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Gender differences in treatment of Coronavirus Disease-2019

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Abstract

Coronavirus Disease-2019 (COVID-19) is the worst worldwide pandemic with more than 12,000,000 cases and 560,000 deaths until 14th July 2020. Men were more infected by COVID-19 than women, and male subjects with underlying conditions, including diabetes, hypertension, and cardiovascular diseases developed a severe form of the affection, with increased mortality rate. Many factors can contribute to the disparity in disease outcomes, such as hormone-specific reaction and activity of X-linked genes, which modulate the innate and adaptive immune response to virus infection. Until now, only the Remdesivir was approved by FDA (Food Drug Administration) for COVID-19 treatment, although several clinical trials are ongoing worldwide also on other drugs. In this review, we analyzed published studies on several drugs (chloroquine or hydroxychloroquine, remdesivir, favipiravir, lopinavir-ritonavir in combination, tocilizumab, plasma, and immunoglobulins) with some efficacy to COVID-19 in humans, and evaluated if there were a gender analysis of the available data. In our opinion, it is essential to report data about COVID-19 disaggregated by sex, age, and race, because the knowledge of gender differences is fundamental to identify effective and customized treatments to reduce hospitalizations, admissions to intensive care units, and mortality.

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Introduction

Coronavirus disease-2019 (COVID-19) originated in the city of Wuhan and rapidly spread to most countries in the world, so on 12th March 2020 the WHO declared "pandemic" the COVID-19 outbreak [1]. Until 14th July 2020, more than 12 million confirmed cases of COVID-19 and 560 thousand deaths had been reported worldwide [2]. In Italy 243,230 total case of COVID-19 with 34,967 deaths were described [3].

In our previous review, we underlined that, in China and in Italy, men were more infected by COVID-19 than women, most patients were aged 30-79 years, and men with underlying conditions, including diabetes, hypertension and cardiovascular disease developed a severe form of this affection with an increased mortality rate [4]. Many factors can contribute to the disparity in sex-specific disease outcomes. The reduced susceptibility of females to viral infections could be attributed to the protection from X chromosome and sex hormones, which play an essential role in innate and adaptive immunity. Women may have a lower viral load level than men, a higher number of CD4+ T cells, and higher levels of antibodies. Moreover, the expression of Toll-like receptor 7 (TLR7), encoded by the X chromosome [5], is higher in women than in men leading to better immune response and viral infection resistance. TLR7 recognizes a single strand RNA virus promoting the production of antibodies against the virus.

Interestingly, in women, the production of pro-inflammatory interleukin-6 (IL-6) after the viral infection is lower than in males and often correlated with better longevity [6].

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) invades human alveolar epithelial cells through angiotensin-converting enzyme 2 (ACE2) [7]. Xie *et al.* [8] in animal models showed that ACE2 expression dramatically

reduced with aging in both sexes; also, ACE2 expression appeared to be higher in young than in elderly individuals, and in females than in males, and circulating ACE2 activity was increased in patients with cardiovascular complications [9]. Indeed, the ACE2 gene may be transcriptionally regulated by DNA methylation [10]. The localization of ACE2 on the X chromosome [11] raises the possibility of gender differences in susceptibility and progression of COVID-19 [12]. In particular, theACE2 gene could possibly experience differences in methylation due to X-chromosome activation [13]. Moreover, the male predominance in the COVID-19 pandemic could partially be explained by transmembrane serine protease 2 (TMPRSS2), which could be involved in viral entry and spread in the host. Constitutive expression of TMPRSS2 in lung tissue did not appear to differ between men and women, and low levels of androgens present in women might suffice to sustain TMPRSS2 expression [14].

In our opinion, it is fundamental to report data disaggregated by sex, age, and race, according to the Global Health 50/50 research initiative [15], because the knowledge of gender differences is essential to identify effective and customized treatments to reduce hospitalizations, admissions to intensive care units and mortality.

At the moment, only remdesivir was approved by FDA for COVID-19 treatment, although several clinical trials have been implemented worldwide.

Many drugs, including chloroquine or hydroxychloroquine, remdesivir, favipiravir, lopinavir-ritonavir (used in combination), tocilizumab, plasma, and immunoglobulins, have been highlighted for their promising *in vitro* results and therapeutic experiences from two other coronavirus diseases – the Severe Acute Respiratory Syndrome and the Middle East Respiratory Syndrome [16]. Several agents have demonstrated some efficacy in human COVID-19 therapy, but mostly through case reports or preliminary data of clinical trials with small sample sizes. Many randomized controlled trials are currently ongoing, to further confirm these results.

The present review aims to investigate the existence of studies evaluating gender differences in the therapeutic response and outcomes in different types of COVID-19 treatment.

Methods

The included studies were identified by using Pubmed, until 30th June 2020.The search included the following keywords: SARS-CoV-2, COVID-19, gender, sex, chloroquine, hydroxychloroquine, remdesivir, favipiravir, lopinavir-ritonavir, tocilizumab, plasma, and immunoglobulins. We conducted a non-systematic review. Clinical trials, retrospective and prospective studies were included. Studies written in languages other than English were excluded. Three authors (I.A., E.B., and T.C.) reviewed all study abstracts. Studies were included if gender differences in SARS-CoV-2 infection were reported. All selected studies were qualitatively analyzed.

Chloroquine and hydroxychloroquine

Chloroquine (CQ) and its hydroxyl analogue hydroxychloroquine (HCQ), a widely-used antimalarial and autoimmune disease drug, are prominent on the list of potential COVID-19 treatments.

Chloroquine is known to block virus infection by increasing endosomal pH required for virus/cell fusion, as well as by interfering with the glycosylation of cellular receptors of SARS-CoV-2 [17]. Wang *et al.* demonstrated that chloroquine functioned at both entry and post-entry stages of the 2019-nCoV infection *in vitro* [18]. Moreover, Yao *et al*. [19] evidenced that HCQ was more potent than CQ in *vitro*.

Besides its antiviral capability, CQ has an immune-modulating activity, which may synergistically enhance its antiviral effect *in vivo*. After oral administration, CQ distributed in the whole body, including lung. The effectiveness of HCQ for treating COVID-19 is the object of several studies.

In an observational study published on New England Journal of Medicine [20] (Table 1), a large sample of consecutive patients (n=1446), hospitalized with COVID-19 between 7th March and 8th April 2020, was recruited. Of 1376 included patients, 811 (58.9%) received HCQ (with a median duration of treatment of 5 days), and 565 (41.1%) did not. 45.8% received HCQ in the 24 hours between their presentation to the emergency department and the start of study follow-up, and 85.9% received the treatment within 48 hours after admission to the emergency department. In the unmatched sample, HCQ exposure differed according to age group, sex, race and ethnic group, body-mass index, insurance, smoking status, and current use of other medications. Hydroxychloroquine-treated patients had a lower PaO_2:FIO_2 at baseline than patients who did not receive HCQ.

In this analysis, hydroxychloroquine administration was not associated with either a greatly lowered or an increased risk of the composite endpoint of intubation or death, but no gender analysis was available.

Tang *et al*. [21] (Table 1) conducted a multicentre randomized open-label trial in which patients with COVID-19, admitted from 11th to 29th February 2020 to the hospitals of three provinces in China (Hubei, Henan, and Anhui), were enrolled, stratified according to disease severity (mild/moderate or severe), and randomised into treatment (hydroxychloroquine plus standard of care) and control (standard of care only) group.

Of 150 randomised patients, 75 patients were assigned to standard care (SOC) and 75 patients to SOC plus HCQ at a loading dose of 1200 mg daily for 3 days, followed by a maintenance dose of 800 mg daily for the remaining days (SOC plus HCQ). The trial showed that among 150 patients, 82 (55%) were male of whom 42 (56%) were in the SOC plus HCQ group, while 40 (53%) were in the SOC group. The mean age of the patients was 46 years, of whom 48 years in the SOC plus HCQ group, and 40 years in the SOC group. Gender analysis was not carried out in this trial. The study concluded that the administration of hydroxychloroquine did not result in a significantly higher probability of negative conversion than SOC alone in patients admitted to hospital with mainly persistent mild to moderate COVID-19, and the number of adverse events was higher in hydroxychloroquine recipients than in non-recipients.

In the observational study of Mahévas *et al*. [22] (Table 1) two groups (treatment group with HCQ at 600 mg/day and control group with no HCQ treatment) were identified, through the electronic health records' examine of all patients with COVID-19 pneumonia, who required oxygen but not intensive care, and admitted to four French tertiary hospitals between 12th and 31st March 2020. The study showed a median age of patients of 60 years, 72% of them were men. The HCQ treatment at 600

mg/day added to SOC was not associated with a reduction of admissions to the intensive care unit or death, 21 days after hospital admission, compared with SOC alone. Also, the rate of survival without acute respiratory distress syndrome did not increase. The results of this study did not support its use in patients admitted to the hospital with COVID-19 requiring oxygen. This study did not reveal differences in response to therapy in the two sexes, in different age groups or related to different comorbidities.

In a retrospective multicenter cohort study [23] (Table 1) from a sample of 7914 patients with COVID-19 admitted in New York metropolitan hospitals during March 15th through 28th, a total of 2362 records were randomly selected, and 1438 were abstracted and included in the analyses. Of these patients, 735 (51.1%) received HCQ+azithromycin, 271 (18.8%) received HCQ alone, 211 (14.7%) received azithromycin alone, and 221 (15.4%) received neither drug.

Black or Hispanic patients were as likely to receive HCQ and/or azithromycin. Median patient age was similar in the 4 groups (HCQ+azithromycin, 61.4 years; HCQ alone, 65.5 years; azithromycin alone, 62.5 years; and neither drug, 64.0 years). Patients receiving HCQ+azithromycin and HCQ alone were more likely to be obese and have diabetes than those in the groups receiving azithromycin alone and neither drug. Patients receiving alone had the highest levels of chronic lung disease (25.1%) and cardiovascular conditions (36.5%). Among patients hospitalized in metropolitan New York with COVID-19, treatment with HCQ, azithromycin, or both, compared with neither treatment, was not significantly associated with differences in in-hospital mortality. Patients who received hydroxychloroquine with or without azithromycin were more likely (relative to patients receiving neither drug) to be male (hydroxychloroquine +azithromycin, 62%; hydroxychloroquine alone, 58,3%; azithromycin alone, 63,5%; and neither drug, 49,8%), have pre-existing medical conditions, and have impaired respiratory or liver function at presentation. There were no significant differences in mortality between inpatients who received hydroxychloroquine with or without azithromycin and inpatients who received neither drug.

The findings of this study also confirm what other studies shown about the natural history of COVID-19 infection in the US: poor hospital outcomes were associated with male sex; pre-existing conditions such as hypertension, obesity, and diabetes; and presenting findings such as elevated liver enzymes and abnormal kidney function. There was no evidence in this study that black or Hispanic persons were prescribed these medications at a lower rate than white patients, which is relevant given the population-level differences in COVID-19 deaths previously reported by race and ethnicity.

In the open-label non-randomized clinical trial conducted by Gautret *et al*. [24] (Table 1), 26 French confirmed positive COVID-19 patients were included in a single-arm protocol, from early March to March 16th, to receive 600 mg of hydroxychloroquine daily. Their viral load in nasopharyngeal swabs was tested daily in a hospital setting. A control group included 16 patients. Among hydroxychloroquine-treated patients, six subjects received azithromycin (500 mg on day 1 followed by 25 0mg per day, the next four days) to prevent bacterial super-infection under daily electrocardiogram control. Overall, 15 patients were male (41.7%), with a mean age of 45.1 years. No significant difference was observed between hydroxychloroquine-treated and control patients concerning gender, clinical status, and duration of symptoms before the study inclusion. In this trial, there was no analysis of different age groups and comorbidities. At day 6 post-inclusion, 100% of patients treated with hydroxychloroquine and azithromycin combination were virologically cured, compared with 57.1% of patients treated with hydroxychloroquine only, and 12.5% of patients who did not receive hydroxychloroquine ($p<0.001$). Despite its small sample size, this survey showed that hydroxychloroquine treatment is significantly associated with viral load reduction/disappearance in COVID-19 patients, and its effect is reinforced by azithromycin.

In contrast with the previous study, Molina *et al*. [25] (Table 1), in their prospective study, concluded that there was no evidence of rapid antiviral clearance or clinical benefit with the combination of HCQ and azithromycin in patients with severe COVID-19 infection. In their small study including 11 consecutive in-patients who received hydroxychloroquine (600 mg/d for 10 days) and azithromycin (500 mg day 1 and 250 mg days 2 to 5), using the same dosing regimen reported by Gautret *et al*. [24], there were 7 men and 4 women with a mean age of 58.7 years (range: 20-77), and 8 had significant comorbidities associated with poor outcomes (obesity: 2; solid cancer: 3; hematological cancer: 2; HIV-infection: 1).

Also, in the study conducted by Chen *et al*. [26] (Table 1) 30 treatment-naïve patients with confirmed COVID-19 were randomized 1:1 to HCQ group (HCQ 400 mg per day for 5 days plus conventional treatments) and the control group (conventional treatment only). The authors did not found a difference in the rate of virologic clearance at 7 days, with or without 5 days-treatment of hydroxychloroquine, and no difference in duration of hospitalization, temperature normalization, and radiological progression. Again, no gender analysis was performed. In the randomized clinical trial of Chen *et al*. [27] (Table 1) since 4th to 28th February 2020, 62 COVID-19 patients admitted to Renmin Hospital of Wuhan University were randomized in two groups. All received the standard treatment (oxygen therapy, antiviral agents, antibacterial agents, and immunoglobulin, with or without corticosteroids), patients in the HCQ treatment group received additional oral HCQ 400 mg/d (200 mg/bid) between days 1 and 5, patients in the control group only the standard treatment. The total population included 46.8% (29 of 62) of male and 53.2% of (33 of 62) female, the mean age was 44.7 years. The time to clinical recovery (TTCR), the body temperature recovery time and the cough remission time were significantly shortened in the HCQ treatment group. The study concluded that among patients with COVID-19, the use of HCQ could significantly shorten TTCR and promote the absorption of pneumonia. In this study, no difference in the age and sex distribution between the control group and the HCQ group was observed.

Borba *et al.* [28,29] (Table 1) conducted a parallel double-masked randomized, phase IIb clinical trial with 81 adult patients hospitalized with SARS-CoV-2 infection since 23rd March to 5thApril 2020, at a tertiary care facility in Manaus, Brazilian Amazon. All randomized patients were allocated to receive high-dosage HCQ (*i.e*., 600 mg CQ twice daily for 10 days) (41 [50.6%] high-dosage group) or low-dosage CQ (*i.e*., 450 mg twice daily on day 1 and once daily for 4 days) (40 [49.4%] low-dosage group). The enrolled patients had an overall mean (SD) age of 51.1 (13.9) years and a predominance of men (60 [75.3%]). Hypertension (25 of 55 [45.5%]), alcohol use disorder (14 of 51 [27.5%]), and diabetes (14 of 55 [25.5%]) were the most frequent comorbidities. Older age (mean [SD] age, 54.7 [13.7] years *vs* 47.4 [13.3] years), and a higher rate of heart dis-

ease (5 of 28 [17.9%] *vs* 0) was found in the high-dose group. The preliminary findings of this study suggest that the higher CQ dosage should not be recommended for critically ill patients with COVID-19, because of its potential safety hazards, especially when taken concurrently with azithromycin and oseltamivir. These findings cannot be extrapolated for patients with non-severe COVID-19. Aging might be associated with unfavorable outcomes.

Remdesivir

Remdesivir (also GS-5734) is a monophosphoramidate prodrug of an adenosine analogue that has a broad antiviral spectrum including filoviruses, paramyxoviruses, pneumoviruses, and coronaviruses [30].

On 3th July 2020 this drug was approved by the EMA for the treatment of COVID-19 in adults and adolescents. *In vitro*, remdesivir inhibits all human and animal coronaviruses including SARS-CoV-2 [30,31]. Remdesivir is a potent inhibitor of SARS-CoV-2 replication in human nasal and bronchial airway epithelial cells [32]. Recently, remdesivir was regarded as promising for COVID-19 therapy because case studies have reported some benefit in severely ill patients with COVID-19, but interim published results are disappointing. Intravenous remdesivir has been used based on individual compassionate use over the past several months in patients with COVID-19 in some countries [33] (Table 1); in particular 22 patients were enrolled in the United States, 9 in Japan, 22 in Europe, and 1 in Canada.75% of patients were men, the age range was 23 to 82 years, and the median age was 64 years.

In the placebo-controlled randomised trial by Wang *et al.* [34] (Table 1), conducted to assess the effectiveness and safety of intravenous remdesivir in patients with severe COVID-19 admitted to hospital in Wuhan, 237 patients with pneumonia were enrolled, 158 patients were assigned to receive remdesivir and 79 to receive the placebo; sex distribution was 89 (56%) men versus 69 (44%) women in the remdesivir group and 51 (65%) *versus* 27 (35%) in the placebo group. The median age of study patients was 65 years. Remdesivir was adequately tolerated but did not provide significant clinical or antiviral effects in seriously ill patients with COVID-19 [34]. However, there was no gender analysis, so it is not possible to exclude clinically meaningful differences between men and women, and numerical reductions in some clinical parameters.

In the preliminary report of Beigel *et al.* [35] (Table 1) intravenous remdesivir was superior to placebo in shortening the time to recovery in adults hospitalized with COVID-19, in reducing evidence of lower respiratory tract infection; also in this trial male sex was more represented (64.3% of all patients were men), but sex-specific data on adverse reactions or appropriate dose adjustments are missing.

Lopinavir, favipiravir, ritonavir

Lopinavir is a human immunodeficiency virus (HIV) type 1 aspartate protease inhibitor with in vitro inhibitory activity against SARS-CoV, the virus that causes SARS in humans [36]. Similarly, lopinavir has shown activity, both *in vitro* and in an animal model [37] against Middle East respiratory syndrome coronavirus (MERS-CoV), and case reports have suggested that the combination of lopinavir–ritonavir with ribavirin and interferon alfa resulted in virologic clearance and survival [38]. In hospitalized adult patients with severe COVID-19, no benefit was observed with lopinavir–ritonavir treatment. In the randomized, controlled, open-label trial involving hospitalized adult patients with confirmed SARS-CoV-2 infection, 60.3% of the 199 patients who underwent randomization were men but also in this trial lack sex-specific data on adverse reactions or appropriate dose adjustments [39] (Table 1). Similar outcomes have been seen for favipiravir and ritonavir, with the latter causing severe side effects.

There is evidence that women encounter more often adverse drug reactions to antiviral treatment than men. Also, pharmacokinetics and treatment responses to antiretroviral therapy with ritonavir and lopinavir differ between males and females [40]. Higher plasma concentrations of ritonavir and a higher total cholesterol:high-density lipoprotein (HDL) ratio have been reported in young females [41], while an atazanavir plus ritonavir regimen was associated with higher risk of virologic failure in women as compared to men [42].

As long as drug trials continue to enroll both men and women but fail to sex-disaggregated outcome data, costly mistakes will continue.

Tocilizumab

Tocilizumab (TCZ), is a recombinant humanized anti-human monoclonal antibody of the immunoglobulin $G1_k$ subclass, directed against soluble and membrane-bound interleukin 6 receptors [43]. TCZ was firstly approved in 2005 as an orphan drug in Japan for the therapy of Castleman's disease [44]. TCZ is used in the EU, alone or in combination with anti-rheumatic drugs (DMARDs), to treat adults with moderate to severely active rheumatoid arthritis (RA), and over-2-years children with the systemic or polyarticular form of juvenile idiopathic arthritis [45]. TCZ inhibits the binding of IL-6 to its receptors, so it reduces this cytokine's pro-inflammatory activity by competing with both the soluble and membrane-bound forms of the human IL-6 receptor (IL-6R) [46]. It is recommended in seriously ill patients with elevated IL-6 for the treatment of pneumonia by COVID-19.

In one study (Table 1) that enrolled 15 patients (12 males and 3 females) with Covid-19, the authors described that 13% of patients were moderately ill, 40% were seriously ill and 47% were critically ill. However, they describe that only 1 patient (a 80-year-old female) had a clinical outcome of aggravation [47]. In another study (Table 1) that enrolled 21 patients, with mean age 56±16 years-old (18 male and 3 female), the authors reported that within 5 days after TCZ therapy, 75% of patients had lowered their oxygen intake, and 1 patient needed no oxygen therapy [48]. Unfortunately, no data described in literature gender differences in course of TCZ treatment. No real-life data on the effect by gender of TCZ on the inflammatory activity in COVID-19 patients.

Convalescent plasma/immunoglobulins

Convalescent plasma, convalescent serum and hyperimmune immunoglobulin prepared from convalescent plasma, are interventions used in the past to treat conditions when no vaccine or pharmacological interventions were available. It has been reported that the use of convalescent plasma may reduce mortality, appears safe, and the effectiveness of convalescent plasma in reducing hospital length of stay is dependent on early administration of the therapy, and in prophylaxis is more likely to be beneficial than in treating severe disease [49]. Plasma transfusions are also known to cause transfusion-associated circulatory overload (TACO). TACO is especially important to consider, because COVID-19 patients with comorbidities likely eligible for experimental treatment with convalescent plasma therapy, are at an increased risk of these adverse events. Besides, to the mentioned adverse events, transfusion-transmitted infections, red blood cell alloimmunization and hemolytic transfusion reactions have also been described following plasma transfusion, although they are less common [50]. Shen *et al*. reported that convalescent plasma could be a treatment option for COVID-19 patients with respiratory failure [51] (Table 1), and the authors reported that this procedure improved the clinical situation, decreased the patient's viral load, and induced a negativization of patients within 12 days after the transfusion [51]. One limitation of these data is that all patients received antiviral medications and steroids before receiving their convalescent plasma. Another study showed that 2 elderly (1 male and 1 female) patients improved after the application of convalescent plasma [52] (Table 1). No studies reported specifically data on the gender differences in the convalescent plasma treatment.

Immunoglobulin therapy has been used for the prevention and treatment of infectious diseases before the introduction of antimicrobial agents into clinical practice. In the early 1890s, Emil von Behring and Shibasaburo Kitasato set the basis of "serum therapy" showing that antibody preparations derived from the serum of immunized animals have the ability to protect against bacterial toxins [53]. In the pre-antibiotic era, serum therapy significantly reduced the mortality in some infectious such as meningococcal and *Haemophilus* influenzae meningitis, pneumococcal pneumonia, and diphtheria. The efficacy of serum therapy varied with the type and severity of the infections and the timing of treatment administration in relation to symptom onset [54]. The use of immunoglobulins for the infectious diseases can involve the passive transfer of antibodies for pre/post exposure prophylaxis or for treatment. Passive immunization provides temporal immunity to un-immunized individuals either prophylactically or therapeutically [55]. In particular, immunology clearly proves that antibodies in the blood or in the plasma fraction of the blood recognize epitopes on pathogens (*e.g*., viruses). They either neutralize them or reduce the virus load in conjunction with cellular responses to prevent or eventually cure the disease. Thus, antibodies are very efficient endogenous molecules that initiate and carry out self-healing processes in the human body [56]. Few data are reported on the gender differences in Immunoglobulins therapy. In particular, it has been described that in the severe status more female patients had a high level of IgG antibody compared to male patients, and the production of IgG antibody tended to be stronger in female patients in the early phase of COVID-19 [57]. This study analyzed 304 patients (204 female), and the authors demonstrated that, in the severe status, the SARS-CoV-2 IgG antibody, in females, was more than 100 AU/mL, while in males, the IgG antibody was under 100 AU/ml. These data suggest that more female patients generate a high level of SARS-CoV-2 IgG antibody in comparison to male patients, in the severe status of the COVID-19 infection. However, the result showed that the concentration of the SARS-CoV-2 IgG antibody in female patients tended to be higher than male patients in 2 to 4 weeks after disease onset, and the difference in antibody concentration disappeared after 4 weeks of disease onset [57]. Therefore, the authors propose that more attention should be paid to the patients whose IgG antibody was at low levels, and monitoring the IgG antibody may be a potential method to predict COVID-19 prognosis.

Adverse reactions after immunoglobulins treatment have been reported. In particular, it has been described that the dermatological disorders are more frequent in male patients [58], and that donations from female donors, especially those with a history of pregnancy, can induce an adverse reaction in male patients. No studies reported specifically data on the gender differences in the convalescent plasma treatment.

Conclusions

In the current state of knowledge, only remdesivir was approved by FDA for COVID-19 treatment. Some antiviral drugs have been tested in randomized clinical trials, but there has not been explicit consideration of sex biases in drug efficacy or adverse (potentially lethal) reactions. This occurs despite previous studies showing clear and important differences in drug treatment responses, including antivirals. Drug trials are yet designed and analyzed without appropriate attention toward sex-specific dosages or differential side effects. Currently, there are over 1000 registered trials on COVID-19 treatment, more than half of which include pharmacologic intervention or observation, and seven completed trials [59]. All trials to date include both men and women, but take a sex-blind approach to the analyses of outcome data, with no governmental guidelines mentioning sex-specific prophylactic or therapeutic recommendations (except for pregnant and postpartum women).

In our review, we analyzed clinical trials, which evaluated several drugs such as hydroxychloroquine, remdesivir, favipiravir, lopinavir-ritonavir (used in combination), tocilizumab, plasma, and immunoglobulins, in patients with COVID-19. In all the study we did not find COVID-19 disaggregated by sex, age, and race data related to hospitalizations, admissions to intensive care units, and mortality.

In our opinion, these data are essential to evaluate the effectiveness of a drug in men and women, in different age groups and race groups as well as the appearance of side effects and the outcomes. Every patient is different, so we cannot think to treat everyone in the same way. For this reason, it is crucial to collect and analyzed all gender data to test and identify specific therapies for each patient. It is necessary to provide personalized therapy to patients with COVID-19 because using the right therapy to the right patient in the early stage of disease will allow to obtain a reduction of hospitalizations, admissions to intensive care units, and mortality. In conclusion in our opinion supporting gender analysis and sex-disaggregated data is an integral part of a strong and successful COVID-19 response.

Table 1. Clinical trials, retrospective and prospective studies about COVID-19 treatments available until 30th June 2020.

Authors	Journal	Year	Setting	Population	Type of study	Treatment	Main finding	Gender analysis
Hydroxychloroquine								
Geleris *et al.*	N Engl J Med. doi: 10.1056/NEJMoa 2012410	2020	Hospital	1376 patients with Covid-19; 811 HCQ, 565 no HCQ; M/F 781/595 (56.7%/43.3%)	Observational study	HCQ at a dose of 200 mg three times daily for 10 days	HCQ administration was not associated with either a greatly lowered or an increased risk of the composite endpoint of intubation or death	No analysis by gender
Tang *et al.*	BMJ. doi: 10.1136/bmj.m1849	2020	16 government-designated COVID-19 treatment centers	150 patients with persistent mild to moderate COVID-19 (75 HCQ plus SOC and 75 to SOC alone); Mean age 46 ys; M/F 82/68 (55%/45%)	Multicentre randomized open-label trial	HCQ at a loading dose of 1,200 mg daily for three days followed by a maintained dose of 800 mg daily for the remaining days	HCQ administration did not result in a significantly higher probability of negative conversion than SOC alone, and the number of adverse events was higher in HCQ recipients than in non-recipients	No analysis by gender
Mahévas *et al.*	BMJ. doi: 10.1136/bmj.m1844	2020	4 French tertiary care centres	181 patients with SARS-CoV-2 pneumonia who required oxygen but not intensive care; 84 HCQ and 89 SOC alone; median age 60 years (52-68 ys); M/F 130/51 (72%/28%)	Observational study	HCQ at a dose of 600 mg/day within 48 h of admission *versus* SOC	The results did not support HCQ use in patients admitted to the hospital with COVID-19 requiring oxygen	No analysis by gender
Rosenberg *et al.*	JAMA. doi: 10.1001/jama.2020. 8630	2020	25 hospitals	1438 patients from a random sample with laboratory-confirmed COVID-19; 735 HCQ+AZT, 271 HCQ, 211 AZT, 221 no drugs; Median age 63 years M/F 858/580 (59.7%/40.3%)	Retrospective multicenter cohort study	HCQ initiated at a median of 1 day	Treatment with HCQ, azithromycin, or both, compared with neither treatment, was not significantly associated with differences in in-hospital mortality	Poor hospital outcomes, preexisting conditions and abnormal systems function associated with male sex
Gautret *et al.*	Int J Antimicrob Agents. doi: 10.1016/j.ijantimicag. 2020.105949	2020	Hospital	36 hospitalized patients with confirmed COVID-19; 20 HCQ, 16 controls; Mean age 45.1±22 years M/F 15/21 (41.7%/58.3%)	Open-label non-randomized clinical trial	HCQ sulfate 200 mg, three times per day for ten days	HCQ treatment is significantly associated with viral load reduction/disappearance in COVID-19 patients, and its effect is reinforced by azithromycin	No significant difference by gender was found between HCQ and control patients
Molina *et al.*	Med Mal Infect. doi: 10.1016/j.medmal. 2020.03.006	2020	Hospital	11 hospitalized patients Mean age 58.7 years (range 20-77) M/F 7/4 (63.6%/36.4%)	Prospective study	HCQ 600 mg/d for 10 days	No evidence of rapid antiviral clearance or clinical benefit with the combination of HCQ and AZT in patients with severe COVID-19 infection	No analysis by gender

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Table 1. Continued from previous page.

Authors	Journal	Year	Setting	Population	Type of study	Treatment	Main finding	Gender analysis
Chen J *et al.*	Zhejiang Da Xue Xue Bao Yi Xue Ban. doi: 10.3785/j.issn.1008-9292.2020.03.03	2020	Tertiary care hospital	1001 patients with polypharmacy by the MedSafer Pilot study. Median age 80 years; M/F 500/501 (50%/50%)	Controlled before and after deprescribing trial	No information on HCQ dose	No difference in the rate of virologic clearance at 7 days, with or without 5 days-treatment of HCQ, and no difference in duration of hospitalization, temperature normalization, and radiological progression	No analysis by gender
Chen Z *et al.*	medRxiv 2020. doi: 10.1101/2020.03.22.20040758	2020	Hospital	62 patients suffering from COVID-19; 31 HCQ, 31 controls; Mean age 44.7±15.3) years; M/F 29/33 (46.8%/53.2%)	Randomized clinical trial	HCQ 400 mg/d additional 5-day	The use of HCQ could significantly shorten time to clinical recovery and promote the absorption of pneumonia	No analysis by gender
Borba *et al.*	JAMA Netw Open doi: 10.1001/jamanetworkopen.2020.8857	2020	Tertiary care hospital	81 subjects hospitalized with SARS-CoV-2 infection 41 patients to HCQ high-dosage group and 40 to HCQ low-dosage group. Mean age 51.1±13.9 years; M/F 61/20 (75.3%/24.7%)	Parallel, double-masked, randomized, phase IIb clinical trial	HCQ 600 mg twice daily for 10 days or HCQ 450 mg twice daily on day 1 and once daily for 4 days	The higher HCQ dosage should not be recommended for critically ill patients with COVID-19, because of its potential safety hazards, especially when taken concurrently with AZT and oseltamivir	No analysis by gender
Borba *et al.*	medRxiv 2020. doi: 10.1101/2020.04.07.20056424	2020	Hospital and Emergency Room	81 subjects hospitalized with SARS-CoV-2 infection 41 patients to HCQ high-dosage group and 40 to HCQ low-dosage group. Mean age 51.1±13.9 years; M/F 61/20 (75.3%/24.7%)	Parallel, double-masked, randomized, phase IIb clinical trial	HCQ 600 mg twice daily for 10 days (or total dose 12g), or HCQ 450mg for 5 days, twice daily only on the first day (or total dose 2.7g), orally or via nasogastric tube	The higher dosage of CQ (12 g total dose over 10 days) in COVID-19 should not be recommended because of safety concerns regarding QTc prolongation and increased lethality, and more often in older patients in use of drugs such as AZT and oseltamivir	No analysis by gender
Remdesivir								
Grein *et al.*	N Engl J Med. doi: 10.1056/NEJMoa2007016.	2020	Hospitals	53 hospitalized patients with SARS-CoV-2 infection by a compassionate-use cohort; Median age 64 years (range 23-82); M/F 40/13 (75%/25%)	Prospective study	Remdesivir at a loading dose of 200 mg intravenously on day 1, plus 100 mg daily for the following 9 days	Clinical improvement in 68% of patients hospitalized for severe COVID-19 treated with compassionate-use remdesivir	No analysis by gender

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Table 1. Continued from previous page.

Authors	Journal	Year	Setting	Population	Type of study	Treatment	Main finding	Gender analysis
Wang *et al.*	Lancet. doi: 10.1016/S0140-6736 (20)31022-9	2020	10 hospitals in Hubei	237 adult patients admitted to hospital with laboratory-confirmed SARS-CoV-2 infection; 158 patients to remdesivir and 79 to placebo; Median age 65 years (IQR 56-71); M/F 140/97 (59.1%/40.9%)	Randomised, double-blind, placebo-controlled, multicentre trial	Remdesivir 200 mg on day 1 followed by 100 mg on days 2-10 in single daily or the same volume of placebo for a total of 10 days, intravenously	Remdesivir did not provide significant clinical or antiviral effects in seriously ill patients with COVID-19	No analysis by gender
Beigl *et al.*	N Engl J Med. doi: 10.1056/NEJMoa 2007764	2020	60 trial hospitals	1059 hospitalized adult patients; 538 patients to remdesivir and 521 to the placebo; Mean age 58.9±15.0 years; M/F 682/377 (64.4%/33.6%)	Double-blind, randomized, placebo-controlled trial	Remdesivir intravenously at a 200-mg loading dose on day 1, followed by a 100-mg maintenance dose administered daily on days 2 through 10 or until hospital discharge or death, or placebo	Intravenous remdesivir was superior to placebo in shortening the time to recovery in adults hospitalized with COVID-19, in reducing evidence of lower respiratory tract infection	Sex-specific data on adverse reactions or appropriate dose adjustments are missing
Lopinavir, favipiravir, ritonavir								
Cao *et al.*	N Engl J Med. doi: 10.1056/NEJMoa 2001282	2020	Hospital	194 hospitalized adult patients with confirmed SARS-CoV-2 infection; 94 patients to lopinavir-ritonavir, and 100 to SOC; Median age 58 years (IQR 49-68); M/F 120/74 (60.3%/29.7%)	Randomized, controlled, open-label trial	Lopinavir–ritonavir 400 mg and 100 mg, orally twice daily plus SOC, or SOC alone, for 14 days	No benefit was observed with lopinavir–ritonavir treatment in hospitalized adult patients with severe COVID-19	No analysis by gender
Tocilizumab								
Luo *et al.*	J Med Virol. doi: 10.1002/jmv.25801	2020	Tongji Hospital in Wuhan	15 patients with COVID-19; Mean age 71.4 years M/F 12/3 (80%/20%)	Retrospective study	TCZ at various dosages	TCZ appeared to be an effective treatment option in COVID-19 patients with a risk of cytokine storms, and for critically ill patients with elevated IL-6, the repeated dose of the TCZ is recommended	No analysis by gender
Xu *et al.*	Proc Natl Acad Sci USA doi: 10.1073/pnas. 2005615117	2020	2 Hospitals	21 patients before and after treatment with TCZ; Mean age 56.8±16.5 years (range 25-88) M/F 18/3 (85.7%/14.3%)	Prospective study	No specific information on TCZ dosage	TCZ improved the clinical outcome immediately in severe and critical COVID-19 patients and was an effective treatment to reduce mortality	No analysis by gender

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Table 1. Continued from previous page.

Authors	Journal	Year	Setting	Population	Type of study	Treatment	Main finding	Gender analysis
Convalescent plasma								
Shen *et al.*	JAMA. doi: 10.1001/jama.2020.4783	2020	Hospital	5 Patients with laboratory confirmed COVID-19 Mean age 54 years (range 36-73) M/F 3/2 (60%/40%)	Case reports	Convalescent plasma administered between 10 and 22 days after admission	In 5 critically ill patients with COVID-19 and ARDS, administration of convalescent plasma containing neutralizing antibody was followed by improvement in their clinical status	No analysis by gender
Ahn *et al.*	J Korean Med Sci. doi: 10.3346/jkms.2020.35.e149	2020	Community Health Center	2 patients with severe COVID-19 pneumonia	Case report 2	Convalescent plasma administered on day 9 or on day 6	Both two patients with COVID-19 showed a favorable outcome after the use of convalescent plasma in addition to systemic corticosteroid	No analysis by gender

HCQ, hydroxychloroquine; SOC, standard of care; AZT, azithromycin; IQR, interquartile range; TCZ, tocilizumab.

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