the CDC from 1990 to 2016 found that 80% of the reports of anaphylaxis in vaccinated adults came from women [172]. Following the 2009–10 H1N1 (swine flu) pandemic vaccination, four times as many women as men reported an allergic reaction to the H1N1 vaccine in the 20–59 age group [173]. In the case of COVID-19 vaccines, a severe adverse event seems to be plausibly related to AstraZeneca and Janssen vaccine administrations, namely the rare occurrence of thrombosis and thrombocytopenia mainly in women under 60 years [174]. EMA and AIFA recommended attention to prodromic symptoms of thrombosis in vaccinated individuals, and suggested to limit the use of these two vaccines to those over 60. The potential mechanism involved is the production of autoantibodies to platelet factor-4 (PF4), which is more common in young female subjects [175]. Various factors may contribute to these differences in adverse reaction occurrence, gender-related as well as related to biological sex differences [176] including the attitude of women to report more frequently to their doctors.

The new genomic and virus vector based COVID-19 vaccines await surveillance studies and follow-up of mass vaccination to unveil sex disparities in immune response in the same or the opposite directions as conventional vaccines.

Summary Box

- **Highlights**

Immune response to virus and vaccine is stronger in females than males
Antibody levels upon vaccination in women can be two-fold higher than in men
The mRNA vaccines licensed in EU countries as well as viral vector based (Sputnik, Astra Zeneca) included almost equal number of male and female volunteers in phase II/III clinical trials

- **Strengths**

All vaccines administered so far have shown high efficacy in inhibiting COVID-19 disease development

- **Limitations**

Sex disaggregated age-related efficacy of the COVID-19 vaccines in use are not available

Summary of highlights, strength and limitations of vaccines for COVID-19.

11. Pregnancy and COVID-19

So far, over 2000 scientific reports related to COVID-19 and pregnancy have been published. However, at present, disease severity in pregnant women is not apparent, and COVID-19 does not seem to increase the rate of miscarriage, stillbirth, preterm labor or teratogenicity. Pregnant women are not expected to be diagnosed with COVID-19 more than other healthy adults. Approximately two-thirds of pregnant women with COVID-19 have no symptoms at all, and most pregnant women who do have symptoms only have mild cold, breathlessness or flu-like symptoms, with only a small number of them developing severe disease [177]. Therefore, women may be more protected than men under physiological conditions including pregnancy or across the menstrual cycle, when fluctuation of reproductive steroids confers stronger immune protection. However, a small number of pregnant women did develop severe COVID-19. In particular, pregnant women with COVID-19 in the third trimester may have an increased risk of severe symptoms compared to non-pregnant women. In fact, physiological changes during pregnancy have an impact on the entire organism leading to a potential higher risk of COVID-19 progression. [178,179]. Increased rates of ICU admission, need for supplemental oxygen, ventilation and mortality have been observed in pregnant women with COVID-19, compared to non-pregnant women [179].

Two observational studies (NCT04582266: not yet recruiting and NCT04569851: recruiting) reported in the "measure outcome section" that they will investigate pregnancy outcomes. Although data are limited, pregnant women admitted to hospital with COVID-19 infection are likely to be at an increased risk of venous thromboembolic events.

Pregnancy or breastfeeding are contraindications to DOAC therapy [180], thus heparin would be the drug of choice in this case.

Interestingly, an observational study showed that COVID-19 symptoms severity escalated immediately postpartum in some SARS-CoV-2-positive pregnant women, even with mild or no symptoms. These observations have been correlated to the hormonal decrease that normally follows childbirth [181]. However, further studies are necessary to clarify whether the stress associated with the partum and post-partum could affect COVID-19 severity. In fact, stress-associated neuroendocrine-immune mechanisms may contribute to an increase in SARS-CoV-2 infection and influence the course of COVID-19 disease.

To date, most SARS-CoV-2-related clinical trials have excluded pregnant women and lactating women. This makes it difficult to provide evidence-based recommendations on SARS-CoV-2 therapies in these vulnerable patients and potentially limits their COVID-19 treatment options. The neutralizing monoclonal antibodies tested in the BLAZE-1 study (NCT04427501) included pregnant women along with pediatric population, but results have not been published yet. Another neutralizing antibody cocktail tested in REGN-COV2 study (NCT04425629) included pregnant women upon randomization. Outcomes from these studies are not available yet, but they might represent a valid alternative to the use of drugs contraindicated in pregnancy.

12. Traditional Chinese medicine and COVID-19

Reportedly, since the outbreak start, traditional Chinese medicine (TCM) has been applied to control COVID-19 spread along with government measures, public surveillance and utilization of conventional Western medicine. The therapeutic role of TCM has been included in guidelines on diagnosis and treatment of COVID-19 [182]. Use of traditional medicine to fight COVID-19 may be an option in low-income countries as well as in China.

A systematic review and meta-analysis based on 18 randomized controlled trials involving 2275 patients evaluated the clinical evidence on TCM for COVID-19 treatment. Compared with the conventional Western medicine-treated group, patients in the TCM-treated group showed significant improvements in lung computed tomography, clinical cure rate, ranging from mild to critical cases, length of hospital stay, total score of clinical symptoms and inflammatory biomarkers, with no evidence of severe adverse effects, discomfort or abnormal liver and kidney function [183]. Furthermore, a recent review of clinical studies suggested that TCM in combination with conventional Western treatment may be superior than conventional Western therapy alone in shortening the duration of main symptoms, reducing the aggravation rate and increasing the recovery rate [184]. Consistently, the combination of Chinese and Western medicines appears to be the mainstream for treatment of COVID-19 in China [185]. A retrospective study based on a real-world database suggested benefit in terms of lower mortality in patients receiving Qingfei Paidu Tang, a formula of TCM [186]. This appears to be one of the very few studies where the association was consistently found across sex and age subgroups. Findings from natural product and TCM databases may provide useful hints for mechanistic investigations [187] but tend to overestimate clinical benefit [185].

With regard to potential mechanisms, several TCM preparations activate ERs and flavonoids have estrogen-like effects. For instance, *Salvia miltiorrhiza* (Danshen) significantly upregulates ERα and ERβ mRNA and protein expression, increases serum E_2 levels and decreases follicle stimulating hormone and luteinizing hormone levels, whereas daidzein and genistein produce estrogen-like effects [188]. Overall, available data of TCM protection against CoVID-19 do not adequately take into account the gender variable. Thus, it would be highly enlightening if an ongoing pilot study of a combination of 13 TCM compounds testing the mixture safety for COVID-19 patients [189] performed sex-disaggregated analyses.

Generally speaking, quality and safety standards of TCM formulas appear to be variable, thus limiting widespread acceptance outside China [190]. Finally, specific TCM formulas such as Qingfei Paidu decoction could significantly modulate the pharmacokinetics of CYP3A substrate-drugs via inhibition of CYP3A, which on one hand may be exploited to boost immunomodulating agents but raises the issue of potential clinically relevant drug interactions when using traditional preparations with uncertain potential to interfere with drugs used in COVID-19 treatment [191].

13. Discussion and conclusion

COVID-19 is currently triggering enormous global demands on health systems and presents unprecedented challenges to identify effective drugs for prevention and treatment. At present, no specific drugs for SARS-CoV2 have been developed yet and all patients have been treated with off-label or repurposed drugs (Fig. 2). In the meanwhile, antibodies against the spike protein of SARS-CoV-2 and several vaccines are now becoming available. Unthinkable efforts have been made by the scientific community throughout a large number of clinical trials launched worldwide to fight and treat COVID-19 using biopharmaceuticals, small molecules and even traditional medicine approaches including TCM. However, it is now well established that COVID-19 exhibits gender disparities (Fig. 3). The false assumption that men and women are the same is evidenced by the inclusion of men in clinical trials with direct results extrapolation to women, while it is imperative to incorporate sex- and gender-related data into trials and analyse treatment outcomes disaggregated by sex and gender. Even though it is necessary to consider fetal risk during pregnancy, the hormonal interaction due to menstrual cycle or concomitant use of exogenous hormones, the complications in recruiting and the higher dropout rate of women, women's recruitment into clinical trials is indispensable.

Physiological differences in immune response are a Darwinian way to preserve females when infected by pathogens because of their importance in survival of the fittest. Moreover, females experience three different hormonal phases in their lives (pre-puberty, adulthood, and old age), in which the immune status changes because of physiological

variations in sex hormones before, during and after childbearing age, and because of a natural decline in immune responses due to ageing [101]. Therefore, sexual dimorphism in immunity is determined by a combination of several factors including sex hormones and age, but also epigenetic changes, environmental factors and genetic background [102], and results in greater protection of females against infectious diseases compared to males, who are more susceptible to develop tumors and severe symptoms during infectious diseases, such as MERS, tuberculosis or hepatitis [101].

All the above consideration are in line with differences encountered in COVID-19, where females display faster disease resolution and lower risk of thrombosis than males. Indeed, consistent with their highly reactive immune system, females experience vaccine-related ADRs to a larger extent than males. These facts are summarized in Fig. 3.

Clinical trials should indeed be powered to address sex-specific endpoints in pharmacological evaluation. This approach would help to avoid missing opportunities for identifying appropriate personalized sex- and gender-specific treatments and to achieve equality. Contrariwise, reinforcing sex-neutral claims into COVID-19 research may dangerously lead to exacerbating health inequities in care.

It has been too often overlooked by the scientific community, regulatory agencies and pharmaceutical companies that the initial phases of clinical trials are particularly and crucially important for detecting sex-related differences regarding pharmacokinetics and pharmacodynamics and providing data required to proceed to the following phases. In this regard, cost and economics should not be reasons for not conducting analyses by sex or of possible interactions of both endogenous and exogenous hormones with drugs. This is particular true for both basic and applied research.

In conclusion, the authors believe that, based on the relevant differences coming from the studies in the current literature, a sex- and gender-related approach is crucial and cannot be ignored anymore. Indeed, a call on scientists and medical Institutions to acknowledge the critical role of sex- and gender-specific investigation to develop a fair approach to prevention and treatment addressing the acute and long-term effects of this pandemic focusing on appropriateness and health equity towards the entire population.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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