Research Paper

The "sex gap" in COVID-19 trials: a scoping review

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A R T I C L E   I N F O

A B S T R A C T

Background: Many studies investigate the role of pharmacological treatments on disease course in Corona Virus Disease 2019 (COVID-19). Sex disparities in genetics, immunological responses, and hormonal mechanisms may underlie the substantially higher fatality rates reported in male COVID-19 patients. To optimise care for COVID-19 patients, prophylactic and therapeutic studies should include sex-specific design and analyses. Therefore, in this scoping review, we investigated whether studies on pharmacological treatment in COVID-19 were performed based on a priori sex-specific design or post-hoc sex-specific analyses.

Methods: We systematically searched PubMed, EMBASE, UpToDate, clinical trial.org, and MedRxiv for studies on pharmacological treatment for COVID-19 until June 6th, 2020. We included case series, randomized controlled trials, and observational studies in humans ($\geq$18 years) investigating antiviral, antimalarial, and immune system modulating drugs. Data were collected on 1) the proportion of included females, 2) whether sex stratification was performed (a priori by design or post-hoc), and 3) whether effect modification by sex was investigated.

Findings: 30 studies were eligible for inclusion, investigating remdesivir ($n = 2$), lopinavir/ritonavir ($n = 5$), favipiravir ($n = 1$), umifenovir ($n = 1$), hydroxychloroquine/chloroquine ($n = 8$), convalescent plasma ($n = 6$), interleukin-6 (IL-6) pathway inhibitors ($n = 5$), interleukin-1 (IL-1) pathway inhibitors ($n = 1$) and corticosteroids ($n = 3$). Only one study stratified its data based on sex in a post-hoc analysis, whereas none did a priori by design. None of the studies investigated effect modification by sex. A quarter of the studies included twice as many males as females.

Interpretation: Analyses assessing potential interference of sex with (side-)effects of pharmacological therapy for COVID-19 are rarely reported. Considering sex differences in case-fatality rates and genetic, immunological, and hormonal mechanisms, studies should include sex-specific analyses in their design to optimise COVID-19 care.

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Research in context

Evidence before this study

Given the impact of sex on diseases and therapy as revealed in the past, we systematically reviewed this potential knowledge gap by performing a scoping review on clinical trials investigating pharmacological therapies for COVID-19. Searching the literature in PubMed, EMBASE, UpToDate, clinical trial.org and Medrixv up to June 6th 2020, we included case series, randomized controlled trials and observational studies in humans, which investigated antiviral, antimalarial and immune system modulating drugs.

Added value of this study

This scoping review reports four main findings. First, none of thirty clinical trials on pharmacological treatment for COVID-19 included sex-stratified randomization in its design. Second, only one study stratified its results based on sex by post-hoc analysis. Third, none of the studies evaluated sex as a potential effect modifier. Finally, almost a quarter of the studies included two times more males than females.

Implications of all the available evidence

We call investigators who are developing and testing therapeutic and prophylactic approaches for COVID-19 to incorporate sex-stratified randomization into their study protocol. For already published studies, we recommend investigators to perform post-hoc sex-specific analyses, while considering potential power insufficiencies in the interpretation of the results. Furthermore, we recommend generating an open access database with data from completed clinical COVID-19 trials, to improve the power to detect sex-differences compared to the current trials.

1. Introduction

In early 2020, a novel β-coronavirus causing Severe Acute Respiratory Syndrome (SARS-CoV-2) rapidly spread around the world, resulting in a pandemic with global impact [1,2]. On June 9th, 2020, SARS-CoV-2, causing Corona Virus Disease 2019 (COVID-19), reached a worldwide case fatality rate of 5.7% [3,4]. Although patients are unique individuals, they are often categorised according to disease or condition and treated using a 'one-size-fits-all'-approach. However, the disease can unfold in individuals diversely and variably. This heterogeneity may have significant implications in therapy effectiveness. For COVID-19, heterogeneity in ethnicity, comorbidities and age might impact disease course (ranging from common flu-like symptoms to critical illness requiring intensive care admission) and complications (pulmonary embolisms, kidney failure or cardiac injury) [2].

Although males and females are affected by COVID-19 at comparable incidence, case fatality rates are higher for males (10.4%) compared to females (7.0%), resulting in a markedly male-to-female case fatality ratio of 1.5, according to the Global Health 50/50 data tracker [5]. Sex-stratified proportions differ from global numbers as not all countries report their data specified for males and females, including

the United States of America. Age and comorbidities also strongly affect the fatality rates as mainly elderly, and patients with underlying cardiovascular diseases appear to be affected [6]. Despite these differences in fatality rates, a thorough analysis of underlying contributory factors is lacking [7-9]. Sex has been shown to contribute to disparities in widespread diseases in the past and may have an influence on vulnerability and differentials in incidence and case fatality between males and females [10].

There is growing evidence that sex differences play a role in the immunological, hormonal, and cardiovascular pathophysiological responses to SARS-CoV-2 [10,11]. Historically, in medical research on other cardiovascular and infectious diseases, women seem underrepresented in clinical and pharmacological trials, and data are rarely reported separately for males and females [10-12]. Consequently, unrevealed differences in disease presentation and progression between men and women may have been missed, and system-biological differences in (side)-effects of pharmacological therapy undetected. In COVID-19 patients, it is expected that these disparities also affect the severity of the virus infection, disease course, and (side)-effects of initiated therapy [11,12].

In this scoping review, we systematically reviewed completed clinical studies on pharmacological therapy for COVID-19 patients. For these studies, we reported male-to-female ratios of included patients and whether the studies were performed based on an a priori sex-specific design or post-hoc sex-specific analyses.

2. Methods

This scoping review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guideline [13]. Four independent investigators (E.J., V.S., L.J., and C.G.) systematically searched PubMed and EMBASE. They reviewed original research articles investigating antiviral, antimalarial, and immune-modulating pharmacological treatments for COVID-19, that were thought to be potentially effective to treat symptoms of COVID-19 at time of study inclusion and/or mentioned in the "Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19" [14] (for keywords used in the literature search, see Supplementary file). Randomized controlled trials (RCTs), observational studies, and case series (defined as ≥5 reported patients) were eligible for inclusion. Besides, studies had to investigate a single, specific therapy in COVID-19 patients aged ≥18 years. To be eligible for inclusion, RCTs and observational studies had to investigate both a treatment and control group, in which the latter was allowed to vary between standard care, a specific pharmacological treatment or no pharmacological treatment. We excluded in vitro studies, animal studies, trials investigating different doses or settings of one similar drug in different groups, and trials not reporting the proportion of male and female patients. The search was limited to English and Dutch studies published between December 2019 and June 6th, 2020.

The initial study selection, based on title and abstract, and the subsequent selection, based on the full-text, were performed independently by four investigators (E.J., V.S., L.J., and C.G.). All disagreements were resolved by discussion and mutual agreement. Furthermore, reviews, UpToDate, clinicaltrial.org, and MedRxiv, were examined for additional eligible studies. After checking the preselected publications and cross-checking the reference lists, the relevant data were extracted from the final selection of studies, as described in the section below.

2.1. Data extraction

A pre-defined data-extraction sheet, including characteristics and outcomes of interest, was used. Data were extracted on the description of sex, sex stratification (predesigned a priori or by post-hoc analyses), and effect modification by sex. The potential effect of treatments was beyond the scope of this review. Extractions were performed independently by two investigators (E.J. and V.S.). Discrepancies were resolved by dialogue (E.J. and V.S.) and discussion with a third investigator (C.G.). The proportion of female inclusions was reported for the total population (pooling case series, observational studies, and RCT's) and separately for treatment and control groups (pooling only observational studies and RCT's). Pharmacological treatment modalities were clustered in the following groups: antiviral, antimalarial, and immune system modulating drugs. We reported male-to-female ratios of included patients for each study and each pharmacological treatment under investigation. To calculate treatment-stratified male-to-female ratios, we used the absolute inclusion numbers and reported a minimum and maximum range of the individual study ratios. A ratio of >1 indicates a higher proportion of included men compared to women.

2.2. Role of the funding source

There were no funders or sponsors that had any contribution to the study design, data collection, analysis, preparation or decision to publish this manuscript.

3. Results

3.1. General

Our database search resulted in 1978 studies and by cross-checking reviews, clinicaltrial.org [15], UpToDate [16], and MedRxiv [17] we added seven additional studies that were in preprint stage by the time we performed our search. After removing duplicates, we started our first selection with 1811 studies (see Fig. 1). After screening articles based on title and abstract, we excluded 1664 studies, resulting in 147 studies eligible for the second screening based on full-text assessment. Based on the second screening, we additionally excluded 117 studies, amongst which the study of Mehra et al. [18] as it was retracted and the study of Klopfenstein et al. [19] as it did not report the number of included females and males. As a result, we included 30 eligible unique research articles on pharmacologic therapies for COVID-19 in this scoping review (Fig. 1).

The total number of 30 included studies consisted of seven case series, eight RCTs, and fifteen observational studies. As shown in table 1, included studies investigated remdesivir ($n = 2$), lopinavir/ritonavir ($n = 5$), favipiravir ($n = 1$), umifenovir ($n = 1$), hydroxychloroquine/chloroquine ($n = 8$), convalescent plasma ($n = 6$), interleukin-6 (IL-6) pathway inhibitors ($n = 3$), interleukin-1 (IL-1) pathway inhibitors ($n = 1$) and corticosteroids ($n = 3$). The five included case series reported individual patient data, including sex. Of all observational studies and RCTs, only one study by Beigel et al. [20] performed post-hoc sex-specific analysis (Table 2). As a result, none of the 30 included studies incorporated sex-stratified randomization a priori into their design, and 29 of 30 studies (97%) did not stratify their results based on sex post-hoc (Table 1 and 2). None of the included studies investigated effect modification by sex using interaction-terms between therapy and sex in their analyses (Table 1 and 2). Study characteristics are comprehensively described in Supplementary Table 1.

Table 1 and 2 present the treatment- and study-specific inclusion rates of females and males with the corresponding male-to-female ratio. A total of 6156 patients were reported in the 30 included studies, of which 2531 (41%) were female. In the treatment group, 3292 patients were included, of which 1325 (40%) women. In the control group, 2757 patients were included, of which 1181 (43%) women. The average overall male-to-female ratio was 1•4 (range 0•7–7•0), indicating an overall inclusion of more males than females (Table 1). In the 23 studies reporting treatment and control groups, the male-to-female ratio in the treatment group was 1•5 (range 0•8–5•0) and in the control group 1•3 (range 0•5–7•0). A quarter of the studies included twice as many males as females (i.e. male-to-female ratio >2).

3.2. Antiviral agents (viral entry and replication inhibitors)

3.2.1. Remdesivir (nucleoside analogue)

Two RCTs investigated remdesivir in COVID-19 patients [20,21], and none of them predesigned a priori sex-stratified randomization (Table 2). Of both studies, only Beigel et al. [20] stratified their results based on sex in a post-hoc analysis (Table 1). They reported a Recovery Rate Ratio (RRR) in favour of remdesivir, showing a 1•31 (95% CI 1•07–1•59) RRR for men and 1•38 (95% CI 1•05–1•81) for women (not shown). Although the authors did not investigate the interaction between therapy and sex to test for effect modification by sex statistically, the largely overlapping 95% confidence intervals around the estimated RRRs suggest no difference in treatment effect of remdesivir between males and females. Wang et al. did not stratify their outcomes based on sex and did not perform interaction analyses [21]. A total of 1299 patients were included in both studies, of which 475 (37%) were female (Table 1). In the treatment groups, 699 patients were included, of which 255 (36%) were female. In the control groups, 600 patients were included, of which 217 (36%) were female. Pregnancy was an exclusion criterion in both studies.

The male-to-female ratio in both studies on remdesivir was 1•7 (range 1•5–1•8) (Table 1, Fig. 2). The ratio in the treatment group was 1•7 (range 1•3–1•9) and in the control group 1•8 (range 1•7–1•9).

3.2.2. Lopinavir/ritonavir (boosted protease inhibitor)

Lopinavir/ritonavir was reported in five studies for their effectivity and side-effects in the treatment for COVID-19, including one case series, two RCTs, and two observational studies [22-26] (Table 2). Five studies compared the use of lopinavir/ritonavir with a control group, consisting of standard care or treatment with umifenovir. None of these studies stratified their randomization for sex a priori by design (i.e. for RCTs), nor stratified their results for sex in a post-hoc analysis, nor performed interaction analyses to investigate effect modification by sex (Table 1). A total of 460 patients were included in the studies, of which 218 (47%) were female (Table 1). The treatment groups included 247 patients, of which 113 (46%) were female. The control groups included a total of 196 patients, of which 95 (48%) were female. The average male-to-female ratio in studies on lopinavir/ritonavir was 1•1 (range 0•7–1•5) (Table 1, Fig. 2). In the treatment groups, the average male-to-female ratio was 1•2 (range 0•8–1•6) and in the control groups 1•1 (range 0•5–1•4). Li et al. excluded pregnant women; the other four studies did not report any data on pregnancy.

3.2.3. Favipiravir (viral RNA polymerase inhibitor)

Chen et al. [27] performed a RCT to investigate the effect of favipiravir in COVID-19 patients compared to umifenovir (Table 2). This study neither stratified its randomization for sex a priori, nor stratified its results for sex in a post-hoc analysis, nor performed interaction analyses to examine effect modification by sex (Table 1). A total of 236 patients were included, of which 126 (53%) were female (Table 1). In the treatment group, 116 patients were included, of which 57 (49%) were female. In the control group, 120 patients were included, of which 69 (58%) were female. The total male-to-female ratio in this study was 0•9 (Table 1, Fig. 2). In the treatment group, the male-to-female ratio was 1•0, and in the control group 0•7.
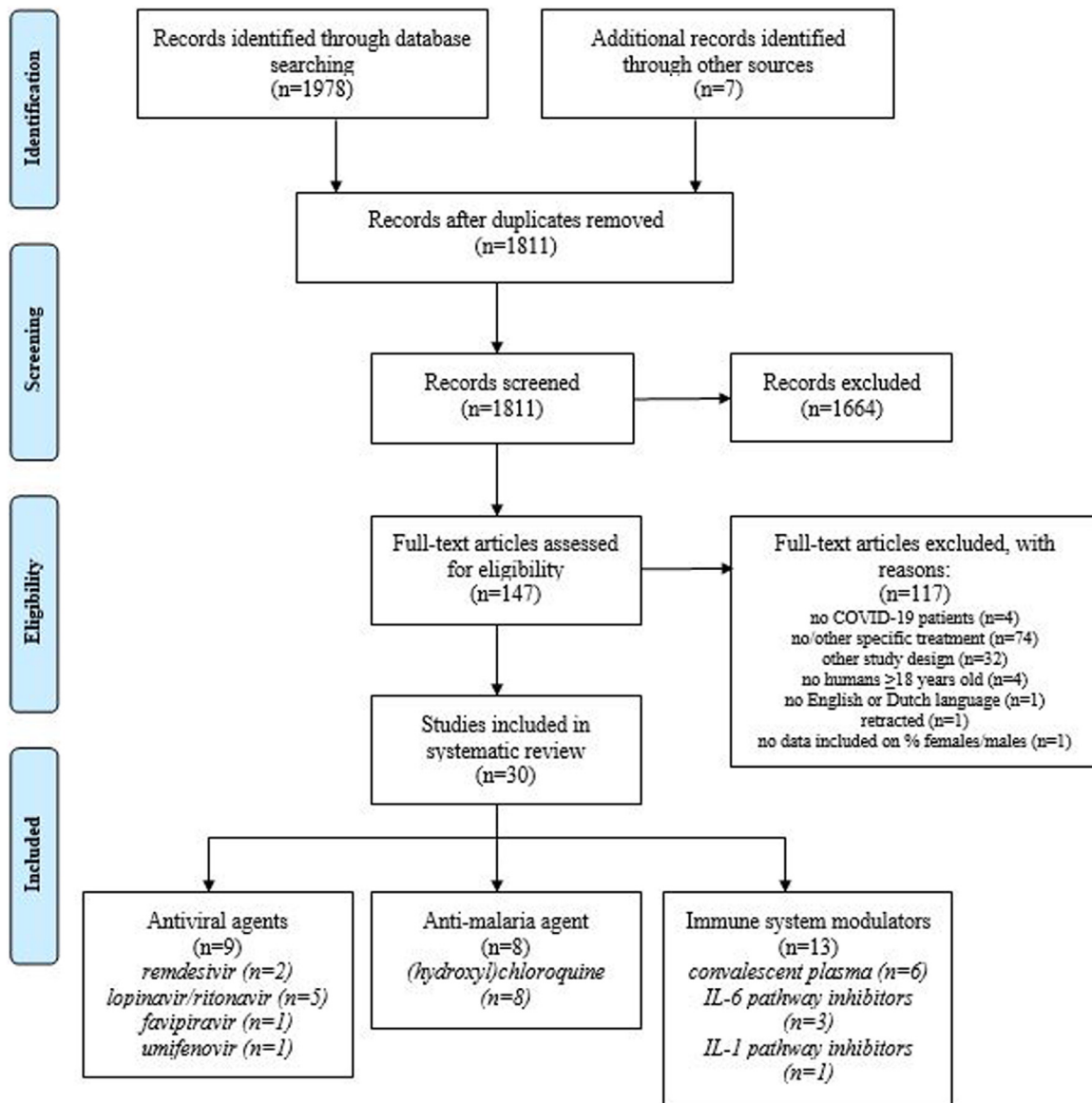
Fig. 1. Flowchart of study selection and inclusion after systematic literature search.

3.2.4. Umifenovir (viral entry inhibitor)

Lian et al. performed an observational study on umifenovir and did not stratify its results for sex, nor performed interaction analyses to examine effect modification by sex [28] (Table 2). A total of 81 patients were included, of which 36 (44%) were female (Table 1). In the treatment group, 45 patients were included, of which 17 (38%) were female. In the control group (receiving standard care), 36 patients were included, of which 19 (53%) were female. The total male-to-female ratio in this study was 1•3 (Table 1, Fig. 2). In the treatment group, and 1•6 in the control group.

4. Anti-malaria agent

4.1. (Hydroxy)chloroquine

(Hydroxy)chloroquine was investigated in eight studies; three RCTs and five observational studies [29-36] (Table 2). None of these studies stratified their randomization for sex a priori, nor stratified their results for sex in a post-hoc analysis, nor performed interaction analyses to investigate effect modification by sex (Table 1). A total of 3325 patients were included in these studies, of which 1369 (41%) were female (Table 1). In the treatment groups, 1814 patients were included, of which 733 (40%) were female . In the control groups, 1511 patients were included, of which 654 (43%) were female. The male-to-female ratio for included patients in studies on (hydroxy) chloroquine was 1•4 (range 0•7−2•7) (Table 1, Fig. 2). The male-to-female ratio in the treatment groups was 1•5 (range 0•8−3•4) and in the control groups 1•3 (range 0•6−2•1). Five studies reported pregnancy as an exclusion criterion (Supplementary Table 1).

5. Immune system modulators

5.1. Convalescent plasma

Six studies investigated convalescent plasma in COVID-19 patients [37-41] (Table 2). Five studies were case series, whereas Zeng et al. [39] performed an observational study comparing the efficacy of the patients who received plasma collected from recovered COVID-19 individuals with a control group who did not receive convalescent plasma. None of these studies stratified their results for sex, nor performed interaction analyses to investigate effect modification by sex (Table 1). The five case series described in total 54 cases,

Table 1
Total and therapy-stratified male-to-female ratios of included studies.

	Studies (n)	Sex-specific analysis (n)	Patients (n)	Female (%)	Male-to-female ratio (range)
I. TOTAL	30	1	6156	41	1•4 (0•7−7•0)
treatment group	23	.	3292	40	1•5 (0•8−5•0)
control group	23	.	2757	43	1•3 (0•5−7•0)
II. THERAPY GROUPS					
II.I ANTIVIRAL AGENTS					
Viral entry and replication inhibitors					
Remdesivir	2	1	1299	37	1•7 (1•5−1•8)
treatment group	2	.	699	36	1•7 (1•3−1•9)
control group	2	.	600	36	1•8 (1•7−1•9)
Lopinavir/ritonavir	5	0	460	47	1•1 (0•7−1•5)
treatment group	5	.	247	46	1•2 (0•8−1•6)
control group	5	.	196	47	1•1 (0•5−1•4)
Favipiravir	1	0	236	53	0•9 (-)
treatment group	1	.	116	49	1•0 (-)
control group	1	.	120	58	0•7 (-)
Umifenovir	1	0	81	44	1•3 (-)
treatment group	1	.	45	38	1•6 (-)
control group	1	.	36	53	0•9 (-)
II.II ANTIMALARIA AGENT					
(hydroxy)chloroquine	8	0	3325	41	1•4 (0•7−2•7)
treatment group	8	.	1814	40	1•5 (0•8−3•4)
control group	8	.	1511	43	1•3 (0•6−2•1)
II.III IMMUNE MODULATORS					
Convalescent plasma	6	0	75	39	1•6 (1•0−7•0)
case series	5	.	54	44	1•3 (0•8−7•0)
observational study	1	.	21	24	3•2 (-)
treatment group	1	.	6	17	5•0 (-)
control group	1	.	15	27	2•8 (-)
IL-6 pathway inhibitors	3	0	147	27	2•7 (2•3−6•0)
treatment group	1	.	42	21	3•7 (-)
control group	1	.	69	36	1•8 (-)
IL-1 pathway inhibitors	1	0	45	16	5•4 (-)
treatment group	1	.	29	17	4•8 (-)
control group	1	.	16	13	7•0 (-)
Corticosteroids	3	0	488	47	1•1 (1•0−1•8)
treatment group	3	.	294	46	1•2 (1•1−2•7)
control group	3	.	194	49	1•0 (0•9−1•5)

Data are presented as numbers and percentages.

of which 24 (44%) were women (Table 1). Zeng et al. included 21 patients, of which five (24%) were female. Their study population consisted of six patients in the treatment group, of which only one (17%) was female and 15 patients in the control group, of which only four (27%) were female. The total male-to-female ratio for convalescent plasma studies was 1•6 (range 0•8−7•0) (Table 1, Fig. 2). The male-to-female ratio in the treatment group of the study of Zeng et al. was 5•0 and in the control group 2•8. Moreover, only one study reported that 56% of plasma was donated by men [42].

5.2. IL-6 pathway inhibitors and IL-1 pathway inhibitors

Tocilizumab was investigated in one observational study and one case series, whereas siltuximab was investigated in one observational study [43-45] (Table 2). None of these studies stratified their results for sex, nor performed interaction analyses to investigate effect modification by sex (Table 1). These three studies included 147 patients, of whom 40 were female (27%) (Table 1). Quartuccio et al. was the only study reporting a control group consisting of 69 patients, of which 25 (36%) were female (Table 1). The male-to-female ratio in the total group was 2•7 (range 2•3−6•0) (Table 1, Fig. 2).

Cavalli et al. observationally investigated anakinra in both low and high dosages in patients with COVID-19 [46] (Table 2). Given the design of this review, to evaluate male-to-female ratios, we used the high-dose group as the treatment group and the standard as the control group. Cavalli et al. study did neither stratify its results for sex, nor performed interaction analyses to examine effect modification by sex (Table 1). A total of 45 patients were included in their study, of which 7 (16%) were female, resulting in a male-to-female ratio of 5•4

(Table 1, Fig. 2). A total of 29 patients received high-dose anakinra, of which five (17%) were female, resulting in a male-to-female ratio of 4•8 in the treatment group. The control group included 16 patients, of which 2 (13%) were female, resulting in a male-to-female ratio of 7•0 in the control group.

5.3. Corticosteroids

Three observational studies examined the effect of methylprednisolone (n = 2) and the combination with dexamethasone (n = 1) on COVID-19 outcomes [47-49] (Table 2). None of these studies stratified their results for sex, nor performed interaction analyses to investigate effect modification by sex (Table 1). A total of 488 patients were included in these studies, of which 231 (47%) were female (Table 1). In the treatment groups, 294 patients were included, of which 135 (46%) were female. In the control groups, a total of 194 patients were included, of which 96 (49%) were female. The average male-to-female ratio was 1•1 (range 1•0−1•8) (Table 1, Fig. 2). In the treatment group, the male-to-female ratio was 1•2 (range 1•1−2•7) and in the control group 1•0 (range 0•9−1•5).

6. Discussion

Our scoping review reports four main findings. First, none of thirty clinical trials on pharmacological treatment for COVID-19 included sex-stratified randomization in its design. Second, only one study stratified its results based on sex by post-hoc analysis. Third, none of the studies evaluated sex as a potential effect modifier. Finally,

Table 2
Study-specific male-to-female ratios of included studies.

Author (reference number)	Design	Sex-stratified randomization (a priori)	Sex-specific analyses (post hoc)	Patients (n)	Female (%)	Male-to-female ratio
REMDESIVIR						
Beigel et al. (19)	RCT	No	Yes	1063	36	1•8
Wang et al. (20)	RCT	No	No	236	41	1•5
LOPINAVIR/RITONAVIR						
Cao et al. (21)	RCT	No	No	199	40	1•5
Li et al. (22)*	RCT	No	No	86	54	0•9
Yan et al. (23)	OBS	–	No	120	55	0•8
Cheng et al. (24)	CASE	–	No	5	60	0•7
Zhu et al. (25)	OBS	–	No	50	48	1•1
FAVIPIRAVIR						
Chen et al. (26)*	RCT	No	No	236	53	0•9
UMIFENOVIR						
Lian et al. (27)	OBS	–	No	81	44	1•3
(HYDROXY)CHLOROQUINE						
Huang et al. (28)	RCT	No	No	22	41	1•2
Tang et al. (29)	RCT	No	No	150	45	1•2
Gautret et al. (30)	OBS	–	No	36	58	0•7
Chen et al. (31)	RCT	No	No	62	53	0•9
Geleris et al. (32)	OBS	–	No	1376	43	1•3
Yu et al. (33)	OBS	–	No	550	38	1•7
Rosenberg et al. (34)	OBS	–	No	956	41	1•5
Mahévas et al. (35)	OBS	–	No	173	27	2•7
CONVALESCENT PLASMA						
Shen et al. (36)	CASE	–	No	5	40	1•5
Duan et al. (37)	CASE	–	No	10	40	1•5
Zeng et al. (38)	OBS	–	No	21	24	3•2
Ye et al. (39)	CASE	–	No	6	50	1•0
Adeli et al. (40)	CASE	–	No	8	13	7•0
Salazar et al. (41)	CASE	–	No	25	56	0•8
IL-6 PATHWAY INHIBITORS						
Luo et al. (42)	CASE	–	No	15	20	4•0
Gritti et al. (43)*	OBS	–	No	21	14	6•0
Quartuccio et al. (44)	OBS	–	No	111	31	2•3
IL-1 PATHWAY INHIBITORS						
Cavalli et al. (45)	OBS	–	No	45	16	5•4
CORTICOSTEROIDS						
Fadel et al. (46)	OBS	–	No	213	49	1•0
Zha et al. (47)	OBS	–	No	31	36	1•8
Lu et al. (48)	OBS	–	No	244	48	1•1

RCT = randomized controlled trial, OBS = observational study, CASE = case series.*In preprint and not peer reviewed at time of study inclusion.
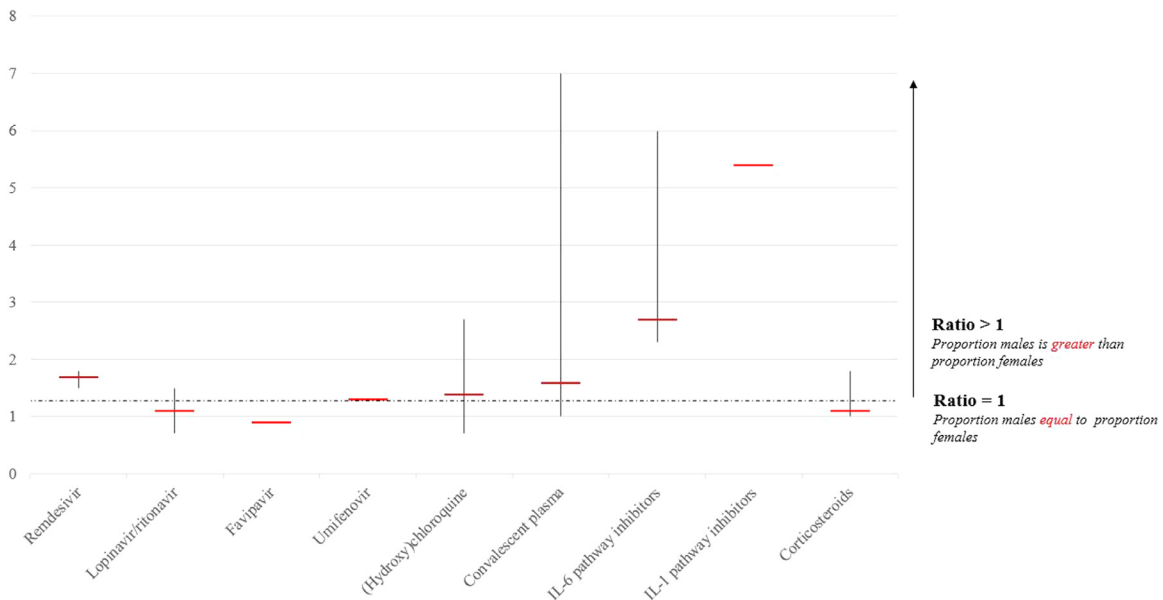
Fig. 2. Total male-to-female ratio of included patients stratified per pharmacological treatment under investigation, including the range of study-specific male-to-female ratios.

almost a quarter of the studies included two times more males than females.

The main findings of this study should be interpreted in the context of a large body of evidence showing sex differences in COVID-19 survival. COVID-19 appears to affect men more severely than women [10]. Although this may partly explain the higher male-to-female ratio in the included studies, it does not justify including more than two times more males than females, when evaluating treatment for a novel disease with varying risks worldwide [10]. For example, amongst women in the U.K., women of African ancestry were more severely affected. This stresses the necessity for a more personalised approach [50]. Also, comorbidities, such as chronic lung disease, hypertension, and cardiovascular disease are associated with more severe COVID-19 infection [10]. Worldwide, these comorbidities are more prevalent amongst men than women, except for older age groups, where a reversed prevalence has been observed [51]. Although underlying comorbidities may account for differences in male-to-female outcomes, the possible biological contributions of sex in COVID-19 remain unknown.

To cause infection, SARS-Cov-2 binds to the angiotensin-converting enzyme (ACE) 2 receptor and the cellular serine protease TMPRSS2 for priming to enter cells [52]. Sex hormones affect not only ACE2 but also the Renin-Angiotensin-Aldosterone System (RAAS) components that modulate ACE2 [53-57]. Moreover, TMPRSS2 is sevenfold more frequently expressed in prostate epithelium than in other human tissue, and its transcription is regulated by androgenic ligands and an androgen receptor binding element in the promoter [58]. However, its function is not understood yet, allowing speculation on a potential sex-specific role of TMPRSS2 in the worse prognosis in males compared to females [59]. Not only the initial cell-entering mechanisms are subject to biological interference, but also immune responses to viruses can vary with changes in sex hormone concentrations. These fluctuations in sex hormone concentrations are naturally observed during the menstrual cycle, following contraception, after menopause, hormone replacement therapy (HRT), and pregnancy [60]. Sex steroids, particularly testosterone (T), oestradiol (E2), and progesterone (P4), influence the functioning of immune cells by altering cell signalling pathways resulting in differential production of cytokines and chemokines [10,61]. Therefore, a 'one-size-fits-all'-approach to immunotherapies is not expected to be effective, and sex may contribute to treatment success in clinical settings. In addition to the potential sex-specific biological mechanisms driving pharmacodynamic heterogeneity of potential treatment effects for women with COVID-19, sex-related differences in absorption, distribution, metabolism, and excretion of drugs are usually explained by differences in weight, body surface area and water/fat distribution. This often results in higher drug exposure if a fixed dose is given irrespective of body weight or composition, a mechanism which may contribute to more side effects in women.

A large body of evidence shows that responses regarding the pharmacokinetics of antiviral drugs differ between men and women and that women encounter adverse drug reactions to antiviral treatment more often than men, which also applies to lopinavir/ritonavir [62]. For the same dose administered, higher plasma concentrations of ritonavir have been reported in females. On the other hand, an atazanavir plus ritonavir regimen was associated with a higher risk of virologic failure in women than in men [63]. Unfortunately, only one of nine studies on remdesivir, lopinavir/ritonavir, favipiravir or umifenovir performed any post-hoc sex-specific analyses. None of them investigated sex as a potential effect modifier, and none of the RCTs stratified its randomization for sex. Moreover, studies on these antiviral drugs included overall more male than female patients.

Chloroquine and hydroxychloroquine are known to trigger life-threatening polymorphic ventricular tachycardia (torsades de pointes) by prolonging the heart rate-corrected QT (QTc) interval [32, 64]. Previous reports indicate that women are more prone to develop drug-induced torsades de pointes than men, with 65−75% of drug-induced torsades de pointes occurring in women [65]. Substantial sex differences in the electrocardiographic pattern of ventricular repolarisation are observed, with a longer QTc interval at baseline in women [55,66]. Protective effects of testosterone have been suggested to account for the shorter QTc interval and the reduced incidence of drug-induced torsades de pointes in men. However, underlying mechanisms are not fully understood.

Besides antiviral and antimalarial medication, the immune-modulating therapies IL-6 inhibitors, IL-1 inhibitors, convalescent plasma, and corticosteroids were evaluated. IL-6 and IL-1 inhibitors are monoclonal antibodies against IL−6 and IL-1. The latter are cytokines that play an essential role in inflammatory reaction and immune response. Three studies investigated IL-6 pathway inhibitors, of which none performed sex-specific analyses. Almost three times more male than female patients were included in these studies.

Convalescent plasma is plasma from COVID-19 recovered donors, being transfused to treat severe COVID-19 patients [37]. The majority of studies on convalescent plasma were case series, which all reported the sex of their included cases. One observational study on convalescent plasma did not perform sex-specific analyses. This study included five times more male patients than female patients in the treatment group and almost three times more male than female patients in the control group.

For proof of principle, a study in mice revealed that the transfer of serum from female immune mice was significantly better at protecting naïve mice (both males and females) against influenza than the transfer of immune serum from males [67]. It is unknown whether these findings also account for in vivo studies, which stresses the importance of sex-specific randomization and analyses, not only for the patient but also for the donor.

Overall, more awareness in scientific research is needed to understand the role of sex in causing differential outcomes and effects related to COVID-19 between women and men. Although outside the scope of this review, the distinction and interplay between sex (system-biological) and gender (socio-economic) and their effect on differences in outcome remain subject for elaboration and investigation in future studies.

There are several limitations to mention. First, three of the included studies were not peer-reviewed, which increases the risk of bias amongst these studies. However, we believe that this potential bias does not impact our conclusions, as our outcome was based on sex stratification and randomization rather than therapy outcome. Second, we did not use a risk of bias assessment tool as analysing outcome concerning drugs was outside the scope of this review. Finally, the higher survival rate and more favourable disease course of COVID-19 in women compared to men may have influenced the numbers of women included in the studies, as often disease severity increased the chance of inclusion. However, this should not influence sex-stratified randomization in its design or post hoc, or evaluating sex as a potential effect modifier. Strengths of the study are; first, the extensive systematic search aimed to include all relevant studies which resulted in a numeric analysis of the lack of sex consideration in COVID-19. Second, we provided numeric evidence that strengthens arguments and debates on the extent of sex-neglect in clinical trials. Finally, the results show literature-based, novel and easily applicable recommendations to improve future COVID-19 research in an early stage, as described below.

Concluding, in currently available clinical studies on pharmacological therapies for COVID-19 patients, none of the RCTs incorporated sex-stratified randomization, nor investigated sex as a potential effect modifier. Only one out of 30 studies stratified for sex in their analyses post-hoc. Moreover, almost a quarter of the included studies reported twice as many males compared to females. To allow for more personalised patient care, we call investigators to incorporate sex-stratification into their study protocol when developing and

testing therapeutic and prophylactic approaches for COVID-19. Although we are aware that these designs are expensive, the trial costs can be reduced by specifying the power to detect a clinically relevant interaction effect between sex and treatment a priori, recruiting a pre-specified number of women and men and ceasing enrolment of the particular sex when the sample size target is reached. For already published studies, we recommend investigators to perform post-hoc sex-specific analyses, while considering potential power insufficiencies in the interpretation of the results [68,69]. Furthermore, we recommend generating an open-access database with data from completed clinical COVID-19 trials in order to improve the power to detect sex-differences compared to current trials.

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Author's contribution

EJ and VS: performed the search, study selection, analysed the data, wrote the initial draft of the paper, revised the paper and finalized the manuscript

LJ and CG: study selection, wrote the paper

CG, BvB, IvdH: initiated the project, developed the idea and coordinated the writing process

JT, JS, DB, TD, SvK, AH, JS, CS, DM, BS, GM, AvtH, MS, WvM: wrote the paper and critically reviewed the content.

Data sharing statement

No individual patient data are included in this study. Search strategy and results of included papers are presented within the manuscript and are available at the corresponding author upon request.

Declaration of Competing Interest

Dr. Marx reports grants and personal fees from Bbraun Melsungen AG, grants and personal fees from Sphingotec AG, grants and personal fees from 4TEEN4 Pharmaceuticals GmbH, outside the submitted work. In addition, Dr. Marx has a patent Modulation ofTLR4 signalling European Patent 2855519/US Patent: US9,745,369 B2 issued, and a patent Combination of C1-Inh and Lung surfactant for the treatment of respiratory disorders PatentÐo.: US 7053,176 B1 PCT/EP99/06845 issued. All other authors declare no interest. Furthermore, there are no known conflicts of interest associated with this publication, and there has been no significant financial support for this work that could have influenced its outcome.

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that all have approved the order of authors listed in the manuscript.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.eclinm.2020.100652.

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