Increased Circulating Cytokines Have a Role in COVID-19 Severity and Death With a More Pronounced Effect in Males: A Systematic Review and Meta-Analysis

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Background: Coronavirus disease 2019 (COVID-2019), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has become a worldwide epidemic and claimed millions of lives. Accumulating evidence suggests that cytokines storms are closely associated to COVID-19 severity and death. Here, we aimed to explore the key factors related to COVID-19 severity and death, especially in terms of the male patients and those in western countries.

Methods: To clarify whether inflammatory cytokines have role in COVID-19 severity and death, we systematically searched PubMed, Embase, Cochrane library and Web of Science to identify related studies with the keywords “COVID-19” and “cytokines”. The data were measured as the mean with 95% confidence interval (CI) by Review Manager 5.3 software. The risk of bias was assessed for each study using appropriate checklists.

Results: We preliminarily screened 13,468 studies from the databases. A total of 77 articles with 13,468 patients were ultimately included in our study. The serum levels of cytokines such as interleukin-6 (IL-6), IL-10, interleukin-2 receptor (IL-2R), tumor necrosis factor (TNF)-α, IL-1β, IL-4, IL-8 and IL-17 were higher in the severity or death group. Notably, we also found that the circulating levels of IL-6, IL-10, IL-2R and TNF-α were significantly different between males and females. The serum levels of IL-6, IL-10, IL-2R and TNF-α were much higher in males than in females, which implies that the increased mortality and severity in males was partly due to the higher level of these cytokines. Moreover, we found that in the severe and non-survivor groups, European patients had elevated levels of IL-6 compared with Asian patients.

Conclusion: These large-scale data demonstrated that the circulating levels of IL-6, IL-10, IL-2R, IL-1β, IL-4, IL-8 and IL-17 are potential risk factors for severity and high mortality in COVID-19. Simultaneously, the upregulation of these cytokines may be driving factors for the sex and region predisposition.

Keywords: COVID-19, cytokines, sex bias, mortality, meta-analysis
INTRODUCTION

Coronavirus disease 2019 (COVID-2019), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has raised major public health concerns since 2019. Though many patients with COVID-19 present no symptoms or only mild symptoms (including fever, cough, and fatigue), some suffer severe symptoms and may progress to pneumonia, acute respiratory distress syndrome (ARDS), multi organ dysfunction and even death. The severity of COVID-19 is known to be closely correlated to cytokines storms, when the immune system is unable to counteract the virus, cytokine storms in patients may lead to macrophage hyperactivity and further systemic abnormal reactions (Lang et al., 2020; Liang et al., 2020; Makaronidis et al., 2020). However, the characteristics of the cytokine storms in COVID-19 patients have not been fully illustrated.

In death cases, patients with COVID-19 shows a higher risk of mortality in males sex (Griffith et al., 2020). According to the largest sex-disaggregated data from 47 countries, men with COVID-19 have higher morbidity than women with COVID-19 (63.8% men; 36.2% women). In addition, the overall mortality of COVID-19 is more than 2.3 times higher in men than in women (Control and Response, 2020). The discrepancy in COVID-19 outcomes between male and female patients may be attributed to several biological and social factors, especially cytokine storms (Griffith et al., 2020). Moreover, as the Covid-19-related literatures grows increasingly, the racial and ethnic disparities showed that the death and severity rate of Asians are lower than the other population (Tirupathi et al., 2020a; Mackey et al., 2021a).

To this end, we conducted a systematic review and meta-analysis to identify the key factors associated to COVID-19 severity and death, especially in terms of the sex and race bias detected in severe COVID-19 patients.

METHODS

Search Strategy

We screened databases (Web of Science, Embase, the Cochrane Library, and PubMed) from December 2019 to June 2021. We also registered on the INPLASY (International Platform of Registered Systematic Review and Meta analysis Protocols platform). The number for our study is INPLASY2021120050.

To search for more articles, we also screened related reference lists from relevant studies. The search terms included (“2019 novel coronavirus disease”) OR (“COVID19”) OR (“COVID-19 pandemic”) OR (“SARS-CoV-2 infection”) OR (“COVID-19 virus disease”) OR (“2019 novel coronavirus infection”) OR (“2019-nCoV infection”) OR (“coronavirus disease 2019”) OR (“coronavirus disease-19”) OR (“2019-nCoV disease”) OR (“COVID-19 virus infection”) OR (“cytokines”).

Inclusion and Exclusion Criteria

All the included studies met the following criteria: 1) the types of studies considered for inclusion were prospective or retrospective cohort studies comparing mild groups and severe groups; 2) the circulating levels of cytokines were analyzed before treatment. The exclusion criteria were reviews, studies of interventions other than cytokines, in vitro studies and in vivo animal experiments. To further reduce the accidental error of our study, each analysis of cytokines should contain more than two studies. Only English studies were screened in our study. After screening and collecting the literature, two authors removed duplicate publications by Endnote and independently evaluated each study based on their title and abstract. The symptom criteria are listed as follows.

For the mild group, patients had respiratory symptoms (fever, cough, fatigue, anorexia, headache), without evidence of viral pneumonia or hypoxia.

For the severe group, patients had one or more of the following conditions: respiratory distress, respiratory rate ≥30 times/minute, oxygen saturation (SpO2) ≤93% at rest, arterial partial pressure of oxygen (PaO2)/Fraction of inspiration O2 (FiO2) in arterial blood ≤300 mmHg, >50% lung imaging progress in the short term within 24–48 h, respiratory failure and mechanical ventilation required, shock, combined with other organ failure, and transfer to the intensive care unit (8).

Data Extraction and Quality Assessment

Two authors (Hu & Pan) collected data from the included studies, including the first author, study country, inclusion time, age, sex, sample sizes, mild group/severe group, survivors/non-survivors, study design, and outcomes. Another two authors assessed the quality of the studies using the Newcastle-Ottawa Scale (NOS) and scored points for each included study independently.

Statistical Analysis

Review Manager 5.3 was used to perform all statistical analyses. The mean and standard deviation (SD) were used as measurements across articles. We calculated the sample mean and SD by the sample size and interquartile range (IQR) (Wan et al., 2014; Luo et al., 2018). The circulating levels of cytokines between different groups were collected from the selected articles and analyzed using a random-effects model when $I^2$>50%. The standard Cochran’s Q test and $I^2$ statistics were also used to identify heterogeneity from the included articles. Significant heterogeneity was determined when $I^2$ value > 50% and $p$-value < 0.05.

RESULTS

Large Scale Data From Clinical Reports

A total of 13,468 studies were screened out by the database search. After removing 826 duplicates, we excluded 8452 articles by reading the titles and abstracts of the studies. Then, we read the remaining literature and excluded studies that were not matched to the inclusion and exclusion criteria. There were 77 articles with 13,986 patients ultimately included in this study (Han et al., 2020; Yang et al., 2020; Rutkowska et al., 2021) (Figure 1). The baseline features of all included studies are presented in Table 1.
Studies were published between December 2019 and June 2021. Among the 77 studies, 57 studies were performed in China, eight in Spain, three in Germany, three in Italy, two in Poland, and one each in Austria, the USA, France and Algeria. Seventy-three studies were published in normal journals, and four were published in preprint journals. 14 cytokines were reported in these 77 studies, including IL-1β, IL-2, IL-2R, IL-4, IL-5, IL-6, IL-8, IL10, IL-15, IL-17, TNF-α, IFN-γ, MCP-1, and CXCL-10. Review Manager 5.3 was used to calculate and compare the sample mean and SD by the sample size and interquartile range. After removing the cytokines that having no statistical difference in either severe or death group, the cytokines that only contain two articles were also removed. Totally eight cytokines were included in our meta-analysis, containing IL-1β, IL-2R, IL-4, IL-6, IL-8, IL-10, IL-17, and TNF-α. Furthermore, we also screened the cytokines associated with gender or regions of COVID-19 patients. IL-2R, IL-6, IL-10 and TNF-α, which were correlated with gender or regions of COVID-19 patients, were finally presented in this study. All the included studies detected the serum levels of IL-6, while 13 studies focused on IL-2R, 31 studies analyzed IL-10 and 29 studies were related to the serum levels of TNF-α. Five studies analyzed IL-1β, 12 studies analyzed IL-4, 11 studies analyzed IL-8 and IL-17 was studies by four studies. Moreover, five studies analyzed the correlation between genders and cytokines. Fifty-seven and twenty-four studies analyzed the serum levels of cytokines in severity and mortality groups. All 77 studies had NOS quality scores greater than 6, indicating that all these studies have high levels of quality, as shown in Table 2.

**Proinflammatory Cytokines as the Driving Factor for Severity and High Mortality in COVID-19 Patients**

To determine whether the circulating levels of inflammatory cytokines are risk factors for severity and mortality of COVID-19 patients, we classified the patients into mild and severe groups. There were 57 studies and 7,807 patients included in...
| Author            | Study region | Inclusion time                                                                 | Mean age (years) | gender | Sample sizes | Mild group/ Severe groups or survival/non-survival groups | Study design     | Outcomes                | Journal types |
|------------------|--------------|------------------------------------------------------------------------------|------------------|--------|--------------|------------------------------------------------------|------------------|-------------------------|----------------|
| Ai-Ping Yang et al. (2020) | China       | N/A                                                                          | 46.4             | 60% male | 93           | 69/24                                                | retrospective cohort | IL-6, IL-10, TNF-α, IL-β, IL-4, IL-8, IL-17 | Normal         |
| Bo Xu Xu et al. (2020a) | China       | 26 Dec 2019 to 1 Mar 2020                                                    | 62               | 55% male | 187          | 159/28                                               | retrospective observational study | IL-6, IL-10, TNF-α, IL-β | Normal         |
| Changcheng Zheng et al. (2020a) | China       | 15 Feb 2020                                                                  | 60               | 43.6 male | 55           | 34/21                                                | retrospective observational study | IL-6             | Normal         |
| Changsong Wang et al. (2020a) | China       | N/A                                                                          | 62.9             | 50% male | 45           | 33/12                                                | retrospective cohort | IL-6, IL-10, IL-4 | Normal         |
| Chaomin Wu et al. (2020a) | China       | 25 Dec 2019, to 26 Jan 2020                                                   | 51               | 43.7% male | 201          | 117/84                                               | retrospective cohort | IL-6             | Normal         |
| Chuan Qin et al. (2020a) | China       | Jan 10 to 12 Feb 2020                                                         | 58               | 52% male | 452          | 166/286                                              | retrospective cohort | IL-6, IL-2R, IL-10, TNF-α, IL-8 | Normal         |
| Egon Burian et al. (2020) | Germany     | Mar and April 2020                                                            | 61.54            | 35% male | 65           | 37/28                                                | retrospective cohort | IL-6             | Normal         |
| Fangfang Liu et al. (2020a) | China       | Jan 20 to 23 Feb 2020                                                         | 48               | 55.38% male | 65          | 42/23                                                | retrospective cohort | IL-6             | Normal         |
| Fei Zhou et al. (2020a) | China       | 29 Dec 2019 to 31 Jan 2020                                                    | 56               | 62% male | 191          | 137/54                                               | retrospective cohort | IL-6             | Normal         |
| Fengqin Zhang et al. (2020a) | China       | Feb to March 2020                                                             | N/A              | N/A      | 34           | 27/7                                                 | retrospective observational study | IL-6, IL-10, TNF-α, IL-8 | Normal         |
| Guang Chen et al. (2020a) | China       | Jan 2–7, 2020                                                                | 56               | 81% male | 21           | 10/11                                                | retrospective observational study | IL-6, IL-2R, IL-10, TNF-α, IL-8 | Normal         |
| Hailun Wang et al. (2020a) | China       | Jan 2 to 5 Feb 2020                                                           | 49               | 43.6% male | 83           | 33/50                                                | retrospective cohort | IL-6             | Normal         |
| Han Huang et al. (2020a) | China       | Jan 2020 and February 2020                                                    | N/A              | 50% male | 102          | 42/60                                                | retrospective cohort | IL-6, IL-10, TNF-α, IL-4 | Normal         |
| Hong Huang et al. (2020a) | China       | Feb and March 2020                                                            | 36               | 46% male | 31           | 27/4                                                 | retrospective cohort | IL-6, IL-10, TNF-α, IL-2R | Normal         |
| Hua Fan et al. (2020a) | China       | 30 Dec 2019 to 16 Feb 2020                                                    | 58.36            | 67% male | 73           | 47/26                                                | retrospective observational study | IL-6             | Normal         |
| Huizheng Zhang et al. (2020a) | China       | N/A                                                                          | N/A              | 51.2% male | 43           | 29/14                                                | retrospective observational study | IL-6, IL-10, TNF-α, IL-17 | Preprint      |
| Jia Ma et al. (2020a) | China       | 1 Jan 2020 to 30 Mar 2020                                                     | 62               | 54.5% male | 37           | 17/20                                                | retrospective observational study | IL-6             | Normal         |
| Lang Wang et al. (2020a) | China       | Jan 1 to 6 Feb 2020                                                           | 71               | 49% male | 339          | 274/65                                               | retrospective observational study | IL-6             | Normal         |
| Lai Liu et al. (2020a) | China       | N/A                                                                          | 45               | 62.7% male | 51           | 44/7                                                 | retrospective case series observational study | IL-6             | Preprint      |
| Lucas Quartuccio Quartuccio et al. (2020) | Italy   | N/A                                                                          | 66.5             | 79% male | 24           | 18/6                                                 | retrospective case series cohort | IL-6             | Normal         |
| Maria efgenberger et al. (2020a) | Austria   | 26th February to 21st April 2020                                              | 60.69            | 62.5% male | 96           | 81/15                                                | retrospective case series cohort | IL-6             | Normal         |
| Maria J. Pérez-Sáez et al. (2020a) | Spain    | 18th March 2020                                                               | 59.3             | 67.5% male | 80           | 54/26                                                | retrospective case series cohort | IL-6             | Normal         |
| Mario Fernández-Ruiz et al. (2020a) | Spain    | 16th March to 27th March 2020                                                  | 46.8             | 65.9% male | 88           | 39/49                                                | retrospective cohort | IL-6             | Normal         |
| Marta Crespo et al. (2020a) | Spain       | Mar to April 2020                                                             | 71               | 75% male | 16           | 8/8                                                  | Prospective cohort study | IL-6             | Normal         |
| Miao Luo et al. (2020a) | China       | Jan and March 2020                                                            | 61               | 51.2% male | 1018         | 817/201                                              | retrospective case series | IL-2R, IL-6, IL-10, TNF-α, IL-8 | Normal         |
| Michael Dreher et al. (2020a) | Germany  | Feb and March 2020                                                             | 65               | 66% male | 50           | 26/24                                                | retrospective case series | IL-6             | Normal         |

(Continued on following page)
| Author                  | Study region | Inclusion time                          | Mean age (years) | gender | Sample sizes | Mild group/Severe groups or survival/non-survival groups | Study design | Outcomes                  | Journal types |
|-------------------------|--------------|-----------------------------------------|------------------|--------|--------------|----------------------------------------------------------|--------------|---------------------------|----------------|
| Ming Ni Ni et al. (2020) | China        | 1 to 21 February 2020                   | 60               | 50%    | male 27      | male 14/female 13                                      | retrospective case series | IL-6, IL-10, TNF-α | Normal         |
| Paola Tonioni Tonioni et al. (2020) | Italy       | Mar 9th and 20 Mar 2020                 | 62               | 88%    | male 100     | male 77/23                                              | retrospective case series | IL-6          | Normal         |
| Pingzheng Mo Mo et al. (2020) | China        | Jan 1st to 5 Feb 2020                   | 54               | 55.5   | male 155     | male 70/85                                              | retrospective case series | IL-6          | Normal         |
| Qin Lu Qin et al. (2020b)  | China        | 26 January 2020 and 5 February 2020     | 55.2             | 57.9   | male 233     | male 135/98                                             | retrospective cohort       | IL-6, IL-2R, IL-10, TNF-α | Normal         |
| Qiu Rong Ruan Ruan et al. (2020) | China       | N/A                                     | N/A              | N/A    | N/A 150      | N/A 82/68                                               | retrospective observational study | IL-6          | Normal         |
| Ruirui Wang Wang et al. (2020c) | China        | Jan 20 to 9 Feb 2020                    | 38.7             | 57%    | male 125     | male 100/25                                             | IL-6                     | Normal         |
| Shaohua Li Li et al. (2020a)   | China        | 20 Jan 2020, to 20 Mar 2020             | 48.5             | 58%    | male 69      | male 43/26                                              | IL-6, TNF-α, IL-1β        | IL-8           | Normal         |
| Susu He He et al. (2020)    | China        | Jan 17 to 12 Feb 2020                   | 44.5             | 53%    | male 93      | male 60/33                                              | IL-6, IL-10               | Normal         |
| Susin Wan Wan et al. (2020)  | China        | 26 January to 4 February 2020           | 43.1             | 53.6%  | male 123     | male 102/21                                             | IL-6, IL-10, TNF-α, IL-4, IL-17 | Normal         |
| Takahisa Mikami Mikami et al. (2020) | United States | Mar and April 2020                      | 59               | 54.5%  | male 2820    | male 2014/806                                           | retrospective observational study | IL-6, TNF-α, IL-8 | Normal         |
| Tao Chen Chen et al. (2020c) | China        | 13 January to 12 February 2020          | 62               | 62%    | male 274     | male 161/113                                            | retrospective case series | IL-6          | IL-2R, IL-10 | Normal         |
| TAO Liu Liu et al. (2020c)   | China        | December 2019 to July 2020              | 53.9             | 42.2%  | male 77      | male 11/66                                              | IL-6, IL-10               | Normal         |
| Tielong Chen Chen et al. (2020c) | China       | 1 Jan 2020, to 10 Feb 2020              | 54               | 53.2%  | male 55      | male 36/19                                              | IL-6                     | Normal         |
| Tobias Herold Herold et al. (2020c) | Germany    | Feb 29 to 27 Mar 2020                   | 61               | 70%    | male 89      | male 57/32                                              | IL-6                     | Normal         |
| Wenjun Tu Tu et al. (2020)   | China        | 3 Jan to 24 February 2020               | 70               | 76%    | male 174     | male 149/25                                             | IL-6                     | Normal         |
| Xiaohong Yuan Yuan et al. (2020) | China       | Feb 15 to 30 Mar 2020                   | 67               | 47.9%  | male 117     | male 61/56                                              | IL-6, IL-10, IL-4          | Normal         |
| Xia Xu Xu et al. (2020b)     | China        | 3 Feb 2020, to 20 Mar 2020              | 57               | 40.91% | male 88      | male 47/41                                              | IL-6, IL-2R, TNF-α        | IL-8           | Normal         |
| Xiong Bei Xiong et al. (2023) | China        | 21 Mar 2020                             | 66               | 61.4%  | male 57      | male 19/38                                              | IL-6                     | Normal         |
| Yang Lu Liu et al. (2020c)   | China        | 22 Jan 2020, to 15 Feb 2020             | 45               | 64.4%  | male 76      | male 46/30                                              | IL-6, IL-2R, IL-10, IL-1β, IL-8 | Normal         |
| Yang Xu Xu et al. (2020c)    | China        | N/A                                     | 57               | 50.7%  | male 69      | male 44/25                                              | IL-6                     | Preprint       |
| Yang Xu Xu et al. (2020b)    | China        | N/A                                     | N/A              | N/A    | N/A 10       | N/A 8/2                                                 | IL-6                     | Preprint       |
| Yang Zhao Zhao et al. (2020)  | China        | Jan 13 and 4 Mar 2020                   | 58               | 47.3%  | male 539     | male 414/125                                            | retrospective observational study | IL-6          | Normal         |
| Yaying Xie Xie et al. (2020)  | China        | Feb and March 2020                      | 66               | 43.5%  | male 62      | male 38/24                                              | retrospective case series | IL-6          | Normal         |
| Yanli Wang Wang et al. (2020c) | China        | 25 Jan 2020 and 8 Mar 2020              | 52               | 65%    | male 43      | male 35/6                                               | retrospective observational study | IL-6          | IL-10, IL-4 | Normal         |
| Yaqing Zhou Zhou et al. (2020c) | China       | 28 Jan 2020 to 2 Mar 2020               | 66               | 65.9%  | male 21      | male 8/13                                               | IL-6                     | Normal         |
| Yi Li Li et al. (2020b)      | China        | 28 January 2020, to 12 March 2020       | 6                | 56.8%  | male 125     | male 48/77                                              | retrospective case series | IL-6, IL-10, TNF-α, IL-4 | Normal         |
| Ying Chi Chi et al. (2020)    | China        | N/A                                     | 45.21            | 58%    | male 66      | male 58/8                                               | retrospective case series | IL-6, IL-2R, IL-10, TNF-α, IL-1β, IL-4, IL-8, IL-17 | Normal         |
this meta-analysis. Compared to patients in the mild group, circulating levels of IL-6 was found to be significantly increased in patients in the severe group (19.76 [16.59, 22.93], \( p < 0.00001 \), Supplementary Figure S1). The serum level of IL-6 in the non-surviving group was also significantly elevated compared with that in the surviving group (52.33 [44.16, 60.50], \( p < 0.00001 \), Supplementary Figure S2). In addition to IL-6, the serum levels of IL-2R, IL-10, IL-1β, IL-4, IL-8, IL-17 and TNF-α were also elevated in both severe and non-surviving COVID-19 patients (Supplementary Figures S3–S6). Suggesting that the upregulation of these cytokines were correlated with the prognosis of COVID-19 patients.

### Table 1 (Continued) Basic characteristics of 77 studies included in Meta-analysis.

| Author | Study region | Inclusion time | Mean age (years) | gender | Sample sizes | Mild group/Severe groups or survival/non-survival groups | Study design | Outcomes | Journal types |
|--------|--------------|----------------|------------------|--------|--------------|--------------------------------------------------------|-------------|----------|---------------|
| Yingjie Wu Wu et al. (2020c) | China | 29 December 2019 to 20 February 2020 | 61 | 63.3% male | 71 | IL-6, IL-10, TNF-α, IL-4 | retrospective case series | Normal |
| Ying Sun Sun et al. (2020) | China | N/A | 47 | 58.7% male | 63 | IL-6 | retrospective case series | IL-6 | Normal |
| Yi Zheng Zheng et al. (2020) | China | Jan, 22 and Mar. 5, 2020 | 66 | 67.6% male | 34 | IL-6 | retrospective case series | IL-6, IL-10 | Normal |
| Yong Gao Gao et al. (2020d) | China | 23 Jan 2020 to 2 Feb 2020 | 44 | 60.6% male | 43 | IL-6 | retrospective case series | IL-6 | Normal |
| Zhe Zhu Zhu et al. (2020) | China | Jan 23 to Feb 20, 2020 | 50.9 | 36.43% male | 127 | IL-6, IL-10, TNF-α, IL-4 | retrospective cohort | IL-6, IL-10, TNF-α, IL-4 | Normal |
| Zhuhua Lv Lv et al. (2020) | China | 4 Feb 2020 to Feb 28, 2020 | 62 | 49.4% male | 354 | IL-6, IL-10, TNF-α, IL-4 | retrospective cohort | IL-6, IL-10, TNF-α, IL-4 | Normal |
| Zhilin Zeng Zeng et al. (2020) | China | 28 Jan 2020, to 12 Feb 2020 | 62 | 51.1% male | 317 | IL-6, IL-10, TNF-α, IL-4 | retrospective cohort | IL-6, IL-10, TNF-α, IL-4 | Normal |
| Zhongxiang Wang Wang et al. (2020a) | China | Dec 2019 to February 2020 | 42 | 46% male | 59 | IL-6, IL-10, TNF-α, IL-4 | retrospective cohort | IL-6, IL-10, TNF-α, IL-4 | Normal |
| Sophie Hue Hue et al. (2020) | France | Mar 2020 | 60 | 91% male | 38 | IL-6, IL-10 | retrospective cohort | IL-6, IL-10 | Normal |
| Elżbieta Kalicka Kalicka et al. (2021) | Poland | Dec 2020 | 62 | 52% male | 82 | IL-6, TNF-α | Prospective cohort | IL-6, TNF-α | Normal |
| Diarmgrad Li Li et al. (2020c) | China | Mar 2020 | 56 | 62.5% male | 65 | IL-6 | retrospective cohort | IL-6 | Normal |
| Francisco Javier Gil-Etayo Gil-Etayo et al. (2021) | Spain | Sep 2020 | 55 | 67% male | 34 | IL-4 | Prospective cohort | IL-6, IL-10 | Normal |
| Feng Gao Gao et al. (2021) | China | Feb 2020 | 49 | 42.5% male | 121 | IL-6, IL-10 | retrospective cohort | IL-6, IL-10 | Normal |
| Wei Zhu Zhu et al. (2021) | China | Mar 2020 | 65 | 45% male | 1106 | IL-6 | retrospective cohort | IL-6, IL-10, TNF-α, IL-4 | Normal |
| Zhirui Meng (Meng et al. 2020) | China | Apr 2020 | 48 | 63% male | 98 | IL-6, IL-10, TNF-α, IL-4 | retrospective cohort | IL-6, IL-10, TNF-α, IL-4 | Normal |
| Chenzhe Li Li et al. (2020c) | China | Apr 2020 | 63 | 49.6% male | 989 | IL-6, IL-10, TNF-α, IL-4 | retrospective cohort | IL-6, IL-10, TNF-α, IL-4 | Normal |
| Vahid Balaei Balaei et al. (2021) | Iran | Apr 2020 | 59 | 70.18% male | 57 | IL-6, IL-10, TNF-α, IL-4 | retrospective cohort | IL-6, IL-10, TNF-α, IL-4 | Normal |
| Ricó Laguna-Goya Laguna-Goya et al. (2003) | Spain | Apr 2020 | 52 | 63.3% male | 501 | IL-6 | retrospective cohort | IL-6 | Normal |
| José J. Guirao Guirao et al. (2020) | Spain | Apr 2020 | 65 | 52% male | 50 | IL-6 | retrospective cohort | IL-6 | Normal |
| Jose Maria Galvan-Roman Galván-Román et al. (2021) | Spain | Mar 2020 | 63 | 66% male | 146 | IL-6 | retrospective cohort | IL-6 | Normal |
| Li-Da Chen Chen et al. (2020c) | China | Mar 2020 | 52 | 50% male | 94 | IL-6, IL-10, TNF-α, IL-4 | retrospective cohort | IL-6, IL-10, TNF-α, IL-4 | Normal |
| Lucia Guillén Guillén et al. (2020) | Spain | Apr 2020 | 62 | 73% male | 64 | IL-6, IL-10, TNF-α, IL-4 | retrospective cohort | IL-6, IL-10, TNF-α, IL-4 | Normal |
| Enrico Maria Treccarichi Treccarichi et al. (2020) | Italy | May 2020 | 80 | 57.1% male | 48 | IL-6 | retrospective cohort | IL-6 | Normal |
| Elżbieta Rutkowska Rutkowska et al. (2021) | Poland | Jan 2021 | 56 | 56% male | 38 | IL-6 | retrospective cohort | IL-6 | Normal |
| First author | Study design | Selection | Comparability | Assessment of outcome | Total quality scores |
|--------------|--------------|-----------|---------------|-----------------------|----------------------|
| Ai-Ping Yang | Cohort       | ***       | **            | **                    | 7                    |
| Bo Xu        | Cohort       | ***       | **            | **                    | 8                    |
| Changcheng Zheng | Cohort | **       | **            | **                    | 7                    |
| Changsong Wang | Cohort   | ***       | **            | **                    | 8                    |
| Chaoxun Wu  | Cohort       | ***       | **            | **                    | 7                    |
| Chuan Qin   | Cohort       | ****      | **            | **                    | 9                    |
| Egon Burian | Cohort       | ***       | **            | **                    | 7                    |
| Fangfang Liu | Cohort      | ***       | **            | **                    | 7                    |
| Fei Zhou    | Cohort       | **        | **            | **                    | 7                    |
| Fengqin Zhang | Cohort    | ***       | **            | **                    | 8                    |
| Guan Chen   | Cohort       | ***       | **            | **                    | 7                    |
| Haijun Wang | Cohort       | ***       | **            | **                    | 7                    |
| Han Huang   | Cohort       | ***       | **            | **                    | 8                    |
| Hong Huang  | Cohort       | ****      | **            | **                    | 9                    |
| Hua Fang    | Cohort       | ***       | **            | **                    | 7                    |
| Huizheng Zhang | Cohort   | ***       | **            | **                    | 8                    |
| Jia Ma      | Cohort       | ***       | **            | **                    | 7                    |
| Lang Wang   | Cohort       | ****      | **            | **                    | 9                    |
| Lei Liu     | Cohort       | ****      | **            | **                    | 9                    |
| Lucas Quartuccio | Cohort | ***       | **            | **                    | 7                    |
| Maria effenberger | Cohort | ***       | **            | **                    | 8                    |
| Maria J. Pérez-Sáez | Cohort | **       | **            | **                    | 7                    |
| Marco Fernández-Ruiz | Cohort | ****      | **            | **                    | 9                    |
| Marta Crespo | Cohort   | ****      | **            | **                    | 7                    |
| Miao Luo    | Cohort       | ***       | **            | **                    | 8                    |
| Michael Dreher | Cohort   | ***       | **            | **                    | 8                    |
| Ming Ni     | Cohort       | ***       | **            | **                    | 8                    |
| Paola Tonyati | Cohort    | ***       | **            | **                    | 7                    |
| Pingzheng Mo | Cohort      | ****      | **            | **                    | 7                    |
| Qin Lu      | Cohort       | ****      | **            | **                    | 9                    |
| Qiurong Ruan | Cohort      | ****      | **            | **                    | 7                    |
| Ruirui Wang | Cohort       | **        | **            | **                    | 7                    |
| Shaohua Li  | Cohort       | **        | **            | **                    | 7                    |
| Sophie Hue  | Cohort       | ***       | **            | **                    | 8                    |
| Susu He     | Cohort       | ****      | **            | **                    | 7                    |
| Suxin Wan   | Cohort       | ***       | **            | **                    | 8                    |
| Takahisa Mikami | Cohort  | ****      | **            | **                    | 8                    |
| Tao Chen    | Cohort       | ***       | **            | **                    | 8                    |
| TAO Liu     | Cohort       | ***       | **            | **                    | 8                    |
| Tielong Chen | Cohort      | ****      | **            | **                    | 7                    |
| Tobias Herold | Cohort    | ****      | **            | **                    | 9                    |
| Wenjun Tu   | Cohort       | ***       | **            | **                    | 8                    |
| Xia Xu      | Cohort       | ****      | **            | **                    | 8                    |
| Xiaohong Yuan | Cohort | ***       | **            | **                    | 8                    |
| Xiong Bei   | Cohort       | ***       | **            | **                    | 8                    |
| Yang Liu    | Cohort       | **        | **            | **                    | 7                    |
| Yang Xu     | Cohort       | **        | **            | **                    | 7                    |
| Yang Xu 2   | Cohort       | ****      | **            | **                    | 9                    |
| Yang Zhao   | Cohort       | ***       | **            | **                    | 8                    |
| Yangjing Xie | Cohort     | ***       | **            | **                    | 8                    |
| Yanli Wang  | Cohort       | ***       | **            | **                    | 8                    |
| Yaqing Zhou | Cohort       | ***       | **            | **                    | 8                    |
| Yi Li       | Cohort       | ***       | **            | **                    | 8                    |
| Yi Zheng    | Cohort       | ***       | **            | **                    | 7                    |
| Ying Chi    | Cohort       | ***       | **            | **                    | 8                    |
| Ying Sun    | Cohort       | ***       | **            | **                    | 8                    |
| Yirting Wu  | Cohort       | ****      | **            | **                    | 9                    |
| Yong Gao    | Cohort       | ***       | **            | **                    | 8                    |
| Zhe Zhu     | Cohort       | **        | **            | **                    | 6                    |
| Zhilua Lv   | Cohort       | ****      | **            | **                    | 9                    |
| Zhilin Zeng | Cohort       | ***       | **            | **                    | 8                    |
| Zhongliang Wang | Cohort | ***       | **            | **                    | 8                    |
| Elzbieta Kalkowska | Cohort | ***       | **            | **                    | 9                    |
| Dianming Li | Cohort       | ***       | **            | **                    | 8                    |

(Continued on following page)
Table 2 (Continued) Methodological quality of the 77 studies based on the NOS for studies.

| First author              | Study design | Selection | Comparability | Assessment of outcome | Total quality scores |
|---------------------------|--------------|-----------|---------------|-----------------------|----------------------|
| Francisco Javier Gil-Etayo| Cohort       | ***       | **            | ***                   | 8                    |
| Feng Gao                  | Cohort       | ***       | **            | ***                   | 8                    |
| Wei Zhu                   | Cohort       | **        | **            | ***                   | 7                    |
| Ziru Meng                 | Cohort       | ***       | **            | ***                   | 8                    |
| Chenze Li                 | Cohort       | ****      | **            | ***                   | 9                    |
| Brahim Belaid             | Cohort       | ****      | **            | **                    | 8                    |
| Rocio Laguna-Goya         | Cohort       | ****      | **            | ***                   | 9                    |
| Jose J. Gurao             | Cohort       | ***       | **            | ***                   | 8                    |
| Jose Mana Galvan-Roman    | Cohort       | ****      | **            | ***                   | 9                    |
| Li-Da Chen                | Cohort       | ****      | **            | *                     | 7                    |
| Lucía Guillén             | Cohort       | ***       | **            | ***                   | 8                    |
| Enrico Maria TrecaRichi   | Cohort       | ***       | **            | ***                   | 8                    |
| Elzbieta Rubiowska        | Cohort       | ***       | **            | ***                   | 8                    |

Altering of the Distinctive Cytokines Are Related to Sex Bias in COVID-19 Patients

In this meta-analysis, four cytokines were found to be correlated with severity of male COVID-19 patients. Five studies reporting circulating interleukin-6 (IL-6) levels in male ($n = 488$) and female ($n = 509$) COVID-19 patients were included. In addition, interleukin-2 receptor (IL-2R), interleukin-10 (IL-10) and tumor necrosis factor α (TNF-α) were also different between male and female patients. Compared to female patients, the expression levels of circulating IL-6 (11.76 [7.56, 15.96], $p = 0.000001$), IL-2R (85.75 [3.91, 167.59], $p = 0.04$), IL-10 (1.54 [0.99, 2.08], $p = 0.000001$) and TNF-α (1.39 [0.81, 1.97], $p = 0.000001$) were found to be significantly elevated in male patients (Figure 2).

Additionally, we conducted a sensitivity analysis to confirm the robustness of the model, and a significant sex gap was detected in circulating levels of IL-6, IL-2R, IL-10 and TNF-α.

The Levels of IL-6 Related to Severity and High Mortality in COVID-19 Patients From Different Continents

We further analyzed the correlation between cytokines and continents. We classified the articles into Asia, Europe, Africa and North America groups, and there were 840 European patients, 6,910 Asian patients and 57 African patients in the selected studies. To better interpret the differences between countries, we compared the ages, sex distributions and the severe rate of the included patients in the two territories. Results showed that ages and the proportions of severe or dead patients were comparable, while the male patients in the severe COVID-19 patients in Europe was significantly higher than that in Asia (Supplementary Tables 1, 2). The results of our meta-analysis showed that Asian, European, and African patients with severe COVID-19 had elevated circulating IL-6 levels and the circulating IL-6 levels of European and African was higher than the Asian patients (Figure 3).

Notably, we found that there were 997 Asian, 223 European, 19 African and 1007 North American in the analysis of mortality. Among them, all the death patients with COVID-19 had higher IL-6 levels than the survive patients. Moreover, Asian death patients still have the lowest circulating IL-6 levels than the other continents’ patients (Figure 4). Unlike IL-6, the serum level of IL-10 had the potential to predict the risk of mortality in Asian patients, but it showed no correlation with mortality in European patients (Supplementary Figure S7).

DISCUSSION

The SARS-CoV-2 S protein engages with the host ACE2 receptor and is subsequently cleaved at S1/S2 and S2’ sites by TMPRSS2 protease, which leads to activation of the S2 domain and drives fusion of the viral and host membranes. The secretion of interferon is the first step to start the antiviral program. Alveolar cells are an important part of the epithelial endothelial barrier. After respiratory epithelial cells were first infected by virus, virus infection activates pattern recognition receptors in these cells, triggering the production and release of type I and type III interferons (IFNs) and other proinflammatory mediators (such as cytokines, chemokines and antimicrobial peptides), so as to start the host’s innate and acquired immune response, which further activated the secondary cytokines (such as IL-10, IFN-y, MCP-1, IL-4, and IL-17) and lead to cytokines storm (Vabret et al., 2020). In the mild patients, immune cells have the ability of eliminating viruses completely and inhibit the them from invading alveoli, which lead to low cytokines in serum (Figure 5). In this study, we identified that the serum levels of IL-6, IL-2R, IL-10, TNF-α, IL-1β, IL-4, IL-8 and IL-17 were significantly elevated in the severe or death cases and probably play crucial roles in the progression of COVID-19. Male sex was identified as a hazard for more severe disease and
higher mortality in COVID-19 (Takahashi et al., 2020; Zeng et al., 2020). The recognition of how sex influences COVID-19 outcomes have important significance for clinical management and remission tactics. In this large-scale worldwide meta-analysis, the related cytokines affecting the development of severe disease in male patients were identified and the serum of IL-6, as well as IL-10, IL-2R and TNF-α, in males was obviously higher than that in females.

IL-6, the core factor of “cytokine storm”, plays a pivotal role in the severity and high mortality of COVID-19. It enhances the production of TNF-α and IL-8 by stimulating the differentiation of T follicular helper cells, inhibits antiviral helper T cell 1 (Th1) cell commitment and improves the differentiation of helper T cell 2 (Th2) cells by regulating the circulating of IL-4 and interferon γ (IFN-γ) (Ahmadpoor and Rostaing, 2020; Wu and Yang, 2020). Moreover, elevated levels of IL-6 lead to acute lung injury.
and suppress the functions of T lymphocytes, macrophages and dendritic cells, which impair the immune system (Zhang et al., 2004). Tocilizumab, an IL-6 antagonist, revealed good capacity in inhibiting inflammation and cytokine storms in COVID-19 and various clinical studies have verified the beneficial effect of IL-6 and its receptor antagonists in COVID-19.

FIGURE 3 | The serum levels of IL-6 in the different continent of mild and severe.

| Study or Subgroup | Severe | Mild | Mean Difference (IV, Random: 95% CI) |
|-------------------|--------|------|-----------------------------------|
| Europe            |        |      |                                  |
| Egen Burian       | 103.9  | 43.6 | 25.1                             |
| Elzbieta Kalki    | 92.0524| 44.0685| 30.072 18.43695 51.1% | 61.98 [45.66, 78.30] |
| Elzbieta Rutkowska| 14.179 | 9.662 | 5.571 3.24722 23.2% | 6.40 [4.22, 14.57] |
| Jose A Garcia     | 24.168 | 16.52 | 8.202 5.87 42.0% | 3.95 [1.52, 6.36] |
| Jose Mar Av Galvan-Ran  | 51.3926 | 19.66 6.4932 20.01 22.9% | 34.37 [28.39, 40.34] |
| Lucia Guillen     | 118.5949| 56.4794| 62.124 | 37.24 [28.42, 46.84] |
| Maria Esteban     | 94.0786| 125.6285| 31.4276 | 47.5518 81.02% | 62.66 [1.75, 127.07] |
| Maria Fernandez-Ruiz| 430.44 | 46.08 | 24.06 39.81 1.0% | 119.30 [43.46, 242.06] |
| Michael Dohren    | 171.6444| 229.3247| 49.01 47.06 22.1% | 147.34 [93.83, 240.86] |
| Paola Tomati      | 81.0305| 104.3028 | 23.301 65.7491 76.97% | 39.91 [5.13, 64.96] |
| Tobias Herold    | 185.6342| 122.3274 | 65.0697 | 155.6677 57.1% | 104.97 [14.20, 224.14] |

Total (95% CI) 268 572 9.6% 49.33 [30.69, 67.98]

Heterogeneity: Tau² = 494.10; Ch² = 89.13; df = 10 (P < 0.00001); I² = 89%

Test for overall effect: Z = 5.19 (P < 0.00001)

1.2 Asia

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treating severe and critical COVID-19 patients (Xu et al., 2020d; Potere et al., 2021). Besides IL-6, TNF-α inhibitor can also reduce lung exudation and inflammatory reactions, it has been used in the treatment of patients with covid-19 patients (Tirupathi et al., 2020b; Mackey et al., 2021b). However, blocking IL-6 and TNF-α inhibitor may not be used to all patients due to its potential adverse events and expensive price (Wang et al., 2020f; Keewan et al., 2021). The identification of which COVID-19 patients are suitable for treatment with IL-6 antagonists and TNF-α inhibitor are meaningful in the clinic. In our study, the cytokines IL-6, IL-10, and TNF-α were significantly upregulated in severe COVID-19 patients, especially in male patients, indicating that IL-6 antagonists and TNF-α inhibitors are more appropriate used in male patients to reduce both severity and mortality rate of COVID-19.

An increasing number of studies have pointed out that there are ethnicity-related differences in cytokines in systemic lupus erythematosus, chronic rhinosinusitis and other autoimmunity diseases (Niewold et al., 2012; Wang et al., 2016; Slight-Webb et al., 2020). We also focused on ethnicity-related differences in cytokines in COVID-19 patients and the results showed that there were lower circulating levels of IL-6 in Asian patients than in European and African patients, suggesting that IL-6 antagonists are recommended to use earlier in western countries.

This study had some limitations. Firstly, the articles that described the differential serum levels of cytokines in males and females were all from China. More clinical experiments should focus on the sex bias of cytokines in COVID-19. Secondly, our meta-analysis mainly investigated studies written in English, which might lead to language bias.

![Image](https://example.com/image.png)
CONCLUSION

These large-scale data revealed that the serum levels of IL-6, IL-10, IL-12R, TNF-α, IL-1β, IL-4, IL-8, and IL-17 are potential risk factors for severity and high mortality in COVID-19. The IL-6 antagonist and TNF-α inhibitor are likely to be a proper therapeutic strategy to reduce mortality in males with COVID-19 and in Western countries.

AUTHOR CONTRIBUTIONS

HH wrote the manuscript, HP conceived and designed the study, HH and HP reviewed and revised the manuscript. HH and KH searched the database and extracted the data, HH and RL carried out the Meta-analysis and made figures, HP and HZ revised and sorted out the data, LL designed and performed the final review of the manuscript, all authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2022.802228/full#supplementary-material

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