Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Review article

The dynamics of inflammatory markers in coronavirus disease-2019 (COVID-19) patients: A systematic review and meta-analysis

Roshan Kumar Mahat [a,*], Suchismita Panda [a], Vedika Rathore [b], Sharmistha Swain [a], Lalendra Yadav [c], Sumesh Prasad Sah [d]

[a] Department of Biochemistry, Pandit Raghunath Murmu Medical College and Hospital, Baripada, Mayurbhanj, Odisha, 757107, India
[b] Department of Biochemistry, Shyam Shah Medical College, Rewa, Madhya Pradesh, 486001, India
[c] Department of Pharmacology, Teerthanker Mahaveer Medical College and Research Center, Moradabad, Uttar Pradesh, 244001, India
[d] Department of Biochemistry, Muzaffarnagar Medical College, Muzaffarnagar, Uttar Pradesh, 251203, India

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ABSTRACT

Background: Coronavirus disease-2019 (COVID-19) is a global pandemic and high mortality rate among severe or critical COVID-19 is linked with SARS-CoV-2 infection-induced hyperinflammation of the innate and adaptive immune systems and the resulting cytokine storm. This paper attempts to conduct a systematic review and meta-analysis of published articles, to evaluate the association of inflammatory parameters with the severity and mortality in COVID-19 patients.

Methods: A comprehensive systematic literature search of medical electronic databases including Pubmed/Medline, Europe PMC, and Google Scholar was performed for relevant data published from January 1, 2020 to June 26, 2020. Observational studies reporting clear extractable data on inflammatory parameters in laboratory-confirmed COVID-19 patients were included. Screening of articles, data extraction and quality assessment were carried out by two authors independently. Standardized mean difference (SMD)/mean difference (MD/WMD) and 95% confidence intervals (CIs) were calculated using random or fixed-effects models.

Results: A total of 83 studies were included in the meta-analysis. Of which, 54 studies were grouped by severity, 25 studies were grouped by mortality, and 04 studies were grouped by both severity and mortality. Random effect model results demonstrated that patients with severe COVID-19 group had significantly higher levels of C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), procalcitonin (PCT), interleukin-6 (IL-6), interleukin-10 (IL-10), interleukin-2R (IL-2R), serum amyloid A (SAA) and neutrophil-to-lymphocyte ratio (NLR) compared to those in the non-severe group. Similarly, the fixed-effect model revealed significant higher ferritin level in the severe group when compared with the non-severe group. Furthermore, the random effect model results demonstrated that the non-survivor group had significantly higher levels of CRP, PCT, IL-6, ferritin, and NLR when compared with the survivor group.

Conclusion: In conclusion, the measurement of these inflammatory parameters could help the physicians to rapidly identify severe COVID-19 patients, hence facilitating the early initiation of effective treatment.

Prospero registration number: CRD42020193169.

1. Introduction

Coronavirus disease 2019 (COVID-19) is caused by the zoonotic agent severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This virus emerged in the human population in the late December 2019 in Wuhan, Hubei province, central China and has since spread across the globe.[1,2] Owing to the rapid increase in the number of COVID-19 cases and uncontrolled worldwide spread, it was declared by the WHO a Public Health Emergency of International Concern on January 30, 2020, and furthered labeled as a pandemic on March 11, 2020.[3,4] As of September 28, 2020, COVID-19 pandemic had over 32.7 million confirmed cases with 991000 deaths.[4]

The clinical presentation of COVID-19 ranges from mild to critically ill. While most COVID-19 patients have a mild influenza-like illness and may be asymptomatic, a minority of patients are experiencing severe pneumonia, acute respiratory distress syndrome (ARDS), multiple organ

* Corresponding author.
E-mail address: mahatroshan79@gmail.com (R.K. Mahat).

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failure (MOF), and even death.[5] As soon as patients progress to the severity or critical stage, the risk for poor outcomes increases significantly.[6] It is estimated that around 10–15% of mild COVID-19 patients advance to severe, and 15–20% of severe cases progress to become critical, with many of the individuals in the critical category needing treatment in intensive care units (ICU).[7] As the number of COVID-19 cases increasing globally and treatment in intensive care units (ICU) has become a major challenge, early identification of severe forms of COVID-19 is crucial for the timely triaging of patients.[8]

Severe or critical COVID-19 is strongly linked with mortality[9] and the high mortality rate amongst these cases is linked with SARS-CoV-2 infection-induced hyperinflammation of the innate and adaptive immune systems and the resulting cytokine storm, a cytokine release syndrome (CRS)-like syndrome in severe/critical COVID-19 cases.[10–13] Studies have reported that the inflammatory parameters are closely linked to the COVID-19 severity and mortality.[14–17] In addition, two recent meta-analyses have also shown an association of inflammatory parameters with the COVID-19 severity.[18,19] However, with an increase in the number of studies now published, it is important to carry out more comprehensive reviews and analyses of inflammatory parameters linked to COVID-19 severity. We, therefore, conducted a comprehensive systematic review and meta-analysis of published articles, from January 1, 2020 to June 26, 2020, to evaluate the association of inflammatory parameters with the severity and mortality in COVID-19 patients.

2. Methods

This systematic review and meta-analysis has been conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[20] and was registered with PROSPERO-The International Prospective Register of Systematic Reviews (Registration No. CRD42020193169).[21]

2.1. Search strategy

A comprehensive systematic literature search of medical electronic databases including PubMed/Medline, Europe PMC, and Google Scholar was performed for relevant data published from January 1, 2020 to June 26, 2020. Pubmed/Medline and Europe PMC were searched using the following search terms: (“COVID-19” OR “2019-nCOV” OR “SARS-COV-2” OR “severe acute respiratory syndrome coronavirus 2” OR “novel coronavirus disease” OR “COVID-19 patients” OR “novel coronavirus 2019” OR “coronavirus disease-2019”) AND (“erythrocyte sedimentation rate” OR “C-reactive protein” OR “ferritin” OR “procalcitonin” OR “interleukin-6” OR “interleukin-10” OR “interleukin-2R” OR “tumor necrosis factor-α” OR “serum amyloid A” OR “neutrophil-to-lymphocyte ratio” OR “inflammatory markers” OR “inflammatory parameters”) whereas Google Scholar was searched using the keywords (“COVID-19” OR “2019-nCOV” OR “SARS-COV-2” OR “novel coronavirus disease” OR “COVID-19 patients” OR “novel coronavirus 2019” OR “coronavirus disease-2019”) AND (“inflammatory markers” OR “inflammatory parameters”) owing to the limitation of 256 characters in the search string. Two authors (RKM and SP) independently screened the results from the initial search by titles and abstracts for relevance and the full texts were reviewed for the eligibility criteria. To identify the eligible studies, the reference list of previous studies and systemic reviews were also searched and identified records were screened for the inclusion criteria specified for the current systemic review and meta-analysis. Any ambiguity occurred while the selection of the study was resolved by mutual discussion and consensus.

2.2. Inclusion and exclusion criteria

The inclusion criteria were as follows: (a) observational studies (cohort studies, case-control studies, cross-sectional studies, and case series studies) reporting clear extractable data on inflammatory parameters in laboratory-confirmed COVID-19 patients, (b) compared the inflammatory parameters between severe and non-severe COVID-19 patients or between survivors or non-survivors. The exclusion criteria were as follows: (a) review articles, non-research letters, editorials, commentaries, case reports, animal studies, original research with samples below 10, abstract from meeting proceedings, non-English language articles, (b) studies that were conducted particularly in children or pregnant women, (c) unclear reporting of levels of inflammatory parameters, (d) studies which do not provide a full-text version, (e) articles which were not peer-reviewed or accepted for publication, (f) laboratory information not presented as mean (standard deviation, SD) or median (interquartile range, IQR or range). In addition, when two or more studies were conducted at the same center/hospital recruiting patients during the same or overlapping periods, we selected the one with a larger sample size unless the other studies presented relevant information not included in the study having a larger sample size. In this study, mild and moderate COVID-19 patients were included in the non-severe group whereas severe and critical COVID-19 patients were included in the severe group.

2.3. Data extraction

Data were extracted independently by two reviewers (RKM and SP). A third reviewer (VR) checked the extracted data to ensure that there were no mistakes or duplicated information. The following information of each study was extracted from included articles: first author, country, year of publication, type of publication, hospital, date of data collection, gender, age, the total number of COVID-19 patients, number of severe/non-severe patients, or number of survivors/non-survivors and inflammatory parameters measured.

2.4. Quality assessment

The quality of included studies was assessed using the Newcastle-Ottawa Scale (NOS)[22] which is easy to use with its star rating system. Each of the included studies was judged on three broad perspectives: the selection of study groups (0–4 stars), the comparability of the groups (0–2 stars), and the ascertainment of the outcome of interest (0–3 stars), with a maximum of nine stars representing the highest methodological quality. The quality assessment was carried out independently by two authors (RKM and SP) for each original study included. Any disagreements were discussed between the two authors, and a third author (SS) was involved, if necessary, in reaching a final judgment.

2.5. Statistical analysis

Mean and standard deviation of inflammatory markers were extrapolated from sample size, median and interquartile range (IQR) or range according to Luo et al.[23] and Wan et al.[24] when the results of the included studies were present in median and interquartile range (IQR) or range. A pooled mean difference (MD/WMD) with 95% CI was used to assess the difference between inflammatory markers measured in COVID-19 patients with and without severe disease or COVID-19 patients who survived and those who did not survive in studies with the same clinical units and measures; otherwise, the standardized mean difference (SMD) was used. Statistical heterogeneity among studies was assessed using Cochran’s Q test and I^2 statistics. A Cochran’s Q value of <0.10 indicates substantial heterogeneity between studies whereas I^2 statistics were interpreted as 25%, 50%, and 75% for low, moderate, and substantial heterogeneity, respectively. If heterogeneity existed, the random effect model was used; otherwise, the fixed effect model was used. Funnel plots were designed to assess the publication bias and the plot’s symmetry was assessed by Egger’s linear regression test (a p-value <0.1 indicated significant bias). If publication bias was confirmed, Duval and Tweedie’s nonparametric trim-and-fill method was used to adjust potential publication bias.[25] A leave-one-out sensitivity analysis

was performed by removing one study at a time through influence analysis to assess the stability of results. The results of individual studies were pooled using Review Manager Version 5.4. All other statistical analyses were done using STATA (version 16; Stata Corporation, College Station, TX). A *p*-value <0.05 was considered statistically significant except for Egger's test and test of heterogeneity i.e. Cochran's Q test.

3. Results

3.1. Outcome of the database search

A total of 5612 articles were retrieved through the database search and from the reference lists of published articles, of which 4261 remained after the removal of duplicates. Following the screening of title/abstracts, 263 articles were selected for full-text assessment. 83 studies were finally selected for data extraction and meta-analysis after excluding ineligible studies for the following reasons: studies not stratified by severity or mortality (n = 82), not relevant for inclusion (n = 10), data not extractable/unclear reporting of inflammatory parameters/data not clearly presented (n = 18), full text not available (n = 2); overlap of samples between the groups (n = 1), inflammatory parameters not reported (n = 6), diagnosis not clear (n = 3), not laboratory diagnosed COVID-19 (n = 12), laboratory information not presented as mean (standard deviation, SD) or median (interquartile range, IQR or range) (n = 23) and hospital and study period overlap with other included studies (n = 23). The flow diagram of the number of studies screened and included in the meta-analysis is shown in Fig. 1.

3.2. Characteristics of the included studies and quality assessment

We have included all the articles that were published between January 1, 2020 and June 26, 2020. All the included studies were published in the year 2020 and written in English. The main characteristics of the included studies are shown in Table 1. Of 83 articles[14–17,26-50,51–78,79-104], 67 were from China[14–17,26-32,34–39,43-49,52–54,56-73,75–80,82,83,85,87,90,91,93,94,96,97,99–104] and 16 were from other countries [Italy (4),[81,84,86,92] Iran (2),[51,88] Turkey (1),[95] Korea (2),[40,89] UK (1),[98] Germany (1),[33] Oman (1),[41] Greece (1),[42] Mexico City (1),[50] Switzerland (1)[55] and Singapore (1)[74]]. 54 articles[15,16,26-43,45–50,52-65,67–80] were grouped by severity, 25 articles[17,81–104] were grouped by mortality and 04 studies[14,44,51,66] were grouped by both severity and mortality. The 58 studies which were grouped by severity contributed 10096 patients, of whom 3315 were severe COVID-19 patients and 6781 were non-severe COVID-19 patients. Among 10096 participants, 5234 were males and 4862 were females. COVID-19 severity was classified using the National Health Commission of China in 34 studies, WHO guidelines in 5 studies, American Thoracic Society guidelines for community-acquired pneumonia in 2 studies, Chinese Center for Disease Control (CDC) guidelines in 2 studies, ICU admission in 6 studies, ARDS in 2 studies, SOFA score in 1 study, the requirement of supplemental oxygen in 1 study, SpO_2 in 1 study, the composite endpoint in 1 study and unspecified guidelines in 3 studies. The 29 articles which were grouped by mortality contributed 7203 patients, of whom 5644 were survivors and 1559 were patients who died of COVID-19. Among 7203 participants in the studies grouped by mortality, 3921 were males and 3282 were females. The quality of included studies was assessed based on the Newcastle-Ottawa Scale and the quality results are presented in Table 1. Studies were awarded between 0 and 9 points, with higher scores indicating lower risk of bias.

3.3. Metaanalysis of inflammatory markers in patients with COVID-19 stratified by severity

Information on C-reactive protein (CRP) was available in 44 studies with 2623 severe and 5275 non-severe COVID-19 patients. The analysis of the random effect model showed that compared with the non-severe group, the severe group had a significantly higher CRP [SMD = 1.14, 95% CI: 0.97–1.32; $p < 0.00001$] with a substantial heterogeneity [I^2 = 90%]. 17 studies analyzed erythrocyte sedimentation rate (ESR) involving 1075 severe and 2362 non-severe COVID-19 patients. The value of ESR was significantly higher in the severe group when compared with the non-severe group [MD = 12.08, 95% CI: 8.04–16.11; $p < 0.00001$] with a high heterogeneity [I^2 = 75%] in a random effect model. 30 studies with 2217 severe and 3682 non-severe COVID-19 patients were included for the meta-analysis of procalcitonin (PCT). The random effect model demonstrated that the severe group had significantly increased PCT than the non-severe group [SMD = 0.88, 95% CI: 0.68–1.08; $p < 0.00001$] with a substantial heterogeneity [I^2 = 90%]. A total of 18 studies with 1564 severe and 2054 non-severe COVID-19 patients were included in this metaanalysis for interleukin-6 (IL-6). In a random effect model, the value of IL-6 was significantly higher in the severe group when compared with the non-severe group [MD = 16.94, 95% CI: 12.72–21.16; $p < 0.00001$] with a substantial heterogeneity [I^2 = 96%]. In total, 8 studies with 864 severe and 762 non-severe COVID-19 patients were taken in the metaanalysis for interleukin-10 (IL-10). The estimated pooled MD indicated that the severe group had a significantly higher level of IL-10 than the non-severe group [MD = 2.03, 95% CI: 1.36–2.70; $p < 0.00001$] with a substantial heterogeneity [I^2 = 82%] in a random effect model. Information on interleukin-2R (IL-2R) was available in two studies, including 345 severe and 186 non-severe COVID-19 patients. In a random effect model, the value of IL-2R was significantly higher in the severe group when compared with the non-severe group [MD = 238.26, 95% CI: 31.90–444.62; $p = 0.02$] with high heterogeneity [I^2 = 84%]. For tumor necrosis factor-α (TNF-α), 7 studies with 758 severe and 682 non-severe COVID-19 were included in the meta-analysis and the random effect model analysis showed that compared with the non-severe group, the severe group had higher TNF-α, but the difference was not significant [MD = 0.05, 95% CI: -0.57-0.68; $p = 0.87$, I^2 = 91%]. We obtained information about ferritin from 9 studies including 835 severe and 774 non-severe COVID-19 patients. The estimated pooled standardized mean difference indicated that the severe group had significantly higher ferritin than the non-severe group [SMD = 0.71, 95% CI: 0.60–0.81; $p < 0.00001$] without evident heterogeneity [I^2 = 5%] in a fixed-effect model. Nine studies with 482 severe and 807 non-severe COVID-19 patients were included in the metaanalysis for serum amyloid A (SAA). The estimated pooled standardized mean difference revealed a significant increase in SAA in the severe group compared with the non-severe group [SMD = 1.16, 95% CI: 0.64–1.68; $p < 0.0001$] with a substantial heterogeneity [I^2 = 93%] in a random effect model. The meta-analysis included 819 severe and 1700 non-severe COVID-19 patients from 12 studies for neutrophil-to-lymphocyte ratio (NLR) and a random effect model analysis revealed significant higher NLR in severe patients when compared with non-severe COVID-19 patients [MD = 3.27, 95% CI: 1.99–4.55; $p < 0.00001$] with a substantial heterogeneity [I^2 = 90%] (Table 2; Supplement 1).

3.4. Metaanalysis of inflammatory markers in patients with COVID-19 stratified by mortality

We obtained information about CRP from 19 studies including 3427 survivors and 891 non-survivors. Random effect model analysis showed significantly increased CRP in the non-survivor group when compared to the survivor group [SMD = 1.18, 95% CI: 0.80–1.55; $p < 0.00001$] with a substantial heterogeneity [I^2 = 94%]. Seven studies with 815 survivors and 347 non-survivors with COVID-19 were included in the meta-analysis for ESR. The non-survivor group had an insignificant increase in the level of ESR compared with the survivor group [MD = 12.98, 95% CI: -1.79-27.75; $p = 0.08$] with a substantial heterogeneity [I^2 = 91%] in a random effect model. Information on PCT was available in 12 studies with 2260 survivors and 762 non-survivors. The pooled median difference revealed a significant increase in the level of PCT in the non-

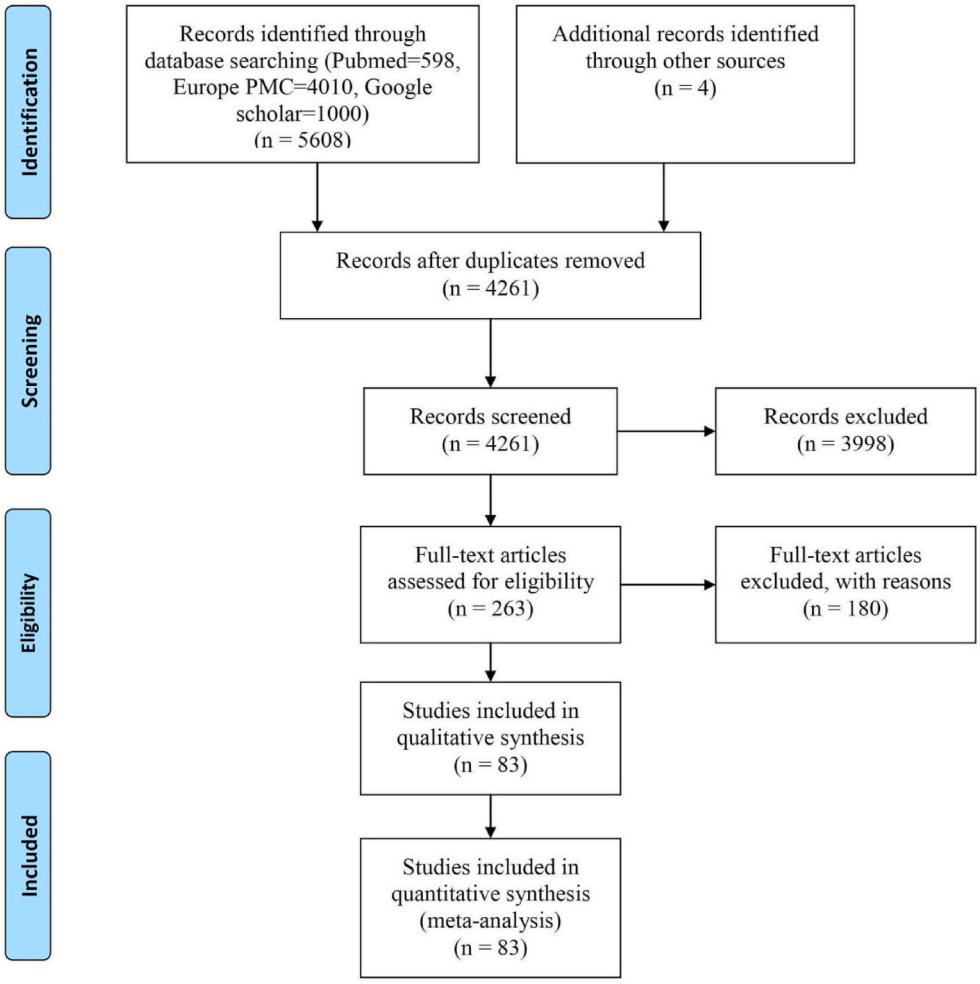

Fig. 1. PRISMA flow chart of the study selection procedure.

survivor group compared with the survivor group [MD = 0.26, 95% CI: 0.18–0.34; $p < 0.00001$] with a high heterogeneity [$I^2 = 85\%$] in a random effect model. For IL-6, eight studies involving 1478 survivors and 587 non-survivors were included in the meta-analysis. The random effect model demonstrated a significantly higher level of IL-6 in non-survivors than the survivors [MD = 15.62, 95% CI: 10.67–20.57; $p < 0.00001$] with a substantial heterogeneity [$I^2 = 96\%$]. A total of 11 studies with 1904 survivors and 650 non-survivors were included in the present meta-analysis for ferritin. In a random effect model, the value of ferritin was significantly higher in the non-survivor group when compared with the survivor group [SMD = 0.95, 95% CI: 0.74–1.17; $p < 0.00001$] with a high heterogeneity [$I^2 = 76\%$]. Seven studies analyzed NLR involving 2068 survivors and 282 non-survivors. The non-survivor group had a significantly increased level of NLR when compared with survivor [MD = 8.96, 95% CI: 3.97–13.95; $p = 0.0004$] with a high heterogeneity [$I^2 = 99\%$] in a random effect model (Table 3; Supplement 2). IL-10, IL-2R, and TNF-α were not included in the meta-analysis since the information about these parameters were available in only one study. In addition, information about SAA was also available in only one study and hence this was also not included in the meta-analysis.

3.5. Subgroup analysis

In a subgroup analysis by sample size, we did not find any significant differences in the levels of CRP, ESR, PCT, ferritin, SAA, NLR, IL-10, and TNF-α between the sample size ≥100 subgroup and sample size <100 subgroup. However, IL-6 was significantly increased in sample size <100 subgroup compared with the sample size ≥100 subgroup. In both the subgroups, CRP, ESR, PCT, ferritin, SAA, NLR, IL-10, IL-6, and TNF-α were associated with the severity of COVID-19 (Supplement 3).

Subgroup analysis based on sample size showed a significant association of CRP, ferritin, and NLR with mortality of COVID-19 patients in both the sample size <100 subgroup and sample size ≥100 subgroup, whereas PCT was significantly associated with mortality in sample size ≥100 subgroup only. In neither of the subgroup, ESR was significantly associated with mortality. In addition, we did not find any significant differences in the levels of CRP, ESR, PCT, and ferritin between the sample size ≥100 subgroup and sample size <100 subgroup. However, the sample size ≥100 subgroup had a significantly increased level of NLR when compared with sample size <100 subgroup (Supplement 4).

3.6. Publication bias

Funnel plots were constructed for only those parameters which were retrieved from ≥10 studies. Funnel plot analysis showed asymmetrical shape for CRP, ESR, PCT, IL6, and NLR in severity studies (Supplement 5). Regression-based Egger's test showed statistically significant small-study effects for CRP ($p = 0.0000$), ESR ($p = 0.0802$), PCT ($p = 0.0531$), IL-6 ($p = 0.0000$) and NLR ($p = 0.0085$). Therefore, to adjust the publication bias, the trim and fill method was adopted and after adjustment, the funnel plot looks more symmetric than before. The trim and fill method did not impute any study in CRP, PCT, and NLR whereas 5 and 6 studies were imputed in ESR and IL-6 respectively (Supplement 6).

Table 1
Characteristics of included studies.

Studies stratified by severity												
Author	**Country**	**Year of publication**	**Hospitals**	**Type of publication**	**Date of data collection**	**Gender (M/F)**	**Total patients**	**Non-severe patients**	**Severe patients**	**Age, median (IQR) or mean ± SD**	**Parameters extracted**	**NOS**
Cao Z et al.[26]	China	2020	Beijing You'an Hospital	Retrospective study	21 January to 12 February, 2020	38/42	80	53	27	53 ± 20	CRP, PCT	7
Cen Y et al.[27]	China	2020	Huoshenshan Hospital, General Hospital of the Central Theatre Command of the People's Liberation Army, and mobile cabin hospitals in Wuhan	Observational Cohort study	As of 10 February 2020	493/514	1007	720	287	61 (49–68)	CRP, PCT	8
Chen C et al.[28]	China	2020	Third People's Hospital of Shenzhen	Retrospective study	11 January to 18 February, 2020.	198/219	417	325	92	47 (34–60)	CRP, PCT, IL-6, ESR	8
Chen Q et al.[29]	China	2020	Taizhou Public Health Medical Center	Retrospective study	1 January to 11 March, 2020	79/66	145	102	43	47.5 ± 14.6	CRP, ESR, PCT	7
Chen R et al.[14]	China	2020	575 hospitals throughout China	Retrospective study	By March 22, 2020	313/235	548	345	203	56.0 ± 14.5	CRP, PCT, IL-6, SAA, NLR, Ferritin	7
Chen X et al.[30]	China	2020	General Hospital of Central Theater Command, PLA	Retrospective study	February 1 to February 19, 2020	37/11	48	21	27	64.6 ± 18.1	PCT, IL-6	6
Ding X et al.[31]	China	2020	Beijing YouAn Hospital	Retrospective study	21 January to 17 February, 2020	33/39	72	57	15	49 (37–64)	NLR	8
Dong Y et al.[32]	China	2020	Union Hospital	Retrospective study	10 February to 29 February, 2020	63/84	147	94	53	48 (36–62)	ESR, SAA	7
Dreher M et al.[33]	Germany	2020	Aachen University Hospital	Retrospective study	February to March 2020	33/17	50	26	24	65 (58–76)	CRP, PCT, IL-6	8
Duan J et al.[34]	China	2020	Chongqing Three Gorges Central Hospital and Chongqing Public Health Medical Center	Retrospective study	1 January to 29th February, 2020	184/164	348	328	20	Non-severe: 44 ± 15; Severe: 58 ± 15	CRP, PCT, NLR	8
Feng Y et al.[35]	China	2020	Jinyintan Hospital in Wuhan, Shanghai Public Health Clinical Center in Shanghai, and Tongling People's Hospital in Anhui Province	Retrospective study	1 January to 15 February, 2020	271/205	476	352	124	53 (40–64)	CRP, PCT, ESR	8
Fu J et al.[36]	China	2020	Affiliated Infectious Diseases Hospital of Soochow University	Retrospective study	20 January to 20 February, 2020	45/30	75	59	16	46.6 ± 14	CRP, PCT, NLR	8
Gao Y et al.[37]	China	2020	Fuyang Second People's Hospital	Retrospective study	23 January to 2 February, 2020	26/17	43	28	15	43.74 ± 12.12	CRP, PCT, IL-6	7
Gong J et al.[38]	China	2020	Guangzhou Eighth People's Hospital, Zhongnan Hospital of Wuhan University and the Third Affiliated Hospital of Sun Yat-sen University but 189 used in the analysis come only from Guangzhou Eighth People's Hospital	Retrospective study	20 January to 2 March, 2020	88/101	189	161	28	49 (35–63)	SAA, NLR	8

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Table 1 (*continued*)

Huang C et al.[39]	China	2020	Jin Yintan Hospital	Prospective study	16 December 2019 to 2 January, 2020	30/11	41	28	13	49 (41–58)	PCT	7
Jang JG et al.[40]	Korea	2020	Yeungnam University Medical Center	Retrospective study	19 February to 15 April, 2020	48/62	110	87	23	56.9 ± 17.0	CRP, PCT	8
Khamis F et al.[41]	Muscat Oman	2020	The Royal Hospital and Al Nahdha Hospital	A case series	24 February to 24 April, 2020	53/10	63	39	24	48 ± 16	CRP, Ferritin	7
Lagadinou M et al.[42]	Greece	2020	Patras University Hospital	Retrospective study	4 March to 4 April, 2020	31/33	64	16	48	57.11 ± 16.3	CRP, Ferritin, NLR	6
Li H et al.[43]	China	2020	Tianyou Hospital	Retrospective study	18 January to 26 February, 2020	75/57	132	60	72	62.05 ± 12.68	CRP, PCT, SAA	8
Li J et al.[44]	China	2020	Central Hospital of Wuhan	Retrospective study	1 January to 20 February, 2020	75/59	134	45	89	61.00 (46.75–69.25)	CRP, PCT, ESR, IL-6, Ferritin	7
Li K et al.[45]	China	2020	The Second Affiliated Hospital of Chongqing Medical University .	Retrospective study	January 2020 to February 2020	44/39	83	58	25	45.5 ± 12.3	CRP, PCT	7
Liu J et al.[46]	China	2020	Union Hospital	Retrospective study	5 January to 24 January, 2020	15/25	40	27	13	48.7 ± 13.9	SAA	7
Liu T et al.[47]	China	2020	Union Hospital	Retrospective study	21 January to 16 February, 2020	34/46	80	11	69	53.00 (Range: 26.00–86.00)	Ferritin	6
Lo IL et al.[48]	China	2020	Centro Hospitalar Conde de São Januário (C.H.C.S.J.)	Retrospective study	21 January to 16 February, 2020	3/7	10	6	4	54 (27–64)	CRP	7
Lv Z et al.[16]	China	2020	Renmin Hospital of Wuhan University	Retrospective study	4 February to 28 February, 2020	175/179	354	115	239	62 (Range: 23–90)	CRP, PCT, IL-6, IL-10, TNF-α	7
Ma J et al.[49]	China	2020	Renmin Hospital of Wuhan University	Retrospective study	1 January to 30 March, 2020	20/17	37	17	20	62 (59–70)	NLR	6
Ortiz-Brizuela E et al.[50]	Mexico City	2020	Tertiary Care Center located in Mexico City	Prospective cohort study	26 February to 11 April, 2020	85/55	140 (included inpatients only)	111	29	49.00 (39.00–61.25)	CRP, PCT, ESR, Ferritin	7
Qin C et al.[15]	China	2020	Tongji Hospital	Retrospective study	10 January to 12 February, 2020	235/217	452	166	286	58 (47–67)	CRP, PCT, ESR, NLR, Ferritin, IL-6, IL-10, IL-2R, TNF-α	6
Shahriarirad R et al.[51]	Iran	2020	Shiraz University of Medical Sciences	Retrospective study	20 February to 20 March, 2020	71/42	113	102	11	53.75 ± 16.58	CRP, ESR	7
Shang W et al.[52]	China	2020	Wuhan Forth Hospital	Retrospective study	16 January to 28 February, 2020	220/223	443	304	139	56.00 (43.25–66.75)	CRP, PCT, ESR, NLR	7
Shao L et al.[53]	China	2020	Zhongnan Hospital	Retrospective study	10 January to 8 March, 2020	62/93	155	104	51	48(33–63)	CRP, IL-6	8
Shi J et al.[54]	China	2020	Four designated hospitals located in Wenzhou, Wuhan, Huaihua, and Shanghai	Nested case-control study	17 January to 1 February, 2020	49/36	85	69	16	46.6 ± 15.0	CRP	8

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Table 1 (*continued*)

Spinetti T et al.[55]	Switzerland	2020	Inselspital, Bern University Hospital	Prospective study	March to April 2020	12/4	16	7	9	66 (62–77)	CRP, PCT	7
Sun Y et al.[56]	China	2020	The Fifth Medical Center of Chinese PLA General Hospital	Cohort study	NA	37/26	63	44	19	47 (Range: 3–85)	CRP, ESR, IL-6	6
Tian J et al.[57]	China	2020	Tongji Hospital, Wuhan Union Hospital, Wuhan First Hospital, the Central Hospital of Wuhan, Wuhan Fourth Hospital and Puai Hospital, Fifth Hospital of Wuhan, Wuhan Pulmonary Hospital, Wuhan Jinyintan Hospital, and Wuhan Hankou Hospital	Retrospective study	13 January to 18 March, 2020	119/113	232 (taken patients with cancer only)	84	148	64·0 (58·0–69·0)	CRP, PCT, Ferritin, IL-6, IL-10, IL-2R, TNF-α	8
Wan S et al.[58]	China	2020	Chongqing Three Gorges Central Hospital	Retrospective study	26 January to 4 February 2020	66/57	123	102	21	Non-severe: 43.05 ± 13.12 Severe: 61.29 ± 15.55	IL-6, IL-10, TNF-α	6
Wang G et al.[59]	China	2020	Public Health Treatment Center of Changsha	Case series	17 January to 20 February, 2020	105/104	209	193	16	Non-severe: 42 (Range:19–84); Severe: 54 (Range: 35–68)	CRP, ESR	8
Wang L et al.[60]	China	2020	People's Hospital of Qiandongnan Miao and Dong autonomous prefecture & Qiannan Miao and Buyi autonomous prefecture	Retrospective study	23 January to 29 February, 2020	13/14	27	23	4	33.23 ± 13.21	CRP	6
Wang R et al.[61]	China	2020	NO.2 People's Hospital of Fuyang City	Retrospective study	20 January to 9 February, 2020	71/54	125	100	25	38.76 ± 13.799	CRP, PCT, SAA, IL-6	7
Wang Y et al.[62]	China	2020	Guangzhou Eighth People's Hospital	Retrospective study	20 January to 10 February, 2020	128/147	275	230	45	49 (34–62)	CRP, PCT	8
Wang Z et al.[63]	China	2020	Union hospital	Cohort study	16 January to 29 January, 2020	32/37	69	55	14	42.0 (35.0–62.0)	CRP, PCT, ESR, IL-6, IL-10, TNF-α	7
Wei X et al. (b)[64]	China	2020	Union Hospital	Retrospective study	13 February to 3 March, 2020	130/122	252	131	121	64·8 ± 13·3	PCT, IL-10, TNF-α	6
Wei X et al. (a)[65]	China	2020	Union Hospital	Retrospective study	1 February to 3 March, 2020	305/292	597	394	203	66 (59–72)	CRP, IL-6	6
Wu C et al.[66]	China	2020	Jinyintan Hospital	Retrospective study	25 December, 2019 to 26 January, 2020	128/73	201	117	84	51 (43–60)	ESR, IL-6, Ferritin	8
Xie H et al.[67]	China	2020	Jinyintan Hospital.	Retrospective study	2 February to 23 February, 2020	44/35	79	51	28	60.0 (48.0–66.0)	ESR, PCT	7
Xu B et al.[68]	China	2020	Hubei Provincial Hospital of traditional Chinese and Western medicine	Retrospective study	26 December, 2019 to 1 March, 2020	103/84	187	80	107	62 (48.5-71)	CRP, PCT, SAA, IL-6, IL-10	8
Yang A et al.[69]	China	2020	Chongqing Public Health Medical Treatment Center	Retrospective study	24 January to 7 February, 2020	56/58	114	99	15	46.5 ± 15.15	ESR	6
Yang AP et al.[70]	China	2020	Zhejiang Xiaoshan Hospital, The First Affiliated Hospital of Nanchang University	Retrospective study	Until 20 February, 2020	56/37	93	69	24	46.4 ± 17.6	CRP, NLR	8
Yang L et al.[71]	China	2020	Yichang Central People's Hospital	Descriptive study		98/102	200	171	29	55 ± 17.1	CRP	7

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Table 1 (*continued*)

					30 January to 8 February, 2020							
Yang Q et al.[72]	China	2020	Wuhan Third Hospital	Retrospective study	28 January to 12 February, 2020	66/70	136	103	33	56 (44–64)	CRP	6
Yao Q et al.[73]	China	2020	Dabieshan Medical Center	Retrospective cohort study	30 January to 11 February, 2020	43/65	108	83	25	52 (37–58)	PCT	8
Young BE et al.[74]	Singapore	2020	4 hospitals	Descriptive case series	23 January to 3 February, 2020	9/9	18	12	6	47 (Range: 31–73)	CRP	7
Zeng QL et al.[75]	China	2020	12 hospitals in Henan and Shaanxi Provinces	Retrospective study	20 January to 8 February, 2020	91/58	149	122	27	42 (30–55)	CRP, ESR, PCT	7
Zhang JJ et al.[76]	China	2020	No. 7 Hospital of Wuhan	Retrospective study	16 January to 3 February, 2020	71/69	140	82	58	57 (Range: 25–87)	CRP, PCT, SAA	6
Zhang Y et al.[77]	China	2020	Zhongnan Hospital	Retrospective study	18 January to 22 February, 2020	49/66	115	84	31	49.52 ± 17.06	NLR	7
Zheng F et al.[78]	China	2020	North Hospital of Changsha First Hospital	Retrospective study	17 January to 7 February, 2020	80/81	161	131	30	45(33.5- 57)	CRP	6
Zheng Y et al.[79]	China	2020	Chengdu Public Health Clinical Medical Center	Retrospective study	16 January to 20 February, 2020	51/48	99	67	32	49.4 ± 18.45	CRP	7
Zhu Z et al.[80]	China	2020	Hwa Mei Hospital, University of Chinese Academy of Sciences	Retrospective study	23 January to 20 February, 2020	45/82	127	111	16	50.90 ± 15.26	CRP, ESR, NLR, IL-6, IL-10, TNF-α	7

Studies stratified by mortality

Author	Country	Year of publication	Hospitals	Type of publication	Date of data collection	Gender (M/F)	Total patients	Survivors	Non-survivors	Age, median (IQR) or mean (SD)	Parameters extracted	NOS
Bonetti G et al.[81]	Italy	2020	Valcamonica Hospital	Retrospective study	1 March to 30 March, 2020	96/48	144	74	70	Survivors: 62.1 (53.0–72.8) Non-survivors: 78.0 (64.2–84.0)	CRP, Ferritin	8
Chen R et al.[14]	China	2020	575 hospitals throughout China	Retrospective study	Till March 22, 2020	313/235	548	445	103	56.0 ± 14.5	CRP, PCT, NLR, SAA, Ferritin, IL-6	7
Chen T et al.[82]	China	2020	Tongji Hospital	Retrospective case series	13 January to 12 February, 2020	171/103	274	161	113	62.0 (44.0–70.0)	ESR, Ferritin	7
Chen TL et al.[83]	China	2020	Zhongnan Hospital	Retrospective study	1 January to 10 February, 2020	34/21	55	36	19	74 (65–91)	PCT	8
Covino M et al.[84]	Italy	2020	Urban Teaching Hospital	Retrospective study	1 March to 31 March, 2020	37/32	69	46	23	84 (82–89)	CRP, PCT, Ferritin	8
Deng Y et al.[85]	China	2020	Hankou and Caidian branch of Tongji Hospital, and Hankou branch of The Central Hospital of Wuhan	Retrospective study	1 January to 21 February, 2020	124/101	225	116	109	Survivors: 40 (33–57) Non-survivors: 69 (62–74)	CRP	6
Giacomelli A et al.[86]	Italy	2020	Luigi Sacco Hospital, Milan	Prospective study	21 February to 19 March, 2020	161/72	233	185	48	61(50–72)	CRP	8

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Table 1 (*continued*)

Huang J et al.[87]	China	2020	Third People's Hospital of Yichang, Hubei	Retrospective study	25 January to 24 March, 2020	160/139	299	283	16	53.4 ± 16.7	CRP, PCT, ESR, NLR	8
Javanian M et al.[88]	Iran	2020	Ayatollah Rohani, Shahid Beheshti and Yahyanejad hospitals	Retrospective study	25 February to 12 March, 2020	51/49	100	81	19	60.12 ± 13.87	CRP	8
Lee JY et al.[89]	Korea	2020	4 Hospitals	Retrospective study	18 February to 4 March, 2020	44/54	98	78	20	72 (68–79)	CRP	8
Li J et al.[44]	China	2020	Central Hospital of Wuhan	Retrospective study	1 January to 20 February, 2020	36/23	59 (included critical patients only)	17	42	67.00 (56.00–75.00)	PCT, CRP	7
Li L et al.[90]	China	2020	Union Hospital	Retrospective study	10 January to 22 February, 2020	41/52	93	68	25	51.0 ± 17.5	ESR, NLR, Ferritin	8
Luo X et al.[91]	China	2020	Eastern Campus of Renmin Hospital of Wuhan University	Retrospective study	30 January to 20 February, 2020	150/148	298	214	84	57 (40–69)	CRP, PCT, NLR	8
Masetti C et al.[92]	Italy	2020	IRCCS, Rozzano	Retrospective study	28 February to 10 April, 2020	148/81	229	196	33	60.7 ± 14.2	CRP, Ferritin	8
Pan F et al.[93]	China	2020	Union Hospital	Case-control study	27 January to 19 March, 2020	85/39	124	35	89	68 (61–75)	CRP, PCT	8
Ruan Q et al.[94]	China	2020	Jin Yin-tan Hospital and Tongji Hospital	Retrospective study	NA	102/48	150	82	68	Survivors: 50 (44–81) Non-survivors: 67 (15–81)	CRP, Ferritin, IL-6	7
Satici C et al.[95]	Turkey	2020	Gaziosmanpasa Research and Training Hospital, University of Health Sciences	Retrospective study	2 April to 1 May, 2020	347/334	681	626	55	56.9 ± 15.7	CRP, Ferritin	8
Shahriarirad R et al.[51]	Iran	2020	Centers for COVID-19 diagnosis and under the management of Shiraz University of Medical Sciences	Retrospective study	20 February to 20 March, 2020	71/42	113	104	9	53.75 ± 16.58	CRP, ESR	7
Shi S et al.[96]	China	2020	Renmin Hospital of Wuhan University	Retrospective study	1 January to 23 February, 2020	322/349	671	609	62	63 (50–72)	CRP, PCT	8
Sun H et al.[97]	China	2020	Sino-French New City Branch of Tongji Hospital	Retrospective case-control.	29 January to 5 March, 2020	133/111	244	123	121	Survivors: 67 (64–72); Non-survivors: 72 (66–78)	ESR, PCT, Ferritin, IL-6	8
Tomlins J et al.[98]	UK	2020	North Bristol NHS Trust	Retrospective study	10 March to 30 March, 2020	60/35	95	75	20	75 (59–82)	CRP, NLR, Ferritin	7
Tu WJ et al.[99]	China	2020	Zhongnan Hospital	Retrospective study	3 January to 24 February, 2020	79/95	174	149	25	Survivors: 51 (37–62); Non-survivors: 70 (64–80)	CRP, IL-6	8
Wang L et al.[100]	China	2020	Renmin Hospital of Wuhan University	Retrospective study	1 January to 6 February, 2020	166/173	339	274	65	69 (65–76)	IL-6	8
Wang Y et al.[17]	China	2020	Tongji hospital	Case series	25 January to 25 February, 2020	179/165	344	211	133	64 (52–72)	PCT, IL-6, IL-10, IL-2R, TNF-α	8
Wu C et al.[66]	China	2020	Jinyintan Hospital	Retrospective study	25 December, 2019 to 26	60/24		40	44	58.5 (50.0–69.0)	ESR	8

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Table 1 (*continued*)

					January, 2020		84 (included patients with ARDS only)					
Yan X et al.[101]	China	2020	Wuhan Third Hospital & Tongren Hospital of Wuhan University	Retrospective study	11 January to 3 March, 2020	493/511	1004	964	40	Survivors: 62 (50–70); Non-survivors: 68 (58–79)	NLR	8
Yang K et al.[102]	China	2020	Cancer Center of Wuhan Union Hospital, West Branch of Wuhan Union Hospital, Jin Yin-tan Hospital, Wuhan Red Cross Hospital, the Central Hospital of Wuhan, Huanggang Central Hospital, the First People's Hospital Affiliated to Yangtze University, Xianning Central Hospital, and Suizhou Central Hospital	Retrospective study	13 January to 18 March, 2020	96/109	205	165	40	63 (56–70)	PCT, IL-6	8
Zhang N et al.[103]	China	2020	WuGang General Hospital (Wuhan, Hubei Province) and The First Affiliated Hospital of Hunan University of Medicine (Hunan Province)	Retrospective study	9 January to 19 February, 2020	43/17	60	50	10	64.4 ± 11.0	CRP, NLR	7
Zhou F et al.[104]	China	2020	135 from Jinyintan Hospital and 56 from Wuhan Pulmonary Hospital	Retrospective study	29 December, 2019 to 31 January, 2020	119/72	191	137	54	56.0 (46.0–67.0)	PCT, Ferritin, IL-6	6

NA: Not available; NOS: Newcastle-Ottawa scale; M: Male; F: Female; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; PCT: Procalcitonin; IL-6: Interleukin-6; IL-10: Interleukin-10; IL-2R: Interleukin-2R; TNF-α: Tumor necrosis factor-α; SAA: Serum amyloid A; NLR: Neutrophil to lymphocyte ratio.

Table 2
Association of inflammatory parameters with disease severity in patients of COVID-19.

Inflammatory parameters	Number of studies	Participants	Statistical method				Heterogeneity	
			SDM (95% CI)	MD (95% CI)	Model	p-value	I^2	P_h-value
CRP	44	7898	1.14(0.97, 1.32)	–	REM	<0.00001	90%	<0.00001
ESR	17	3437	–	12.08 (8.04, 16.11)	REM	<0.00001	75%	<0.00001
PCT	30	5899	0.88 (0.68, 1.08)	–	REM	<0.00001	90%	<0.00001
IL-6	18	3618	–	16.94 (12.72, 21.16)	REM	<0.00001	96%	<0.00001
IL-10	8	1626	–	2.03 (1.36, 2.70)	REM	<0.00001	82%	<0.00001
IL-2R	2	531	–	238.26 (31.90, 444.62)	REM	0.02	84%	0.01
TNF-α	7	1440	–	0.05 (−0.57, 0.68)	REM	0.87	91%	<0.00001
Ferritin	9	1609	0.71 (0.60, 0.81)	–	FEM	<0.00001	5%	0.39
SAA	8	1289	1.16 (0.64, 1.68)	–	REM	<0.0001	93%	<0.00001
NLR	12	2519	–	3.27 (1.99, 4.55)	REM	<0.00001	90%	<0.00001

CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; PCT: Procalcitonin; IL-6: Interleukin-6; IL-10: Interleukin-10; IL-2R: Interleukin-2R; TNF-α: Tumor necrosis factor-α; SAA: Serum amyloid A; NLR: Neutrophil to lymphocyte ratio; REM: Random effect model; FEM: Fixed effect model; P_h: *p*-value of Q-test for heterogeneity.

Table 3
Association of inflammatory parameters with mortality in COVID-19 patients.

Inflammatory parameters	Number of studies	Participants	Statistical method				Heterogeneity	
			SDM (95% CI)	MD (95% CI)	Model	p-value	I^2	P_h-value
CRP	19	4318	1.18 (0.80, 1.55)	–	REM	<0.00001	94%	<0.00001
ESR	7	1162	–	12.98 (−1.79, 27.75)	REM	0.08	91%	<0.00001
PCT	12	3022	–	0.26 (0.18, 0.34)	REM	<0.00001	85%	<0.00001
IL-6	8	2065	–	15.62 (10.67, 20.57)	REM	<0.00001	96%	<0.00001
Ferritin	11	2554	0.95 (0.74, 1.17)	–	REM	<0.00001	76%	<0.0001
NLR	7	2350	–	8.96 (3.97, 13.95)	REM	0.0004	99%	<0.00001

CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; PCT: Procalcitonin; IL-6: Interleukin-6; NLR: Neutrophil to lymphocyte ratio; REM: Random effect model; P_h: *p*-value of Q-test for heterogeneity.

In mortality studies, a funnel plot regarding the CRP showed that the *p* value of Egger's test was 0.1058, suggesting no stable evidence of publication bias. Regression-based Egger's test showed statistically significant small-study effects for PCT ($p = 0.0005$) and ferritin ($p = 0.0449$). The trim and fill method imputed 2 studies in the PCT whereas no study was imputed in ferritin (Supplement 7 and supplement 8).

3.7. Sensitivity analysis

Sensitivity analysis indicated that the combined results did not change with the exclusion of any one of the studies in CRP, ESR, PCT, IL-6, IL-10, TNF-α, ferritin, SAA, and NLR between the severe and non-severe groups (Supplement 9). Similarly, sensitivity analysis revealed that the results were not influenced with the exclusion of any one of the studies in CRP, ESR, PCT, ferritin, and NLR between the survivor and non-survivor groups. However, for IL-6, the pooled effect sizes changed after omitting Chen R et al.[14] [MD = 24.48, 95% CI: 17.25–31.71], Sun H et al.[97] [MD = 10.31, 95% CI: 6.03–14.58], Wang Y et al.[17] [MD = 9.66, 95% CI: 5.40–13.91], Yang K et al.[102] [MD = 22.48, 95% CI: 15.84–29.12] and Zhou F et al.[104] [MD = 22.33, 95% CI: 15.65–29.01], separately (Supplement 10).

4. Discussion

This systematic review and metaanalysis included 83 studies to investigate the association of inflammatory parameters with the severity and mortality in COVID-19 patients. The findings revealed significantly higher levels of CRP, ESR, PCT, IL-6, IL-10, IL-2R, ferritin, SAA, and NLR in the severe group compared to the non-severe group with COVID-19. However, no significant difference was observed in the level of TNF-α between severe and non-severe groups. Similarly, the levels of CRP, PCT, IL-6, ferritin, and NLR were significantly higher in non-survivors compared with survivors whereas no significant difference was observed for ESR between survivors and non-survivors.

C-reactive protein is an acute-phase inflammatory protein produced by the liver and regulated at the transcriptional level by the cytokine IL-6 and IL-1.[105] It is an important index for diagnosing and evaluating severe pulmonary infectious diseases.[106] SARS-CoV-2 shares similar clinical features with Middle East respiratory syndrome coronavirus[107] and in patients with severe Middle East respiratory syndrome coronavirus pneumonia, increasing in C-reactive protein levels is correlated with clinical deterioration.[108] Similarly, in our meta-analysis, elevated CRP was associated with both severity and mortality in COVID-19 patients, which represent more prominent inflammation in severe patients. ESR is a non-specific inflammatory marker, primarily reflecting changes in plasma protein types.[109] In the present meta-analysis, a higher ESR level was associated with the severity of COVID-19. Similarly, the findings of systematic literature search and pooled analysis conducted by Lapić et al.[110] stated that severe COVID-19 cases are associated with prominent elevations of ESR, as compared to non-severe cases. This increased ESR level in severe COVID-19 cases reflects a more profound inflammatory response and expression of acute-phase proteins.[111]

Procalcitonin, a peptide precursor of the hormone calcitonin, is normally synthesized and released by thyroid parafollicular C cells and is widely researched as a promising biomarker for the initial investigation of bacterial infection.[112,113] Elevated PCT often occurs in sepsis and septic shock patients.[114] In the present meta-analysis, an increased level of PCT was found to be associated with severity and mortality in COVID-19 patients. Similarly, Lippi et al.[115] in their meta-analysis also demonstrated that increased PCT levels are associated with a 5-fold higher risk of severe COVID-19. During bacterial infection, the production and release of procalcitonin into the circulation from extra-thyroidal sources is greatly amplified, which is maintained by increased levels of IL-6, IL-1β, and TNF-α whereas the increased concentration of interferon-γ during viral infection is negatively impacting the synthesis of PCT.[112,116] This is why the level of PCT remains within the normal range in the majority of the patients with non-severe COVID-19 and increased value in severe COVID-19 may indicate secondary bacterial

infection.[115]

Elevated proinflammatory cytokine or chemokine responses induced immunopathology, described as a cytokine storm, has been involved in the pathogenesis of human coronavirus.[13] It is hypothesized that SARS-CoV-2 first binds to alveolar epithelial cells and then the virus triggers the innate immune system and the adaptive immune system, leading to the release of a substantial number of cytokines, including IL-6, which is a pleiotropic cytokine important in regulating immunological and inflammatory responses. Abnormally increased levels of such cytokines or chemokines can cause tissue damage, resulting in respiratory failure or multiple organ failure.[14,117–119] In addition to its strong proinflammatory function, IL-6 induces various acute-phase proteins, such as CRP, SAA, fibrinogen, antitrypsin, hepcidin, and components of complement to deteriorate inflammatory reactions and activate coagulation pathway with resultant disruption of procoagulant–anticoagulant homeostasis, induction of disseminated intravascular coagulation, and multi-organ failure.[120,121] Among various cytokines and chemokines (IL-2, IL-8, IL-17, GCSF, IP-10, and TNF-α) recognized, IL-6 has been considered as the most significant cytokines, which was found increased in both SARS and MERS, as well as in COVID-19.[122–126] In our meta-analysis, high IL-6 has been linked with both severity and mortality in COVID-19 patients. The importance of identifying this elevated biomarker also lies in the potential use of an antibody against IL-6 such as tocilizumab, which has been reported to effectively improve clinical symptoms and repress the deterioration of severe and critical patients.[127] Though IL-10 is an anti-inflammatory cytokine, a higher level of IL-10 was observed in the severe group compared to the non-severe group. Furthermore, higher IL-10 was also associated with mortality in COVID-19.[17] This increased level of IL-10 may be because of the compensatory anti-inflammatory response.[111] The present metaanalysis revealed association of higher level of IL-2R with COVID-19 severity. Wang et al.[17] reported a higher level of IL-2R in non-survivors compared to survivors. Highly expressed IL-2R initiates autoreactive cytotoxic $CD8^+$ T-cell–mediated autoimmunity. In the meantime, IL-2 promotes the proliferation of natural killer cells that strongly express IL-2R, facilitating the release of cytokines, which further induces the deadly "cytokine storm".[128] Another potential proinflammatory biomarker for COVID-19 is TNF-α, which facilitates the apoptosis of both lung epithelial cells and endothelial cells, leading to vascular leakage, alveolar edema, and hypoxia.[13] It also mediates airway hyper-responsiveness and pathogenesis in influenza and SARS-CoV infection.[129] In our meta-analysis, no significant difference was observed in the level of TNF-α between severe and non-severe COVID-19 groups. The possible reason for this insignificant difference could be due to insignificant difference in the level of TNF-α between severe and non-severe groups in 4 studies[58,63,64,80] and a significant decrease in the level of TNF-α in the severe group compared to the non-severe group in 1 study.[16] However, 2 studies[15,57] revealed a significant increase in TNF-α in the severe group compared to the non-severe group.

Serum ferritin is an acute-phase protein, which can be used as a prognostic marker for tissue damage or acute infections.[130] Patients with COVID-19 in the severe group had a higher level of serum ferritin than those in the non-severe group. Furthermore, in our metaanalysis, a higher serum ferritin level was associated with mortality in COVID-19 patients. Though the pathophysiological background responsible for the association of hyperferritinemia and disease severity in patients with COVID-19 is not clearly grasped, it is suggested that hyperferritinemia in COVID-19 patients is most likely due to the cytokine storm and a secondary hemophagocytic lymphohistiocytosis.[131] Serum amyloid A is a non-specific acute phase protein primarily produced in hepatocytes by cytokines IL-1 β, IL-6, and TNF- α, and can be used as a prognostic marker for tissue injury or acute infections.[132–135] It can promote inflammatory responses even at very low concentrations by activating chemokines and inducing chemotaxis.[136,137] The level of SAA was found to be positively associated with the degree of pneumonia in SARS.[138] Similarly, compared to the non-severe group, a significantly higher SAA level was observed in the severe group. Serum amyloid A was also found to be associated with mortality in COVID-19 and the increased SAA in non-survivors indicated the progressive immune-mediated damage in dead patients.[14] Studies reported that severe/critical COVID-19 patients had large amounts of IL-1 β, IFN- γ, IP-10, MCP-1, MIP-1, TNF- α, and other cytokines present in the system, which boost liver cells to produce SAA.[39,139]

Neutrophil-to-lymphocyte ratio (NLR) is the most well established inflammatory marker that reflects systemic inflammatory response and is easily obtainable through routine blood count analysis.[140] Several COVID-19 patients had increased neutrophil counts and decreased lymphocyte counts during the severe phase of COVID-19 infection.[141] Recently, the meta-analysis conducted by Lagunas-Rangel[142] showed that the NLR values were significantly associated with the severity of COVID-19. Similarly, in our meta-analysis, elevated NLR was associated with severity and mortality in COVID-19 patients. This increased NLR reflects the enhanced inflammatory process in severe/critical COVID-19 patients. Therefore, the detection of NLR levels in COVID-19 patients may help in assessing disease severity.

This systematic review and meta-analysis had several limitations that should be addressed. First, we have excluded articles published in foreign languages and the articles in which the data were not presented as mean (standard deviation, SD) or median (interquartile range, IQR, or range), which may have introduced bias in the results. Second, we have converted non-normally distributed data to normally distributed data, which may have biased the results. Third, the majority of included studies were from China, which limits the generalizability of the results. Fourth, most of the included studies were retrospective and observational; therefore, the results obtained must be interpreted with caution. Lastly, substantial heterogeneity exists in almost all meta-analyses.

5. Conclusion

In conclusion, our systematic review and meta-analysis showed significant increased serum concentrations of CRP, ESR, PCT, IL-6, IL-10, IL-2R, ferritin, SAA, and NLR in severe COVID-19 patients when compared to those with non-severe COVID-19 patients. Similarly, we found significant increased levels of CRP, PCT, IL-6, ferritin, and NLR in non-survivors as compared to survivors. These inflammatory parameters could help the physicians to rapidly identify severe COVID-19 patients, hence facilitating the early initiation of effective treatment. In addition, these inflammatory parameters could be used to predict the transition from mild to severe/critical infection in patients of COVID-19.

Authorship statement

R.K. Mahat contributed to the concept, design, methodology, analysis, interpretation, supervision, writing, reviewing and editing. S. Panda contributed to the methodology, interpretation, writing, reviewing and editing. V. Rathore contributed to the methodology, analysis, interpretation, writing, reviewing and editing. S. Swain contributed to the methodology, supervision, reviewing and editing. L. Yadav contributed to the methodology, reviewing and editing. S.P. Sah contributed to the methodology, reviewing and editing.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cegh.2021.100727.

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