The Sex Difference and Potential Influence Factors In 96,237 Patients With Coronavirus Disease 2019 (COVID-19): A Systematic Review and Meta-Analysis

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Abstract

Background: Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This disease was first identified in December 2019 in Wuhan and has since spread globally, resulting in the ongoing 2019–20 coronavirus pandemic. Numerous studies of the clinical characteristics of patients with SARS-CoV-2 have been reported, yet yielded varying results given the sex difference of prevalence, severity and fatality rate. We conducted a review and meta-analysis of the sex differences of COVID-19, aiming to reveal the epidemiological characteristics and potential influencing factors of COVID-19 and provide reference for the prevention and treatment of patients.

Results: By screening 1436 studies, 156 studies including 96237 COVID-19 patients from multiple countries were included. We found out that females account for 0.47 [95% CI (0.45-0.48)] of the diagnosed COVID-19 cases, while males for 0.53 of the cases [95% CI (0.52-0.55)]. Females admitted into intensive care unit (ICU) or with severe/critical illness were also analyzed, and the ratio was 0.14 [95% CI (0.11-0.17)] among all the severely/critically ill patients, which was almost twice lower than the ratio of males (0.24 [95% CI (0.19-0.29)]). The fatality rate of female patients was 0.10 [95%CI (0.05-0.17)], which was much lower than that of males (0.18[95%CI (0.11-0.29)]).

Conclusions: There exists a significantly different clinical outcome between male and female COVID-19 patients. Females are less severely affected, which might be associated with the sex-based difference in immune response, female hormones and behaviors. However, more specific studies are needed to identify more relevant factors.

Background

Since December 2019, the current outbreak of coronavirus disease (COVID-19) caused by a novel coronavirus (SARS-CoV-2, previously named 2019-nCoV) was first identified in Wuhan, Hubei Province of the People's Republic of China [1] and aroused attention of worldwide. On March 11, 2020, The World Health Organization (WHO) officially announced this rapidly spreading coronavirus outbreak as a pandemic based on the fact that the number of confirmed cases of COVID-19 outside China has increased rapidly and dramatically.

The next-generation sequencing and comparative homology analysis revealed that this novel pathogen belongs to a member of lineage B within genus Betacoronavirus with a significantly different genomic sequence from SARS-CoV (about 79% identity) and MERS-CoV (about 50% identity)[2].

The clinical spectrum of COVID-19 is varied, ranging from asymptomatic form or non-specific signs to acute respiratory distress syndrome (ARDS) and systemic manifestations of sepsis and septic shock, i.e. multiple organ dysfunction syndromes (MODS).

At present there is an emerging collection of the basic research, clinical and epidemiological data about COVID-19. The initial report of 41 COVID-19 patients in Wuhan demonstrated that more men (73%) patients were affected than were women [3]. According to Guan et al.'s data [3] on the clinical characteristics of 1099 cases in 30 provinces in China, male patients accounted for 58%. Moreover, 35 (67%) of critically ill patients admitted to the intensive care unit (ICU) were male patients [4]. Based on the public database and the analysis of single-cell RNA expression profiles of human normal lung cells, it was found that the expression level of Angiotensin-converting enzyme 2 (ACE2, considered as an SARS-CoV-2 receptor [5]) in Asian men is higher (preprint)[6]. Thus, it is speculated that there might be differences in susceptibility to COVID-19 between two sexes, and males are more prone to suffering from severe clinical conditions than are females. However, these reports are limited with a small cohort of cases.

Methods

Objective

In order to make a more convincing conclusion, we have conducted a systematic evaluation of the sex predisposition of COVID-19 by analyzing a large cohort of reported clinical studies and cases globally. In our research, the clinical data between December, 2019 and April, 2020 were extracted and collected to discover and reveal the difference of incidence, first symptoms, severity, and outcomes between two sexes. Clarifying the sex difference in susceptibility and severity of COVID-19 and identifying possible risky factors can help protect more vulnerable populations and provide useful information for developing better treatment and prognosis of COVID-19.

Eligibility criteria

Studies were included if they reported confirmed patients with COVID-19, and reported the sex distribution of patients. Repeated cases, reviews, editorials, family or cluster-based studies, only children (including neonates) cases and only pregnant women cases were excluded.

Information sources

A comprehensive systematic literature search of online databases was conducted on April 27, 2020, including Pubmed, Embase, Web of Science, medRxiv, bioRxiv and Arxiv to collect all case studies. The EndNote X9.0 software was used to manage and exclude the duplicated literatures.

Search strategy

The search terms were as follows: "SARS-CoV-2", "COVID-19", "2019 novel coronavirus", "2019-nCoV", "clinical characteristics", "clinical features" and "clinical manifestations" without any language restriction. The database search results were conducted according to the flow of Preferred Reporting for Systematic Reviews of Meta-analyses (PRISMA) statement[7].

Data extraction and analysis

All available publications have been carefully analyzed and strictly reviewed by two reviewers. Microsoft Excel was used to record all available information, including the authors, source place, collection period, age, case load, sex, the number of patients in ICU-male, ICU-female, the prevalence of mild/common illness and severe/critical illness, discharge rate, remained in hospital rate and fatality rate. Any disagreements were resolved by discussion.

Quality assessment and risk of bias

An 11-item checklist for cross-sectional/prevalence study quality provided by Agency for Healthcare Research and Quality (AHRQ) [8] was applied to assess the quality of included studies. When answering 'NO' or 'UNCLAR', the item would be scored '0'; When answering 'YES', the item would be scored '1'. The included studies were rated with following scores: low quality (0–3); moderate quality (4–7); high quality (8–11). Publication bias was examined by using a funnel-plot with Begg's and Egger's test.

Data analysis

The statistical analyses were performed by using R (version 3.6.2) and STATA MP (version 13.0). As there exists heterogeneity between and within studies, a random effect model was used to calculate the pooled prevalence and 95%CI, which was demonstrated by forest plot. Heterogeneity among studies was tested using the Cochran's Q test and I^2 (ranged from 0–100%). When $I^2 < 50\%$, fixed-effects model was used, while when $I^2 > 50\%$, random-effects was selected. The R package "meta" was used to analyze and display plots. Funnel plots were used to assess the publication bias. $P < 0.05$ was considered as statistical significance (2-sided).

Results

A total of 1436 literatures were searched from the online databases based on the strategy. After we removed duplicated studies, screened the title and abstract and reviewed full-text, 156 studies were selected in the meta-analysis. Data was extracted from published manuscripts. The flowchart of the selection process was displayed in Fig. 1. The quality score of each study was displayed in Table 1. 8 studies were of high quality and 148 were of moderate quality. No articles were of low-quality rating.

Table 1
Main Characteristics of included studies in this meta-analysis

Study	collection period	Age	Case load	Male (n)	ICU-Male	ICU-Female	mild	common	severe
Zhu Z, et al. (Wuhan)	Jan 23 to Feb 20, 2020	50.90(15.26)_mean(SD)	127	45	/	/	111_M73_F38		16_M9_F7
Zhou Y, et al. (Huangshi)	Jan 28 to Mar 2, 2020	66.10(13.94)_mean(SD)	21	13	13	8	/	/	8_M3_F5
Zhou B, et al. (Wuhan)	Feb 5 to Feb 13, 2020	/	34	17	/	/	/	/	26_M12_F
Zheng Y, et al. (Chengdu)	Jan 16 to Feb 20, 2020	49.4(18.45)_mean(SD)	99	51	/	/	67		/
Zheng S, et al. (Zhejiang Province)	Jan 19 to Mar 20, 2020	55(44.3–46.8)_median(IQR)	96	58	30		22_M9_F13	/	74_M49_F
Zhao W, et al. (Hunan Province)	/	43 (17–75)_median(range)	101	56	/	/	87_M48_F39	/	14_M8_F6
Zhao W, et al. (Hunan Province)	Jan 16 to Feb 4, 2020	44.06(13.62)_mean(SD)	118	60	/	/	8	100	10
Zhang Y, et al. (Wuhan)	Jan 18 to Feb 22, 2020	49.52 (17.06)_mean(SD)	115	49	/	/	84_M29_55	/	31_M20_F
Zhang X, et al. (Zhejiang Province)	Jan 17 to Feb 8, 2020	46.65(13.82)_mean(SD)	573	295	/	/	/	/	64
Zhang R, et al. (Wuhan)	Jan 10 to Feb 10, 2020	45.4(15.6)_mean(SD)	120	43	/	/	/	90_M30_F60	30_M13_F
Zhang J, et al. (Wuhan)	Jan 11 to Feb 6, 2020	55.6(44–69)_mean(IQR)	663	321	/	/	254_M116_F138		315_M149
Zhang J, et al. (Wuhan)	Jan 6 to Feb 20, 2020	73 (38–91)_median(range)	19	11	11	8	/	/	/
Zhang G, et al. (Wuhan)	Jan 2 to Feb 10, 2020	55.0 (39.0-66.5)_	221	108	44		166_M73_F93		55_M35_F
Yuan M, et al. (Wuhan)	Jan 1 to Jan 25, 2020	60(47–69)_median(IQR)	27	12	/	/	/	/	/
Young BE, et al. (Singapore)	Jan 23 to Feb 3, 2020	47(31–73)_median(range)	18	9	/	/	/	/	/
Yao Q, et al. (Huanggang, Hubei Province)	Jan 30 to Feb 11, 2020	52(37–58)_median(IQR)	108	43	17		/	83_M30_F53	25_M13_F
Yang F, et al. (Wuhan)	Jan 6 to Feb 25, 2020	69.8 (14.5)_mean(SD)	92	49	/	/	/	/	/
Yang A-P, et al. (Zhejiang Province)	until Feb 20, 2020	46.4(17.6)_mean(SD)	93	56	/	/	69_M38_F31		24_M18_F
Xu Y-H, et al. (Beijing)	Jan-to Feb, 2020	43.9(16.8)_mean(SD)	50	29	/	/	9_M7_F2	28_M15_F13	10_M7_F3
Xu B, et al.(Wuhan)	Dec 26 to Mar 1, 2020	62(48.5–71)_median (IQR)	187	103	/	/	80	/	45
Xiong Y, et al. (Wuhan)	Jan 11 to Feb 5, 2020	49.5(14.1)_mean(SD)	42	25	/	/	/	/	/

Study	collection period	Age	Case load	Male (n)	ICU-Male	ICU-Female	mild	common	severe
Xie H, et al.(Wuhan)	Feb 2 to Feb 23, 2020	60.0(48.0–66)_median(IQR)	79	44	/	/	/	51_M26_F25	28_M18_F
Wang X, et al. (Wuhan)	Jan 10 to Feb 24, 2020	56 (32–48.5)_median(IQR)	80	31	/	/	/	/	/
Wang X, et al. (Wuhan)	Feb 7 to Feb 12, 2020	50(39–58)_median (IQR)	1012	524	/	/	1012_M524_F488		/
Wang R, et al. (Fuyang, Anhui Province)	Jan 20 to Feb 9, 2020	28.76(13.80)_mean(SD)	125	71	/	/	100_M55_F45		25_M16_F
Wang L, et al. (Wuhan)	Jan 1 to Feb 6, 2020	71(8)_mean(SD)	339	166	/	/	/	100	159
Wang J, et al. (Zhejiang, Anhui Province)	Jan to Feb, 2020	52.1(18.07)_mean(SD)	93	57	/	/	73_M43_F30		20_M14_F
Wang G, et al. (Zhejiang Province)	Jan 27 to Mar 3, 2020	47.82(15.19)_mean(SD)	889	438	/	/	/	/	/
Sun C, et al. (Nanyang, Henan Province)	Jan 24 to Feb 16, 2020	45(16)_mean(SD)	150	67	/	/	6	105	28
Simonnet A, et al. (France)	Feb 27 to April 5, 2020	60(51–70)_median(IQR)	124	90	90	34	/	/	/
Richardson S, et al. (New York City)	Mar 1 to April 4, 2020	63(52–75)_median(IQR)	5700	3437	248	125	/	/	/
Qian ZP, et al. (Shanghai)	Jan 20 to Feb 24, 2020	51(15–88)_median(range)	324	167	/	/	298_M147_F151		26_M20_F
Niu S, et al.(Beijing)	Jan 20 to Feb 29, 2020	/	60	34	/	/	/	/	/
Lyu P, et al. (Zhengzhou)	Jan 15 to Feb 24, 2020	54(17)_mean(SD)	51	29	23		12_M7_F5		15_M8_F7
Liu Y, et al.(Wuhan)	Jan 1 to Feb 29, 2020	53.95(16.90)_mean(SD)	245	114	/	/	/	/	/
Liu K-C, et al.(Anhui Province)	Jan 21 to Feb 3, 2020	41.6(14.5)_mean(SD)	73	41	/	/	6_M3F3	43_M28F15	21_M10F
Liu K, et al.(Hainan)	Jan 15 to Feb 18, 2020	/	56	31	/	/	/	/	/
Liang W-H, et al. (Mainland China)	/	48.9(16.3)_mean(SD)	1590	904	99		907		36
Li X, et al.(Wuhan)	Jan 26 to Feb 5, 2020	60(48–69)_median(IQR)	548	279	/	/	279_M126F153		269_M153
Li K, et al.(/)	Jan to Feb, 2020	45.5(12.3)_mean(SD)	83	44	/	/	58_M29F29		25_M15F
Lei Z, et al.(Wuhan, Guangzhou)	Jan 22 to Feb12, 2020; Jan 1 to Feb 20, 2020	/	119	77	/	/	/	/	/
He GH, et al. (Guanghzou, Wenzhou)	By Feb 29, 2020	/	811	411	/	/	/	/	/

Study	collection period	Age	Case load	Male (n)	ICU- Male	ICU- Female	mild	common	severe
Han C, et al. (Wuhan)	Feb 13 to Feb 29, 2020	62.5(27–92)_median(IQR)	206	91	/	/	206_M91_F115	/	/
Goyal P, et al.(New York City)	Mar 5 to Mar 27, 2020	62.2(48.6–73.7)_median(IQR)	393	238	/	/	/	/	130_M92I
Gou FX, et al. (Gansu Province)	By Feb 25, 2020	/	91	39	/	/	24	44	23
Fan Z, et al. (Shanghai)	Jan 20 to Jan 31, 2020	50 (36–64)_mean(IQR)	148	75	/	/	/	/	/
Du Y, et al.(Wuhan)	Jan 9 to Feb 15, 2020	65.8(14.2)_mean(SD)	85	62	/	/	/	/	/
Dong XC, et al. (Tianjin)	/	48.62(16.83)_mean(SD)	135	72	/	/	/	/	/
Dai H, et al. (Jiangsu Province)	Jan 10 to Feb 7, 2020	/	234	136	/	/	9	210	13
Chu J, et al. (Wuhan)	Jan 7 to Feb 11, 2020	39(26–73)_median(range)	54	36	/	/	/	11_M6F5	43_M30_F
Chen T, et al. (Wuhan)	Jan 1 to Feb 10, 2020	54(41–68)_median(IQR)	203	108	/	/	/	96	73
Cao J, et al. (Wuhan)	Jan 3 to Feb 1,2020	54(37–67)_median(IQR)	102	53	/	/	/	/	/
Cai Q, et al. (Shenzhen)	Jan 11 to Feb 6, 2020	47.5(33–61)_median(IQR)	298	145	/	/	/	240_M106_F134	58_M39_F
Arentz M, et al. (Washington State)	Feb 20 to Mar 5, 2020	70(43–92)_median(IQR)	21	11	/	/	/	/	/
China CDC (Mainland China)	By Feb 11, 2020	/	44672	22981	/	/	36160		6168
Fu S, et al.(Wuhan)	Feb 9,2020	64 (37–87)_Mean(range)	50	27	/	/	/	/	50_M27_F
Fei J, et al.(Wuhan)	Jan 1 to Jan 30,2020	22–87	192	97	/	/	/	85(44.3%)	107(55.7%)
Fu L, et al.(Wuhan, Anhui)	/	/	355	190	/	/	/	211	88
Mazumder A, et al. (India)	as of Mar 28,2020	36(25–54)_median(IQR)	413	274	/	/	/	/	/
Tan L, et al. (Wuhan)	Jan 14 to Mar 14,2020	/	132	59	/	/	/	96_M36_F60	21_M11_F
Xiao G, et al. (Wuhan)	To March 8, 2020	62(51–70)_median(IQR)	287	160	/	/	/	163	124
Wang Z, et al. (Sichuan)	Jan 16 to Mar 4,2020	/	538	285	/	/	450	/	88
Petrilli CM, et al. (New York City)	March 1 to Apr 2,2020	/	4103	2072	89		/	932_M560_F372	/
Chen X, et al. (Guangzhou)	Jan 20 to Mar 15, 2020	48(33–62)_median(IQR)	284	131	/	/	22	199	40
Jiang X, et al. (Wuxi)	Jan 23 to Feb 16,2020	45(27–60)_median(range)	55	27	/	/	/	/	47_M22_F

Study	collection period	Age	Case load	Male (n)	ICU- Male	ICU- Female	mild	common	severe
Guo A-X, et al.(24 Provinces)	Dec 28, 2019 to Mar 4,2020	/	159	99	/	/	/	/	/
Zheng Y, et al. (Hangzhou)	Jan 22 to Mar 5,2020	66 (58–76)_median(IQR)	34	23	23	11	/	/	/
Shao Z, et al. (Wuhan,Guangzhou and Shenzhen)	Dec,2019 to Mar,2020	58(46–69)_mean(IQR)	325	189	/	/	/	/	222
Lewnard JA, et al. (/)	By April 9,2020	60(47–72)_median(IQR)	1277	725	158		/	/	/
Zeng X, et al.(Xi'an, Beijing and Wuhan)	Feb 5 and Mar 20, 2020	/	234	133	/	/	137_M74_F63	/	97_M59_F
Cummings MJ, et al.(New York City)	Mar. 2 to April 1,2020	62 (51–72)_median(IQR)	257	170	/	/	/	/	/
Argenziano MG, et al.(New York City)	Mar. 1 to April 15,2020	63 (50–75)_median(IQR)	1000	596	156	75	/	/	/
Shi P, et al.(Shaanxi Province)	Jan 23 to Mar 7,2020	46 (34–58)_median(IQR)	134	65	/	/	/	88_M40_F48	46_M25_F
Kong X, et al. (Wuhan)	Feb 23 to Mar 13, 2020	49.98 (13.73)_mean(SD)	144	70	/	/	/	/	/
Huang H, et al.(/)	Jan 20 to Feb 29,2020	/	125	63	/	/	93_M47_F46	/	32_M16_F
Zhou F, et al. (Yichang,Hubei)	Jan 17 to Feb 26, 2020	55.94(18.83)_Mean(SD)	197	98	56		/	/	/
Xie J, et al.(Wuhan)	/	62.0(50.8–71.0)_median(IQR)	444	239	/	/	/	/	/
Zeng L, et al.(/)	Jan 11 to Feb 29,2020	49 (14.5)_mean(SD)	338	162	/	/	/	262_M115_F147	76_M47_F
Chen X, et al. (Wuhan)	Jan 5 to Mar 7, 2020	51(35–66)_median(IQR)	123	50	/	/	/	/	33
Li K, et al.(/)	Jan 31 to Mar 5, 2020	57(45–70)_median(range)	102	59	/	/	/	/	/
Yan D, et al. (Wuhan)	Jan 31 to Mar 9,2020	52(35–63)_	120	54	/	/	/	89	30
Wang Z, et al.(/)	Feb 23 to Mar 11, 2020	61.1(51.0–69.0)_median(IQR)	116	65	/	/	/	101_M53_F48	/
Liao X, et al. (Sichuan)	/	50 (39–65)_median(IQR)	81	51	51		/	/	81_M51_F
Zhang Y, et al. (Wuhan)	Jan 29 to Feb 12, 2020	64(56–70)_median(IQR)	258	138	/	/	/	87	116
Nie S, et al.(Wuhan)	Feb 9 to Feb 28, 2020	39(30–60)_median(IQR)	97	34	/	/	72_M21_F51	/	25_M13_F
Xu S, et al.(Wuhan, Fuyang)	Jan 1 to Jan 30,2020	/	355	193	/	/	/	224	60
Hu L, et al.(Wuhan)	Jan 8 to Mar 10,2020	61 (23–91)_median(range)	323	166	/	/	/	151_M75_F76	146_M77_

Study	collection period	Age	Case load	Male (n)	ICU- Male	ICU- Female	mild	common	severe
Wen Y, et al. (Shenzhen)	Jan 1 to Feb 28, 2020	45.4(17.7)_mean(SD)	417	197	/	/	381_M174_F207		36_M23_F
Yan S, et al. (Hainan)	Jan 22 to Mar 14,2020	51(36–62)_median(IQR)	168	81	/	/	/	132_M60_F72	36_M21_F
Yang Y, et al. (Wuhan)	Feb 12 to March 2,2020	69.4(10.8)_Mean(SD)	36	30	/	/	/	/	/
Choe YJ, et al. (Korea)	as of Mar 13th,2020	/	7755	2947	/	/	/	/	/
Zhao W, et al. (Beijing)	Jan 21 to Feb 8,2020	52(20)_mean(SD)	77	34	/	/	/	57_M23_F34	20_M11_F
Fu L, et al.(Wuhan)	Jan 1 to Jan 30,2020	/	200	99	/	/	/	88	58
Chen L, et al. (Wuhan)	Feb 1 to Mar 1, 2020	/	534	268	/	/	/	/	/
Liu Y, et al. (Guangzhou)	Jan 10 to Feb 24,2020	48.1(34–62)_median(IQR)	291	133	26		/	/	/
Liu J, et al.(Wuhan)	Jan 16 to Feb 15, 2020	35(29–43)_Median(IQR)	64	23	/	/	/	63	1
Chen J, et al.(/)	/	65.46(9.74)_Mean(SD)	101	64	64	37	/	/	/
Wu Y, et al.(Wuhan)	Dec 2019 to Feb2, 2020	/	297	147	/	/	/	/	/
Xu Y, et al.(Wuhan, Beijing,Shanghai)	Feb 7 to Feb 28,2020	57 (43–69)_median(IQR)	69	35	/	/	44_M22_F22	/	25_M13_F
Shi Q, et al.(Wuhan)	By Feb 15, 2020	71.0(59.0–80.0)_median (IQR)	101	60	/	/	/	/	/
Xu Y, et al. (Guangzhou)	Jan 14 to Feb 20, 2020	56.7 (15.4)_Mean(SD)	45	29	29	16	/	/	/
Zhang G, et al. (Wuhan)	Jan 2 to Feb 10, 2020	55.0(39.0-66.5)_Median(IQR)	221	108	22	10	/	166_M73_F93	55_M35_F
Cao M, et al. (Shanghai)	Jan 20 to Feb 15, 2020	50.1(16.3)_Mean(SD)	198	101	17	2	3	176	9
Chen X, et al. (Hunan Province)	Jan 23 to Feb 14, 2020	46.0(34.0–59.0)_median(IQR)	291	145	/	/	29_M16_F13	212_102F_110M	50_M27_F
Wang Y, et al. (Wuhan)	Jan 1 to Feb 10, 2020	/	110	48	48	62	72_M24_F48		38_M24_F
Qi D, et al. (Chongqing)	Jan 19 to Feb 16, 2020	48(20–80)_median(range)	267	149	/	/	217_M110_F107		50_M39_F
Huang Y, et al. (Wuhan)	Jan 21 to Feb 10,2020	69.22(9.64)_mean(SD)	36	25	/	/	/	/	/
Xu L, et al. (Wenzhou)	As of Feb 10,2020	47(37–56)_Median(IQR)	434	228	/	/	/	/	31
Zhang B, et al.(/)	Jan 11 to Feb 10, 2020	72.5(65.0–80.0)_median(IQR)	82	54	14		/	/	/

Study	collection period	Age	Case load	Male (n)	ICU- Male	ICU- Female	mild	common	severe
Li J, et al.(/)	From Feb 8 to Feb 11,2020	62.0(51.0–70.0)_median(IQR)	47	28	/	/	/	/	47_M28_F
Liang Y, et al. (Beijing)	Jan21 to Feb 15,2020	42.0 (34.5–66.0)_median(IQR)	21	11	/	/	18		3
Fan Z, et al. (Shanghai)	Jan 20 to Jan 31,2020	50.5 (36–64)_median(IQR)	148	73	/	/	/	/	/
Cao W(Xiangyang)	Jan to Feb 16,2020	/	128	60	/	/	107_M48_F59		21_M12_F
Jin J-M, et al. (Wuhan)	Jan 29 to Feb 15, 2020	62(51–70)_median(range)	43	22	/	/	13	/	14
Li X, et al.(Wuhan)	Jan 14 to Feb 13, 2020	71.48(12.42)_mean(SD)	25	10	/	/	/	/	/
Wang L, et al. (Wuhan)	Jan 14 to Feb 13,2020	54(38–69)_median(IQR)	116	67	6	5	59_M34_F25	/	46_M27_F
Ai J, et al. (Xiangyang)	Until Feb 10, 2020	50.38(16.86)_mean(SD)	102	52	8		/	/	/
Lei Liu, et al. (Chongqing)	Jan 20 to Feb 3, 2020	45(34–51)_median(IQR)	51	32	/	/	44_M28_F16		7_M4_F3
Liu Y, et al.(/)	Jan 2 to Feb 1, 2020	55(43–66)_median(IQR)	109	59	/	/	/	56_M31_F25	53_M28_F
Wu C, et al.(Wuhan)	Dec 25, 2019 to Jan 26, 2020	51 (43–60)_Median(IQR)	201	128	53 (26.4%)		44 (21.9%)	/	84 _M60 _
Shi H, et al.(Wuhan)	Dec 20, 2019 to Jan 23,2020	49.5(11.0)_ Mean(SD)	81	42	/	/	/	/	/
Pan Y, et al. (Wuhan)	Dec 30,2019 to Jan 31,2020	44.9(15.2)_Mean(SD)	63	33	/	/	/	/	/
Wang K, et al. (Xiaogan)	Jan 25,2020 to Feb 9,2020	53(32–78)_Median(Range)	114	58	/	/	/	/	/
Shi Y, et al. (Zhejiang Province)	To Feb 17,2020	/	487	259	/	/	438_M223_F215	/	49_M36_F
McMichael TM, et al.(Washington)	Feb 28 to Mar 18,2020	72(21–100)_Median(Range)	167	55	/	/	/	/	/
Jin X, et al. (Zhejiang Province)	Jan 17 to Feb 8, 2020	/	651	331	17(2.6%)		/	/	/
Chen N, et al. (Wuhan)	Jan 1 to Jan 20, 2020	55.5 (13.1)_Mean (SD)	99	67	/	/	/	/	/
Zhou F, et al. (Wuhan)	By Jan 31, 2020	56.0 (46.0–67.0)_Median(IQR)	191	119	/	/	/	/	/
Zhang J-J, et al. (Wuhan)	Jan 16 to Feb 3,2020	57 (25 – 7)_Median(range)	140	71	/	/	82(58.6%)		58 (41.4%
Zhang G, et al. (Wuhan)	Jan 16 to Feb 25,2020	49.0 (39.0–58.0)_Median(Range)	95	53	/	/	63_M32_F31		32_M21_F

Study	collection period	Age	Case load	Male (n)	ICU-Male	ICU-Female	mild	common	severe
Yang W, et al. (Wenzhou)	Jan 17 to Feb 10, 2020	45.11 (13.35)_Mean(SD)	149	81	0	0	/	/	/
Xu X-W, et al. (Zhejiang Province)	Jan 10 to Jan 26, 2020	41(32–52)_Median(IQR)	62	35	/	/	/	/	/
Wu J, et al.(Jiangsu Province)	Jan 22 to Feb 14,2020	46.1 (15.42)_Median(SD)	80	39	/	/	28 (35%)	49(61.25%)	3(3.75%)
Wang Z, et al. (Wuhan)	Jan 16 to Jan 29, 2020	42.0 (35.0–62.0)_Median(IQR)	69	32	/	/	/	/	/
Wang D, et al. (Wuhan)	Jan 1 to Jan 28, 2020	56 (42–68)_Median (IQR)	138	75	22 (61.1%)	14 (38.9%)	/	/	/
Wan S, et al. (Chongqing)	Jan 23 to Feb 8, 2020	47 (36–55)_Median(IQR)	135	72	/	/	95_M52_F43	/	40-M21_F
Tian S, et al. (Beijing)	By Feb 10, 2020	47.5 (1–94)_Median(range)	262	127	/	/	/	216 (82.4%)	46 (17.6%)
Qian G-Q, et al. (Zhejiang Province)	Jan 20 to Feb 11, 2020	50 (36.5–57)_Median(IQR)	91	37	/	/	/	/	/
Liu K, et al.(Hubei Province)	Dec 30, 2019 to Jan 24, 2020	57(20–83)_Median (range)	137	61	/	/	/	/	/
Liu K, et al.(Hainan Province)	Jan 15 to Feb 18	Elderly_68(65.25–69.75)_Young and middle-aged 47(35.75–51.25)	56	31	/	/	/	/	/
Lian J, et al. (Zhejiang Province)	Jan 17 to Feb 12,2020	/	788	407	24(3.05%)		710(90.1%)	/	61 (7.7%)
Li Q, et al.(Wuhan)	By Jan 22, 2020	59 (15–89)_Median (range)	425	240	/	/	/	/	/
Lescure FX, et al. (Paris)	Jan 24 to Jan 29,2020	46.0 (20.2)_Median(SD)	5	3	3 (0.6)	2 (0.4)	/	/	/
Huang Y, et al. (Wuhan)	Dec 21,2019 to Jan 28,2020	56.24 (17.14)_Median(SD)	34	14	8 (24.2%)		/	/	/
Huang C, et al. (Wuhan)	By Jan 2, 2020	49 (41–58)_Median (IQR)	41	30	11 (84.6%)	2 (15.4%)	/	/	/
Guan W-J, et al.(30 Pro. in China)	Dec 11,2019 to Jan 29, 2020	47.0 (35.0 ~ 58.0)_Median (IQR)	1099	640	/	/	/	/	/
Easom N,et al. (United Kingdom)	Jan 29 to Feb 24,2020	0–76	68	32	/	/	/	/	/
Deng Y, et al. (Wuhan)	Jan 1 to Feb 21,2020	/	225	124	/	/	/	/	104
Chen T, et al. (Wuhan)	until Feb 28,2020	62.0 (44.0–70.0)_Median(IQR)	274	171	/	/	/	/	/
Chen L, et al. (Wuhan)	Jan 14 to 29,2020	56 (26–79)_Median(Range)	29	21	/	/	/	15	9
Chen J, et al. (Shanghai)	Jan 20 to Feb 6, 2020	51(36–64)_Median(IQR)	249	126	22 (8.8%)		/	/	/

Study	collection period	Age	Case load	Male (n)	ICU-Male	ICU-Female	mild	common	severe
Chang, et al. (Beijing)	Jan 16 to Jan 29, 2020	34 (34–48)_Median(25th–75th percentile)	13	10	/	/	/	/	/
Chen G, et al. (Wuhan)	By Jan 27, 2020	56.0(50.0–65.0)_Median(IQR)	21	17	/	/	/	10_M7_F3	11_M10_F
Liu W, et al. (Wuhan)	Dec 30, 2019 to Jan 15, 2020	38 (33–57)_Median(IQR)	78	39	/	/	/	70 (89.7%)	8 (10.3%)
Feng Y, et al.(China)	Jan 1 to Feb 15, 2020	53 (40–64)_Median(IQR)	476	271	/	/	/	352_M190_F162	54_M33 _
Grasselli G, et al. (Italy)	Feb 20 to March 18, 2020	63(56–70)_Median(IQR)	1591	1304	1304	287	/	/	/

The main characteristics and demographic data of the included studies are listed in Table 1. As of April 27, 2020, 96237 patients were included in this meta-analysis, and 46516 (48.3%) were women. The results of the random effects model meta-analysis showed that in the sex distribution of COVID-19 females accounted for 0.47 [95% CI (0.45–0.48)] (Fig. 2S-A), which was lower than males 0.53 [95% CI (0.52–0.55)]. Funnel plot was used to test publication bias (Fig. 2S-B), indicating no notable evidence of publication bias. The sensitivity analysis based on the random effects model showed that there was not a particular article that greatly affected the result of this meta-analysis, suggesting a stable result (Table 2).

Table 2
Begg's and Egger's test results for all outcomes.

	Included studies	Begg's test <i>p</i> value	Egger's test <i>p</i> value
Proportion of female patients	156	0.2827	0.0346
Proportion of female patients admitted into ICU or with severe/critical illness	67	0.2743	0.3686
Fatality rate of female patients	25	0.4688	0.9036

Females admitted into ICU or with severe/critical illness were also analyzed, the ratio was 0.14 [95% CI (0.11–0.17)] among all the severe/critically ill patients, which was much lower than males 0.24 [95% CI (0.19–0.29)] (Fig. 2-A). The funnel plot (Fig. 2-B) also showed no significant publication bias. As to the fatality rate of the females, the meta-analysis of the female fatality rate was shown in Fig. 2-C and Fig. 2-D, indicating that the overall female fatality rate was 0.10 [95% CI (0.05–0.17)], with male fatality rate 0.18 [95% CI (0.11–0.29)]. In conclusion, female patients are less likely to be infected with COVID-19 than are males, the ratio of females admitted into ICU or with severe/critical illness, and the female fatality rate are lower than those of males.

The results of the Begg's and Egger's tests are displayed in Table 2. There were publication biases in the meta-analysis of female prevalence ($p = 0.0346$) by using Egger's test. Figures 3-A, B, C present the relative publication bias plots according to Begg's tests as examples. No remarkable alterations of the merged proportion and corresponding 95% CI value were observed when each individual study was removed one by one in the sensitivity analysis (Fig. 3-D, E, F), confirming the aforementioned stability of the results.

Discussion

From the above meta-analysis of sex difference in COVID-19, 156 reported studies were selected from hospitals in China, United States, United Kingdom, France, Italy, Korea, Singapore and India, respectively. From this analysis, we observed that more men than women were diagnosed with COVID-19. Also, male patients suffered of more severe symptoms than did female patients, and their mortality rate was twice greater than that of female patients. Moreover, recent findings from Li et al. [9] indicated that male COVID-19 patients are more likely to have complicated clinical conditions and worse prognosis as compared to females, such as secondary infection and heart function damage (preprint). SARS-CoV-2 belongs to the genus *Betacoronavirus* and shared 79.5% of the sequence with SARS-CoV and about 50% with MERS-CoV [10]. Tracing back to the history of SARS in 2003, males (21.9%) had a significantly higher fatality rate ($p < 0.0001$) than did females (13.2%) in the 299 deaths among 1755 SARS cases. The relative risk was 1.62 (95% CI: 1.21, 2.16) after adjustment for age [11]. Other studies indicated that there also exist sex differences in the outbreak of MERS (Middle East respiratory syndrome) in Saudi Arabia and South Korea. Al-Raddadi et al. [12] studied that in Saudi Arabia from 2012 to 2015, males were more susceptible than females (63.2% versus 36.8%) of all the confirmed patients ($n = 835$). The fatality rate of men is 1.4 times great than that of women (47.9% versus 34.9%), which, though, is not statistically significant. Among the 186 MERS cases in South Korea, 111 (59.7%) were males and 75 (40.3%) were females, and the fatality rate of men (23.4%) is also greater than that of women (16%) [13]. The sex differs in the intensity, prevalence, and pathogenesis of epidemic-prone infectious diseases caused by viruses, bacteria, parasites and fungi, with higher prevalence of infections for males than for females [14].

All of these disparities raise an interesting question: What causes the observed sex predisposition in the coronavirus infection? In the following discussion, we will discuss the possible causes of sex differences in the case of coronavirus infections.

Possible genetic factors

It was recently found that *ACE2* serves as the main entry of SARS-CoV-2 into host cells while the transmembrane protease, serine 2 (TMPRSS2) is for S protein priming of this virus [5]. Both genes might serve as the good candidates to explain sex-related effects, as *ACE2* is located on the X chromosome and *TMPRSS2* was found to participate in the non-canonical activation pathway of ER β 2 by estradiol [15]. Asselta et al (preprint) [16] reported that *TMPRSS2* variants and genetic expression levels might play a role in COVID-19 severity by investigating GTEx and GEO databases. One distinct haplotype has been functionally linked to eQTL (rs8134378), which could be regulated through androgens, possibly explaining the sex bias in COVID-19 severity. However, no significant evidence was found for *ACE2* to be associated with COVID-19 severity/sex bias among Italian patients. Lazzeri et al [17] indicated that a reduced androgen stimulation might indeed represent a protective factor for males from an observational study in male population in Lombardy (preprint). Host genetic background is considered to influence the severity of SARS and MERS [18]. Thus, based on currently limited studies, we could not come up with any reasonable genetic explanations for the sex difference in COVID-19 incidents, severity and fatality, and further experimental and clinical studies are needed to achieve this goal.

Sex-specific immune-defense factors

By detecting the difference of SARS-CoV-2 IgG antibody between male and female patients, the plasmas from 331 enrolled patients were analyzed by a study. Most severely ill female patients exhibited a high level of IgG antibody compared to severely ill male patients. In the early phase of COVID-19 progression, the production of IgG antibody in females tended to be stronger than that in male patients (preprint) [19]. However, the exact mechanism remains elusive. Males and females show differences in immunological responses, in which both genes and hormones are engaged. Generally, women have a stronger innate and adaptive (humoral and cellular) immune response than do men [20].

The sex-specific function of innate detection of nucleic acids is mainly accomplished through pattern recognition receptors (PRRs). By infecting Seoul virus in Norway rats, Hannah et al [21] found that expression of antiviral genes (*MYD88*, *IRF7*, *RIG1*, *JAK2*, *STAT3*, *IFN β* and *Mx2*) was higher in the lungs of females than that in males' lungs. Putative androgen response elements (AREs) and estrogen response elements (EREs) are involved in the promoters of several antiviral genes. As to the adaptive immune system, females generally exhibit higher levels of the adaptive immune response to antigenic stimulation, vaccination and infection than do males [22]. Compared to age-matched males, females had higher CD4/CD8 ratios and helper T cell type 1 (Th1) responses, while men had higher CD8⁺ T cell frequencies. Mouse studies also revealed that female mice have higher proportions of Th1, helper T cell type 2 (Th2) and regulatory T cell responses than do male mice. Cytotoxic T cell activity was in a higher level with an up-regulated expression pattern of antiviral and proinflammatory genes in females compared with males, many of which have estrogen-response elements in their promoters [23]. These studies suggest that females possess a much stronger immune system than do males, though more in-dept and systematic studies are needed to validate this statement pertinent to the infection of SARS-CoV-2.

Sex hormone regulation

The putative hormone receptors expressed in the cells of the immune system mainly include estrogen receptor alpha (ER α) and estrogen receptor beta (ER β), androgen receptor (AR) and progesterone receptor (PR) [24].

To date, it is widely documented that in murine models and humans, there are sex differences in the incidence and severity of respiratory viral infections [11] [12] [13] [25]. Sex hormone receptor activity is correlated with the sex differences in immune cell number and functional responses in the respiratory tract. For instance, Channappanavar et al [25] reported that male mice are more susceptible to SARS-CoV infection than are female mice of the same age group. Ovariectomy or adding estrogen receptor (ER) antagonist increased the mortality of female mice, suggesting that the ER signaling pathway may play a role in protecting females in coronavirus infection. ERs are expressed in various lymphoid tissue cells, in lymphocytes, macrophages, and dendritic cells (DCs). Through ovariectomized mice, the amount of inflammatory monocyte macrophages (IMMs) increased compared to intact female mice, suggesting that estrogen signaling in females inhibited the accumulation and function of IMMs in the lungs and might exert protection function in females [25].

Behavioral factors

The aforementioned sex predisposition might be associated with the higher smoking rate in men. In China 2015, smoking prevalence was 27.7% (52.1% among men and 2.7% among women) [26], showing a significant sex difference. From the latest report of the European Centre for Disease Control and Prevention (ECDC), smokers are more susceptible to serious complications from a coronavirus infection (data unpublished). Smokers have also appeared to be more susceptible to severe acute respiratory syndrome. A latest systematic review declared that smoking is most likely associated with the negative progression and adverse outcomes of COVID-19, yet further research is needed [27]. Notably, Guo et al (preprint) [28] reported that there was significantly higher expression of 2019-nCoV receptor, ACE2 in smoker lung samples compared to non-smoker lung samples by using RNA-seq and DNA microarray datasets. However, significant disparity wasn't found between sex groups (male vs female), which needs to be further validated.

In Saudi Arabia, because of the complex culturally-specific social phenomenon for women, sex-segregation is strictly enacted in the country. Saudi Arabian women's roles are largely defined within familial spaces, with the concept of modesty by wearing unique cultural customs (purdah and veil). As a result, this may unintentionally serve to reduce the risk of women contracting the air-borne transmission of respiratory diseases like MERS [29].

Strengths and Limitations

The main strength of this study is that we have provided thus far the largest series analysis of the association between biological sex and severity in COVID-19 patients. However, the main limitation is that more specific and high-quality literature on this topic is still urgently needed.

Conclusions

In conclusion, from our meta-analysis of a large cohort of clinical studies on COVID-19 patients from multiple countries, we can conclude that females are less severely affected by SARS-CoV-2, and sex difference may exist in severely/critically ill and deceased COVID-19 patients. The possible influence factors on this sex difference may include genetic, hormonal, immune and behavioral ones. However, as there lacks the sex-specific clinical data, partly due to the possibility of that sex has not regularly been considered a biological variable for analysis in clinic, additional large-scale clinical and basic studies are required to further investigate the impact of sex on the incidents of and treatments for COVID-19 and to better understand molecule mechanism underlying this sex difference. These lines of information will be vitally important for the health sectors in the world to develop better strategies or approaches for future prevention, diagnosis, and treatment of COVID-19 for both male and female patients.

Abbreviations

ACE2
Angiotensin-converting enzyme 2;
AHRQ
Agency for Healthcare Research and Quality;
AR
androgen receptor;
ARDS
acute respiratory distress syndrome;
AREs
androgen response elements;
DCs
dendritic cells;
ECDC
European Centre for Disease Control and Prevention;
ER
estrogen receptor;
EREs
estrogen response elements;
Era
estrogen receptor alpha;
Erβ
estrogen receptor beta;
ICU
Intensive care unit;
IMMs
inflammatory monocyte macrophages;
MERS
Middle East Respiratory Syndrome;
MODS
multiple organ dysfunction syndromes;
PR
progesterone receptor;
PRISMA
Preferred Reporting for Systematic Reviews of Meta-analyses;
PRRs
pattern recognition receptors;
WHO
World Health Organization

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

Not applicable

Competing interests

Disclosure: The authors declare that there is no competing of interests.

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Authors' contributions

SW and JZ conceived and coordinated the study; LM and HL designed and did the literature review and extracted the data with help from HL; LX analyzed the data. LM, HL, MW, LX, QZ and JZ interpreted the data. LM wrote the initial draft of the manuscript with input from LX; All authors revised the subsequent drafts.

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Figures

Figure 1

A flow diagram of the inclusion criteria of studies eligible for meta-analysis.

Figure 2

Forest plot and funnel plot of the proportion of female admitted into ICU or with severe/critical illness (Fig 2-A, Fig 2-B); Forest plot and funnel plot of the proportion of female death (Fig 2-C, Fig 2-D).

Forest plot and funnel plot of the proportion of female admitted into ICU or with severe/critical illness (Fig 2S-A, Fig 2S-B)

Figure 4

The publication bias plot of Begg's funnel plots and sensitivity analysis. A. Begg's funnel plots to test for the publication bias in the overall analysis of proportion of female patients; B. Begg's funnel plots to test for the publication bias in the female admitted into ICU or with severe/critical illness; C. Begg's funnel plots to test for the publication bias in the proportion of female death; D. Sensitivity analysis of the effect of individual studies in the proportion of female patients; E. Sensitivity analysis of the effect of individual studies in the proportion of female patients admitted into ICU or with severe/critical illness; F. Sensitivity analysis of the effect of individual studies in the fatality rate of female patients.

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