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RESEARCH ARTICLE

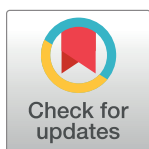
COVID-19 gender susceptibility and outcomes: A systematic review

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Abstract

Background

Epidemiological differences between men and women have been reported with regards to sepsis, influenza and severe coronavirus infections including SARS-CoV and MERS-CoV.

Aim

To systematically review the literature relating to men versus women on SARS-CoV-2 in order to seek differences in disease characteristics (e.g. infectivity, severity) and outcomes (e.g. mortality).

Methods

We searched 3 electronic databases up or observational studies reporting differences between men and women in the SARS-CoV-2 disease characteristics stated. We identified and included 47 studies, reporting data for 21,454 patients mainly from China.

Results

The unadjusted mortality rates of men were higher than those of women, with a mortality OR 0.51 [0.42, 0.61] ($p < 0.001$) for women. The proportion of men presenting with severe disease and admitted to the intensive care unit (ICU) was also higher than that of women (OR 0.75 [0.60–0.93] $p < 0.001$ and OR 0.45 [0.40–0.52] $p < 0.001$ respectively). Adjusted analyses could not be conducted due to lack of data.

Conclusion

COVID-19 may be associated with worse outcomes in males than in females. However, until more detailed data are provided in further studies enabling adjusted analysis, this remains an unproven assumption.

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Introduction

Many infectious diseases, including sepsis, have been associated with gender differences in disease incidence, morbidity and mortality [1–3]. Epidemiological differences between men and women have also been reported with regards to previous outbreaks of highly-pathogenic coronaviruses such as the severe acute respiratory syndrome coronavirus (SARS-CoV-1) [4] and the Middle East respiratory syndrome coronavirus (MERS-CoV) [5]. Men are more likely to be infected with MERS-CoV and SARS-CoV than women and when infected, they also seem to have worse outcomes [4]. These clinical findings are consistent with mouse models suggesting that estrogen reduces the susceptibility and severity of SARS-CoV infection; female mice that had their ovaries removed suffered from increased disease infectivity and severity [6]. SARS-CoV-2 may also affect men and women differently. However, at the time of this writing few epidemiological studies have explored the data on SARS-CoV-2 with regards to COVID-19 disease incidence and case-fatality rate. It therefore remains unclear if the disease characteristics (e.g. infectivity, severity) and outcomes (e.g. mortality) of patients with SARS-CoV-2 infection differ between the genders [7].

The effects of different viral infections on men and women are probably pathogen-specific. For instance, contrary to reports on MERS-CoV and SARS-CoV-1, women have been reported to suffer higher morbidity and mortality than men during influenza outbreaks [8]. Biological factors (referred to as sex-related variables) and sociocultural factors (referred as gender-related variables) are often put forward as explanations for the differences observed between men and women with regards to susceptibility and host response [9–12]. In this review we aimed to compile the data relating to men versus women in the literature on SARS-CoV-2. The intention was to seek differences, if these exist, between men and women in SARS-CoV-2 disease characteristics (e.g. infectivity, severity) and outcomes (e.g. mortality). Despite the nuances in terminology described above, the term “gender” is used throughout the manuscript in relation to all variables for the sake of convenience.

Methods

This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations [13] and was registered in the PROSPERO database prior to study initiation (CRD42020184142).

PICO question

We sought to study whether among adult patients with COVID-19 (P) women (“I”) differ from men (C) with regards to disease characteristics (e.g. infectivity, severity) and outcomes (any outcomemortality, severity and ICU admission rates) (O).

Search strategy

Two of the authors (IL, DLP) conducted a systematic search of PubMed, Medline, Web of Science and the Cochrane Library databases from inception to 1-June-2020 for studies describing any epidemiological characteristic related to patient gender in COVID-19. We initially used a broad search strategy which included any paper regarding the disease at hand. The following search terms were used: “2019 novel coronavirus” OR “SARS-CoV-2” OR “2019-nCoV” OR “novel coronavirus”. We then restricted the search for articles on adult humans. In the last stage of the database search, articles which were not written in English and those which were conducted on animal models and special populations (children, pregnant women) were also

excluded. Among the articles remaining we sought those providing any information regarding gender.

Eligibility criteria and study selection

We included randomized controlled trials, clinical trials, observational cohorts and case series that (1) described adult patients with SARS-CoV-2 infection confirmed by real-time reverse transcriptase polymerase chain reaction (rRT-PCR) and also (2) provided information regarding the relative proportion of men and women with confirmed disease, and/or admitted to hospital and/or the intensive care unit (ICU) and as well as their mortality rates. We also sought information regarding the background and acute disease characteristics of the two populations (men and women) with particular emphasis on severity of disease. We did not include preprints.

The articles were first selected by two of the authors (IL, DLP) in duplicate and independently based on title and abstract. Those selected were downloaded in full to allow full text review and those fulfilling the predetermined inclusion criteria regarding both disease diagnosis and presentation of relevant epidemiological data were included. The reference lists of relevant articles were also screened (i.e. snowballing method). Disagreement over study inclusion was resolved by consensus or, if necessary, by the adjudication of a third author (ML). For the sake of comprehensiveness, we decided to include also relevant single-arm studies without a comparison group. We excluded articles reporting data with complete or partial overlap with other reports. Abstracts, conference proceedings, and publications describing a single treatment arm were included only if they presented sufficient details. The exact details of the inclusion/exclusion process are shown in the PRISMA diagram (Fig 1).

As we also intended to perform an individual patient level meta-analysis (IPDMA), we contacted the corresponding authors of all the included studies (and five of the excluded studies to ensure full data capture) through electronic mail. The authors were requested to share their anonymised data regarding comorbidities, treatment with antivirals, treatment with corticosteroids and age of deceased among men and women. IPDMA allows for a more exact analysis of adjusted outcome. We intended to study in particular the adjusted primary outcome of mortality at any time.

Assessment of risk of bias (RoB)

Two of the authors (IL, DLP) assessed the RoB of the included studies independently and in duplicate. Disagreements over RoB were resolved by consensus or, if necessary, adjudicated by a third author (ML). As in all of the included studies the data were observational and the groups were not randomly assigned we used the Newcastle Ottawa Scale for assessing RoB and did not evaluate the “comparability” item [14]. For each domain we rated the overall RoB as the highest risk attributed to any criterion. A good quality score required at least two stars in the selection domain and three stars in the outcomes domain. The quality score was considered poor if the study obtained zero or one star in the selection and outcomes domains. A poor quality score was determined as no or one star in selection and outcomes domains. Since the element of comparability could not be assessed, the absence of a star in this element was not decisive for a good quality rating for a study. We assessed certainty in overall effect estimates using GRADE (Grade of Recommendations Assessment, Development and Evaluation) methods [15].

Data extraction

Two of the authors (IL, DLP) extracted data from the included studies independently and in duplicate to pre-prepared forms. The data extracted included the characteristics of the

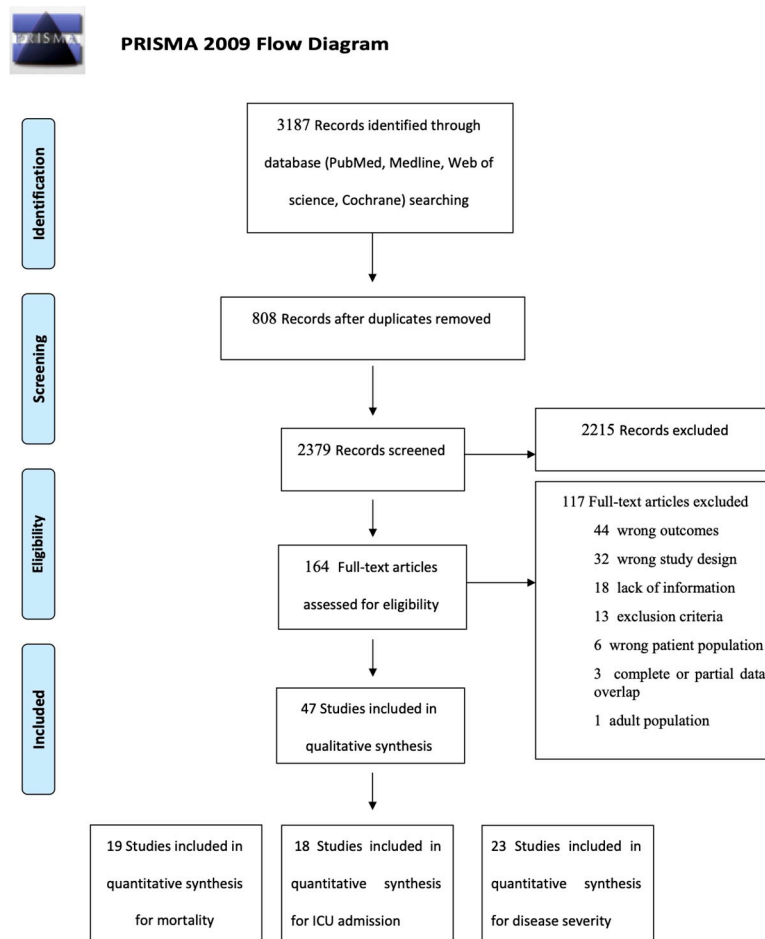


Fig 1. Study selection process.

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included publication (e.g. type of publication, journal name, date of publication) and the information provided (e.g. patients' age, number of men and women reported infected, ill [hospital admissions] and critically ill [ICU admissions], patients' background characteristics, disease severity and mortality).

Outcome measures

As we were unsure whether the authors approached would be forthcoming with their data we set our main outcome measure as the unadjusted all-cause mortality rate, as reported in the included studies (hospital, out-of-hospital, depending on the duration of the follow-up). Secondary outcomes included disease severity (as per author definition), and ICU admission rates as well as the adjusted mortality rates.

Statistical analysis

We set out to perform a quantitative synthesis if two or more studies were identified with sufficient homogeneity in study design, interventions and outcomes and low risk of bias [16]. The odds ratios (OR) were calculated by reporting available data from included studies, with 95% confidence intervals (95% CI). P-values were considered significant if <0.05 . Pooled

prevalences and their 95% CIs were used to summarize the weighted effect size for each study grouping variables using the binary fixed-effects model (Mantel-Haenszel method). Statistical heterogeneity was evaluated by the I^2 , corresponding to the proportion of total variation due to inter-study heterogeneity, and visual inspections of the forest plots. All the analyses were performed using Revman Version 5.4 (Copenhagen, Denmark).

Results

A total of 2,379 studies were screened, of which 47 contributed data to our analysis for a total of 21,454 patients consisting of 11,176 women and 10,278 men [17–61]. Most of the included studies originated from different hospitals in China ($n = 38$), one originated from Hong Kong, two from South Korea, five from Europe and North America and one from Israel (Table 1). The quality of 43 of the studies was rated as poor and of 4 of the studies was rated as good (Table 2).

Crude mortality rates

Characteristics of the studies that contributed data to the analysis of crude mortality rates in men and women. The crude mortality rates were reported separately for 5,589 men and 6,751 women in 19 studies. Among the included studies, 1 was prospective and observational, 10 were retrospective database studies, and 9 were case series. None of the studies aimed a-priori to compare between the genders as the main outcome measure. There were no studies that attempted to assess sex differences as the main outcome measure. Most of the studies included less than 300 patients. The studies reporting crude mortality data involved mainly cohorts of hospitalized patients, except for one Korean epidemiological study of 7,755 patients [61]. Variables such as age, patient comorbidities, and treatments were not reported individually, so mortality data could not be adjusted. The characteristics and the main findings of the included studies are provided in Table 1.

RoB in the studies that contributed data to the analysis of mortality rates in men and women. The results of the quality assessment were highly variable ranging from 1/7 (two studies) to 5/7 (two studies) on the Newcastle Ottawa Scale (Table 2). The main caveats were that patient follow-up was either non-existent or very short, and mortality assessment was not standardized.

Mortality rates in men and women. Overall 280 (4%) women died versus 623 (11%) men ($p < 0.001$, OR 0.51 [0.42, 0.61] for women versus men, see Fig 2) based on a very low-certainty evidence (Table 3). However, there was significant variability in the mortality rates reported in different studies, with OR and 95% CI ranging from 0.14 [0.01, 2.86] to 1.33 [0.27, 6.50]. Heterogeneity reported as I^2 was low at 6% for this analysis. The funnel plot (S1a Fig in S1 File) and the Egger test ($p = 0.54$) both indicated that there was no evidence for publication bias.

Sensitivity analyses. A sensitivity analysis was performed to assess the stability of the results. Heterogeneity as measured by I^2 was already low, therefore omitting studies sequentially had no significant influence on the results (S2 Fig in S1 File).

Unadjusted severe disease presentation

Characteristics of the studies that contributed data to the analysis of severe disease presentation in men and women. The proportion of men and women with severe disease presentation was reported in 23 studies, including 1,721 women and 1,970 men. Among the included studies 1 was prospective observational, 9 were retrospective database studies, and 13 were case series. None of the studies aimed a-priori to compare between the genders as the severity of the disease. Most of the studies included less than 200 patients. As for the definition

Table 1. Studies included in the systematic review.

Newcastle Ottawa Scale	Author	Journal	Centre (country)	Design		No. of patients			Setting	Age (+/-SD or IQR)	Crude in-hospital mortality		ICU admission		Severity		Severity definition
						Total	F	M			F	M	F	M	F	M	
Total grade																	
3/7	Chen G	<i>J Clin Invest.</i>	1 (China)	Retrospective	Case series	21	4	17	Hospital	56 (50–65)	0	4	-	-	1	10	National Health Commission of China
5/7	Chen R	<i>Chest</i>	575 (China)	Retrospective	Cohort	1590	725	865	Hospital	NA	11	39	-	-	-	-	National Health Commission of China
4/7	Chen T	<i>BMJ</i>	1 (China)	Retrospective	Case series	274	103	171	Hospital	62 (44–70)	30	83	-	-	-	-	National Health Commission of China
3/7	Chen X	<i>Clin Infect Dis.</i>	1 (China)	Retrospective	Case series	48	11	37	Hospital	64.6 (+/-18.1)	-	-	2	15	1	9	National Health Commission of China
3/7	Conversano A	<i>Hypertension</i>	1 (Italy)	Retrospective	Consecutive case series	191	60	131	Hospital	63.4 (+/-14.9)	11	31	-	-	-	-	NA
3/7	Gautret P	<i>Travel Med Infect Dis</i>	1 (France)	Retrospective	Cohort	80	37	43	Hospital	52 (18–88)	0	1	0	3	-	-	NA
4/7	Guan W	<i>N Engl J Med</i>	552 (China)	Retrospective	Cohort	1099	459	640	Hospital	47 (35–58)	-	-	22	45	73	100	American Thoracic Society Guidelines
3/7	Hong KS	<i>Yonsei Med J</i>	1 (South Korea)	Retrospective	Cohort	98	60	38	Hospital	55.4 (+/-17.1)	-	-	7	6	-	-	Critically ill based on ARDS definition
3/7	Hou H	<i>Clin Exp Immunol</i>	1 (China)	Retrospective	Cohort	389	189	200	Hospital	61.3 (+/-13.8)	-	-	20	32	75	94	National Health Commission of China
3/7	Huang C	<i>Lancet</i>	1 (China)	Prospective	Observational cohort study	41	11	30	Hospital	49 (41–58)	-	-	2	11	-	-	WHO interim guidelines
3/7	Helman E	<i>Isr Med Assoc J</i>	1 (Israel)	Retrospective	Cohort	162	57	105	Hospital	52 (+/-20)	-	-	-	5	21	-	Clinical definition
1/7	Korea—CDC	<i>Onsong Public Health Res Perspect</i>	multicentre (Korea)	Retrospective	Case series	7755	4808	2947	Epidemiological	NA	29	37	-	-	-	-	NA
2/7	Lagi F	<i>Euro Surveill</i>	1 (Italy)	Retrospective	Cohort	84	29	55	Hospital	62 (51–72)	-	-	2	14	-	-	Critically ill based on ARDS definition
5/7	Liu F	<i>Thrombotics</i>	1 (China)	Retrospective	Cohort	134	71	63	Hospital	51.5 (37–65)	0	0	-	-	4	15	National Health Commission of China
3/7	Liu F	<i>J Clin Virol</i>	1 (China)	Retrospective	Cohort	140	91	49	Hospital	65.5 (54.3–73)	-	-	-	-	25	8	National Health Commission of China
4/7	Liu J	<i>EBioMedicine</i>	1 (China)	Retrospective	Cohort	40	25	15	Hospital	48.7 (+/-13.9)	-	-	-	-	6	7	National Health Commission of China
3/7	Liu K-C	<i>Eur J Radiol</i>	6 (China)	Retrospective	Case series	73	32	41	Hospital	41.6 (+/-14.5)	-	-	3	0	11	10	National Health Commission of China
3/7	Liu Z	<i>Korean J Radiol</i>	3 (China)	Retrospective	Case series	72	33	39	Hospital	46.2 (+/-15.9)	0	0	-	-	5	3	WHO interim guidelines
1/7	Marullo AG	<i>Minerva Cardiol</i>	90 (Europe)	Retrospective	Case series	217	46	171	Hospital	52 (+/-11)	6	26	46	171	-	-	NA
3/7	Pan L	<i>Am J Gastroenterol</i>	3 (China)	Retrospective	Case series	103	48	55	Hospital	52.21 (+/-15.92)	-	-	7	16	7	7	NA
2/7	Perrilli C	<i>BMJ</i>	1 (USA)	Prospective	Observational cohort study	5279	2664	2615	Hospital/ER	54 (38–66)	-	-	334	656	-	-	Critically ill based on ARDS definition or death
2/7	Shi H	<i>Lancet Infect Dis</i>	2 (China)	Retrospective	Case series	81	39	42	Hospital	49.5 (+/-11)	0	3	-	-	-	-	NA
2/7	Sun B	<i>Emerg Microbes Infect</i>	1 (China)	Retrospective	Case series	38	14	24	Hospital	44 (32–56)	-	-	1	10	-	-	NA
3/7	Sun H	<i>J Am Geriatr Soc</i>	1 (China)	Retrospective	Case-control study	244	111	133	Hospital	69 (65–76)	39	82	-	-	-	-	NA
3/7	Sun S	<i>Clin Chim Acta</i>	1 (China)	Retrospective	Case series	116	56	60	Hospital	50 (41–57)	-	-	3	6	9	18	National Health Commission of China
4/7	Tang N	<i>J Thromb Haemost</i>	1 (China)	Retrospective	Cohort	449	181	268	Hospital	65.1 (+/-12)	44	90	-	-	-	-	National Health Commission of China
3/7	Tian S	<i>J Infect</i>	57 (China)	Retrospective	Cohort	262	135	127	Hospital	47.5	1	2	-	-	20	26	Clinical definition
3/7	To K	<i>Lancet Infect Dis</i>	2 (Hong Kong)	Prospective	Observational cohort study	23	10	13	Hospital	62 (37–75)	-	-	-	-	4	6	Clinical definition
5/7	Wan S	<i>Br J Haematol</i>	1 (China)	Retrospective	Case series	123	57	66	Hospital	43 (+/-13.1)	-	-	-	-	10	11	National Health Commission of China
5/7	Wang D	<i>Crit Care</i>	2 (China)	Retrospective	Case series	107	50	57	Hospital	51 (36–65)	3	16	-	-	-	-	Clinical definition
2/7	Wang F	<i>Endocr Pract</i>	1 (China)	Retrospective	Case series	28	7	21	Hospital	68.6 (+/-9)	-	-	4	10	-	-	National Health Commission of China
3/7	Wang J	<i>Clin Radiol</i>	3 (China)	Retrospective	Case series	93	36	57	Hospital	52.1 (+/-18.1)	-	-	6	14	-	-	National Health Commission of China
3/7	Wang L	<i>J Infect</i>	1 (China)	Retrospective	Consecutive case series	339	173	166	Hospital	69 (65–76)	26	39	-	-	-	-	National Health Commission of China
3/7	Wang L	<i>Am J Nephrol</i>	1 (China)	Retrospective	Case series	116	49	67	Hospital	54 (38–69)	-	-	5	6	19	27	WHO interim guidelines
3/7	Wang M	<i>Aging (Albany, NY)</i>	3 (China)	Retrospective	Cohort	66	23	43	Hospital	NA	0	2	-	-	-	-	NA
3/7	Wu C	<i>JAMA Intern Med</i>	1 (China)	Retrospective	Cohort	201	73	128	Hospital	51 (43–60)	15	29	24	60	-	-	Critically ill based on ARDS definition
3/7	Xu Y-H	<i>J Infect</i>	1 (China)	Retrospective	Case series	50	21	29	Hospital	43.9 (+/-16.8)	-	-	0	3	3	7	National Health Commission of China
4/7	Yan Y	<i>BMJ Open Diabetes Res Care</i>	1 (China)	Retrospective	Case series	193	79	114	Hospital	69 (49–73)	32	76	-	-	79	114	National Health Commission of China
3/7	Yang A-P	<i>Int Immunopharmacol</i>	1 (China)	Retrospective	Case series	93	37	56	Hospital	46.4 (+/-17.6)	-	-	-	-	6	18	American Thoracic Society Guidelines
4/7	Yang X	<i>Lancet Respir Med</i>	1 (China)	Retrospective	Cohort	52	17	35	Hospital	59.7 (+/-13.3)	11	21	17	35	-	-	Critically ill based on required mechanical ventilation
4/7	Yang Y	<i>J Allergy Clin Immunol</i>	1 (China)	Retrospective	Case-control series	50	21	29	Hospital	62 (22–78)	-	-	3	8	11	14	National Health Commission of China
4/7	Yuan M	<i>PLoS One</i>	1 (China)	Retrospective	Consecutive case series	27	15	12	Hospital	60 (47–69)	6	4	-	-	-	-	NA
2/7	Zeng F	<i>J Med Virol</i>	1 (China)	Retrospective	Case series	331	204	127	Hospital	NA	-	-	-	-	11	11	NA
3/7	Zhang G	<i>Respir Res</i>	1 (China)	Retrospective	Cohort	95	42	53	Hospital	NA	-	-	9	16	11	21	National Health Commission of China
3/7	Zheng C	<i>Int J Infect Dis</i>	1 (China)	Retrospective	Case series	55	31	24	Hospital	NA	0	0	-	-	13	8	National Health Commission of China
3/7	Zheng S	<i>BMJ</i>	1 (China)	Retrospective	Cohort	96	38	58	Hospital	55 (47.5–56.3)	-	-	-	-	25	49	National Health Commission of China
4/7	Zhou F	<i>Lancet</i>	2 (China)	Retrospective	Cohort	191	72	119	Hospital	56 (46–67)	16	38	-	-	-	-	National Health Commission of China

NA: not applicable

<https://doi.org/10.1371/journal.pone.0241827.t001>

Table 2. Risk of bias assessment according the Newcastle Ottawa Score.

Author	Journal	Design	Selection		Comparability	Outcome			Score
			1	2		1	2	3	
Chen G	<i>J Clin Invest.</i>	Retrospective	Case series	*	*	*			3/7
Chen R	<i>Chest</i>	Retrospective	Cohort	*	*	*	*	*	5/7
Chen T	<i>BMJ</i>	Retrospective	Case series	*	*	*	*		4/7
Chen X	<i>Clin Infect Dis.</i>	Retrospective	Case series	*	*	*			3/7
Conversano A	<i>Hypertension</i>	Retrospective	Consecutive case series		*	*	*		3/7
Gautret P	<i>Travel Med Infect Dis</i>	Retrospective	Cohort	*	*	*			3/7
Guan W	<i>N Engl J Med</i>	Retrospective	Cohort	*	*	*		*	4/7
Hong KS	<i>Yonsei Med J</i>	Retrospective	Cohort	*	*	*			3/7
Hou H	<i>Clin Exp Immunol</i>	Retrospective	Cohort	*	*	*			3/7
Huang C	<i>Lancet</i>	Prospective	Obsevational cohort study	*	*	*			3/7
Itelman E	<i>Isr Med Assoc J</i>	Retrospective	Cohort	*	*	*			3/7
Korea—CDC	<i>Onsong Public Health Res Perspect</i>	Retrospective	Case series			*			1/7
Lagi F	<i>Euro Surveill</i>	Retrospective	Cohort	*		*			2/7
Liu F	<i>Theranostics</i>	Retrospective	Cohort	*	*	*	*	*	5/7
Liu F	<i>J Clin Virol</i>	Retrospective	Cohort	*	*	*			3/7
Liu J	<i>EBioMedicine</i>	Retrospective	Cohort	*	*	*		*	4/7
Liu K-C	<i>Eur J Radiol</i>	Retrospective	Case series	*	*	*			3/7
Liu Z	<i>Korean J Radiol</i>	Retrospective	Case series	*	*	*			3/7
Marullo AG	<i>Minerva Cardioangiol</i>	Retrospective	Case series			*			1/7
Pan L	<i>Am J Gastroenterol</i>	Retrospective	Case series			*	*	*	3/7
Petrilli C	<i>BMJ</i>	Prospective	Obsevational cohort study		*	*			2/7
Shi H	<i>Lancet Infect Dis</i>	Retrospective	Case series	*		*			2/7
Sun B	<i>Emerg Microbes Infect</i>	Retrospective	Case series	*		*			2/7
Sun H	<i>J Am Geriatr Soc</i>	Retrospective	Case-control study			*	*	*	3/7
Sun S	<i>Clin Chim Acta</i>	Retrospective	Case series	*	*	*			3/7
Tang N	<i>J Thromb Haemost</i>	Retrospective	Cohort		*	*	*	*	4/7
Tian S	<i>J Infect</i>	Retrospective	Cohort	*	*	*			3/7
To K	<i>Lancet Infect Dis</i>	Prospective	Obsevational cohort study	*	*	*			3/7
Wan S	<i>Br J Haematol</i>	Retrospective	Case series	*	*	*	*	*	5/7
Wang D	<i>Crit Care</i>	Retrospective	Case series	*	*	*	*	*	5/7
Wang F	<i>Endocr Pract</i>	Retrospective	Case series		*	*			2/7
Wang J	<i>Clin Radiol</i>	Retrospective	Case series	*	*	*			3/7
Wang L	<i>J Infect</i>	Retrospective	Consecutive case series		*	*	*		3/7
Wang L	<i>Am J Nephrol</i>	Retrospective	Case series	*	*	*			3/7
Wang M	<i>Aging (Albany, NY)</i>	Retrospective	Cohort	*		*		*	3/7
Wu C	<i>JAMA Intern Med</i>	Retrospective	Cohort	*	*	*			3/7
Xu Y-H	<i>J Infect</i>	Retrospective	Case series	*	*	*			3/7
Yan Y	<i>BMJ Open Diabetes Res Care</i>	Retrospective	Case series		*	*	*	*	4/7
Yang A-P	<i>Int Immunopharmacol</i>	Retrospective	Case series	*	*	*			3/7
Yang X	<i>Lancet Respir Med</i>	Retrospective	Cohort		*	*	*	*	4/7
Yang Y	<i>J Allergy Clin Immunol</i>	Retrospective	Case-control series	*	*	*			3/7
Yuan M	<i>PloS One</i>	Retrospective	Consecutive case series	*		*	*	*	4/7
Zeng F	<i>J Med Virol</i>	Retrospective	Case series	*		*			2/7
Zhang G	<i>Respir Res</i>	Retrospective	Cohort	*	*	*			3/7
Zheng C	<i>Int J Infect Dis</i>	Retrospective	Case series	*	*	*			3/7
Zheng S	<i>BMJ</i>	Retrospective	Cohort	*	*	*			3/7
Zhou F	<i>Lancet</i>	Retrospective	Cohort	*	*	*		*	4/7

<https://doi.org/10.1371/journal.pone.0241827.t002>

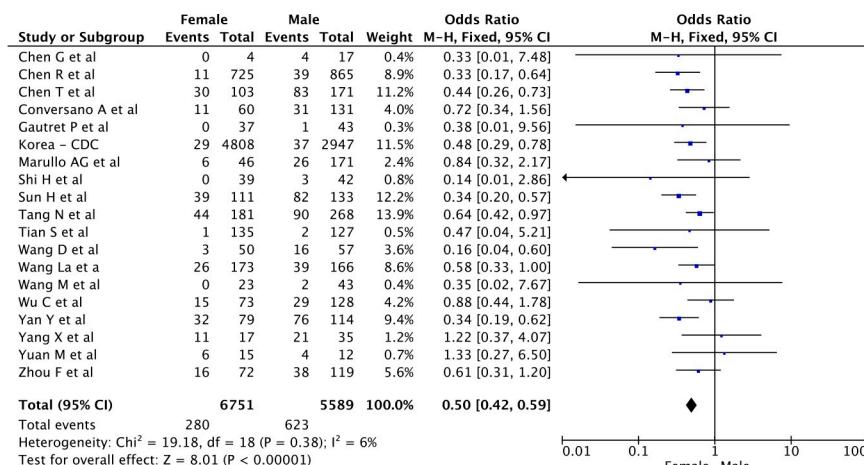


Fig 2. Crude mortality risk according to the gender of COVID-19 patients.

<https://doi.org/10.1371/journal.pone.0241827.g002>

of severity, of the 23 studies, 14 used the definition of the National Health Commission of China [17, 19, 20, 24, 27, 29, 33, 36, 41, 42, 55, 56, 58, 62], 2 used the WHO interim guidelines [49, 52], 2 used the American Thoracic Society guidelines [35, 57], and the last 3 used a pre-determined clinical presentation [44, 60, 63]. All these definitions and scores were based on clinical, biological and radiological parameters assessing respiratory failure, hypoxemia and disease progression. Only one study did not provide the exact definition of severe cases [39].

RoB in the studies that contributed data to the analysis of severe disease presentation in men and women. The assessment of the studies contributing to the severity analysis showed variability ranking from 2/7 to 5/7, as reported in Table 2.

Severe disease presentation in men and women. Overall, 355 (21%) women developed severe disease out of 1,721 women versus 500 (25%) men out of 1,970 men (OR 0.75 [0.60–0.93] for women versus men, $p < 0.001$, see Fig 3). There was great variability in the rates of severe disease in men and women, with OR and 95% CI ranging from 0.23 [0.02, 2.73] to 2.14 [0.47, 9.74]. Heterogeneity reported as I^2 was reaching 28% for this analysis. The funnel plot (S1b Fig in S1 File) and the Egger test ($p = 0.18$) both indicated that there was no evidence for publication bias.

Unadjusted rates of ICU admission

Characteristics of the studies that contributed data to the analysis of mortality rates in men and women. The ICU admission rates were reported separately for 4,222 men and

Table 3. Certainty in overall mortality effect estimates using Grading of Recommendations Assessment, Development and Evaluation (GRADE) methods.

Certainty assessment						Effect	Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision			
47	Observational studies	Serious	Serious	Very Serious	Very Serious	OR 0.51 [0.42–0.61]	VERY LOW	CRITICAL

CI, confidence interval; OR, odds ratio.

<https://doi.org/10.1371/journal.pone.0241827.t003>

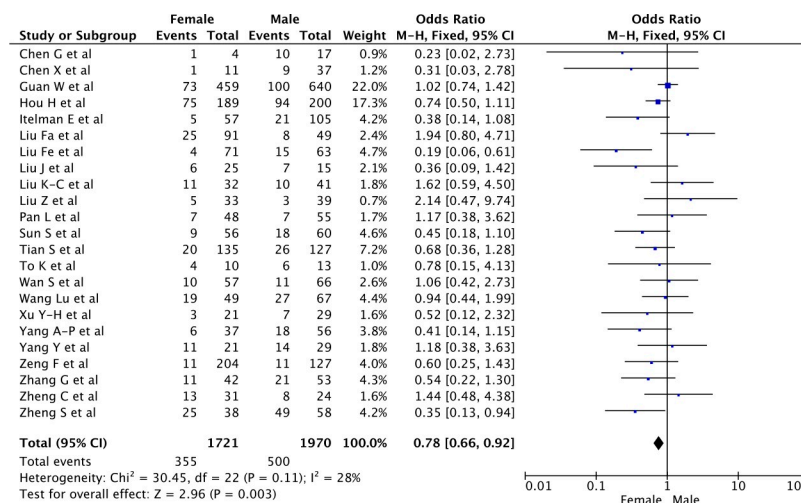


Fig 3. Risk of severe presentation of the COVID-19 according to gender.

<https://doi.org/10.1371/journal.pone.0241827.g003>

3,859 women in 18 studies. Among the included studies 4 were prospective and observational, 5 were retrospective database studies, and 10 were case series. None of the studies aimed a-priori to compare differences between the sexes as the main outcome measure. Most of the studies included less than 100 patients. The characteristics and the main findings of the included studies are provided in Table 1.

RoB in the studies that contributed data to the analysis of ICU admission rates in men and women. The results of the quality assessment were highly variable ranging from 1/7 to 4/7 on the Newcastle Ottawa Scale (Table 2). The lowest scores are explained by the large number of case series included in this analysis.

Unadjusted rates of ICU admission of men and women. The proportion of men and women admitted to ICU was of 454 (12%) women and 931 (22%) men, (OR 0.45 [0.40–0.52], for women versus men, $p < 0.001$, see Fig 4). Heterogeneity reported as I^2 was as low as 0% for this analysis. The funnel plot (S1c Fig in S1 File) and the Egger test ($p = 0.51$) both indicated that there was no evidence for publication bias.

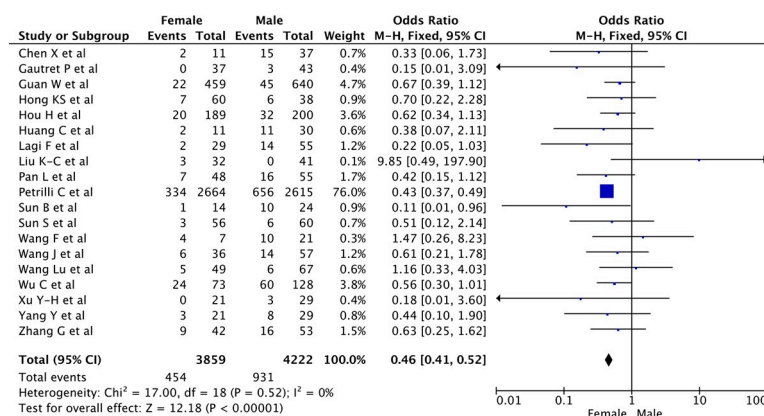


Fig 4. Risk of ICU admission in COVID-19 patients according to gender.

<https://doi.org/10.1371/journal.pone.0241827.g004>

IPDMA and adjusted outcomes

Despite repeated appeals, of all the authors contacted, only two responded to our request for data (the data was anonymized in both cases). This precluded performance of an IPDMA of adjusted outcomes; there were insufficient data on relevant variables (co-morbidities, treatment and age by vital status for males and females).

Discussion

Unadjusted data suggest that men may have a higher risk of developing severe COVID-19 and also have higher associated death rates than women. Lacking detailed patient level data we were unable to determine whether this finding remains consistent after adjusting for the age and the burden of co-morbidity.

Several authors have suggested that men are more likely to be infected with COVID-19, especially after 50 years of age [64]. Alsan et al. reported that the incidence of COVID-19 in men was almost four times higher than in women (4.4% vs 1.2%) [65]. Here we report a similar total number of COVID-19 cases in men and women, suggesting that our findings are not directly related to a frequency argument.

Male-female differences in infectious diseases have already been reported and explored in the literature [9–11]. These differences are usually attributed to three determinants: differences in immune function associated with the X chromosome, the effects of sex hormones and gender-related behavior [12].

In the context of viral infections, men and women exhibit different immune reactions depending on the type of virus [66]. When infected with SARS-Cov, women usually have heightened immunity protecting them from severe forms of the disease, likely due to activation of the X regulatory genes, resulting in lower viral loads and higher CD4 T-cell counts [6, 67]. Women have additional immune characteristics which provide an advantage when exposed to viral infection compared to men. For example women have higher expression of Toll-like receptor 7 (TLR7) which is known to recognize viral RNA. They also produce more interferon- α , which is associated with the protection of lung tissue in animal models. Differences in production of IL-6 have also been observed between men and women [10].

Estradiol is believed to stimulate humoral and cell-mediated immune responses [68] and increase antibody production [73]. Estradiol is also involved in regulating the expression of angiotensin converting enzyme 2 (ACE2), which is known for its protective role in acute respiratory distress syndrome [69, 70]. To date, there is no data available on gender-specific ACE2 expression in the lungs [71]. On the other side of the hormonal spectrum, testosterone is known to be immunosuppressive and decreased testosterone production is associated with elevated levels of pro-inflammatory cytokines [72]. Thus testosterone-related inhibition of the inflammatory response may dampen the antiviral response whereas an estrogen enhanced the increase in antibody and CD8 titers is likely to enhance the antiviral immune response.

Gender differences also exist in the dimension of social behaviour. Alsan et al. reported that men washed their hands 3.8 times per day less than women in a national US survey. Men were also more inclined to go outside than women during lockdown, which may have increased their exposure to SARS-CoV-2 [65]. Comorbidities such as obesity, diabetes and hypertension, which are unequally distributed between men and women at different ages, may also affect the course of disease [73, 74].

Finally, the role of the virus itself should not be underestimated; for example, influenza has higher morbidity and mortality in women than in men [8].

Despite our exhaustive data collection, our analyses are probably tinged with significant selection bias. The studies included report data mainly from China; i.e. the data presented are

from the early stage of the outbreak. Such bias could explain the high mortality rates found in our study. Nonetheless, more recent data from Italy also showed higher mortality rates among men [75]. Men also had a higher rate of ICU admission in the US than women (OR = 2.0; 95% CI: 1.3–3.2) [76]. However, while this finding may indicate worse disease severity in men, it could also stem from admission bias. Another limitation of our study is that most of the studies included were retrospective and had a short follow-up period which may lead to underestimation of long-term mortality. The mortality reported in the included studies was mostly in-hospital mortality (except for one study) and ICU mortality was specifically reported in only five studies. These considerations are reflected in the RoB assessment where they negatively affected study ratings, leading to a very low certainty of evidence. But the greatest limitation of our study is that these data could not be adjusted for age, co-morbidities or treatment.

To conclude, COVID-19 may be associated with greater disease severity and higher mortality rates among males. However, this preliminary finding remains unproven until such time that adjusted analyses can be conducted. Our results are in line with previous studies on viruses and are also supported by a strong biological rationale, but the level of evidence is limited by the poor quality of the available data. We urge researchers to conduct further studies and request sharing of data on gender dimorphism in COVID-19 in order to provide more robust evidence on this topic.

Supporting information

S1 Checklist. PRISMA 2009 checklist.

(DOC)

S1 File.

(DOCX)

Author Contributions

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Supervision: Sharon Einav, Marc Leone.

Writing – original draft: Ines Lakbar, David Luque-Paz.

Writing – review & editing: Jean-Louis Mege, Sharon Einav, Marc Leone.

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