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Systematic Review in Immunology

Associations between Interleukin-4 and COVID-19 severity: A systematic review and meta-analysis

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Abstract

Introduction: This systematic review and meta-analysis aimed to determine the correlation between IL-4 concentrations and COVID-19 severity.

Methods: This study was designed as a systematic review and meta-analysis and was performed in accordance to the PRISMA statement. Titles, abstracts, and full texts of articles were independently reviewed by at least 2 authors. Continuous variables were compared by the mean difference (MD) with 95% confidence interval (CI).

Results: Thirty-three studies reported IL-4 levels among severe versus non-severe COVID-19 patients. Pooled analysis showed that levels of IL-4 among those groups varied and amounted to 2.72 ± 3.76 pg/mL *vs* 3.08 ± 4.14 pg/mL (MD = -0.26; 95%CI: -0.43 to -0.10; p = 0.002. In addition, eight studies reported levels of IL-4 among COVID-19 patients who survived *vs* deceased and was 2.61 ± 0.49 pg/mL *vs* (3.44 ± 16.4 pg/mL, respectively (MD = 0.22; 95%CI: 0.08 to 0.37; p = 0.002).

Discussion: This detailed systematic review and meta-analysis revealed that the plasma concentration of IL-4 is a potential risk factor for COVID-19 severity and mortality. Specifically, old age and male gender were associated with high IL-4 levels. Lung damage could result from the change in IL-4 concentration, thus making critical and severe COVID-19 cases at a very high risk of dying, thereby reducing their quality of life. Therefore, strategies such as using monoclonal antibodies to inhibit Th2 cytokines could be explored in developing an effective treatment regimen for COVID-19 patients.

Take-home message: An independent risk factor for the severity and fatality of COVID-19 is the plasma levels of IL-4. High IL-4 levels are specifically related to old age and male gender. Lung damage may be a result of the change in IL-4 concentration, placing COVID-19 critically and severely ill at a high risk of dying.

Keywords: Interleukin-4; IL-4; COVID-19; SARS-CoV-2; COVID-19 severity.

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INTRODUCTION

Immune responses have been shown to contribute to the onset and progression of COVID-19, and cytokine storms may worsen the prognosis for COVID-19 patients [1–3]. A generalized host inflammatory response occurs with severe sickness, regardless of the underlying cause [4,5]. Fibroblasts, mononuclear macrophages, and T-lymphocytes produce most cytokines, which can then act on these cells [6]. Inflammation may also be brought on by the interactions between these cytokines [7]. Inflammatory substances such as interleukin (IL), colony-stimulating factor, chemokines, interferons, tumor necrosis factors, chemokines, and growth factors are typically increased in severe and critical COVID-19 patients [8,9]. Cytokine storm syndrome will result from a poorly managed or dysfunctional version of this process. In their research, Mehta and colleagues suggested that immunosuppression may be a treatment option for COVID-19 patients and that

cytokine storm syndrome may be related to the severity of an individual's COVID-19 status [10,11]. Serum interleukin levels significantly rose in severe and critical patients compared to mild COVID-19 cases, thus causing lung injury and acute respiratory distress. However, this does not connote that mild cases are not at risk for poor health outcomes [12–15]. Furthermore, there have been notable differences in cytokine profiles between COVID-19 patient survivors and non-survivors [16].

The cytokine storm and abnormal immune system have been noted, with leukocytes, neutrophils, infection biomarkers, and the concentrations of cytokines [interleukin (IL)-2R, IL-6, IL-8, IL-10, and tumor necrosis factor (TNF)-] being significantly higher in patients with SARS-CoV-2 infection [17,18]. These abnormal immune system changes include a decrease in the total number of T- and CD4+ cells [17]. The worse infection prognosis, the heightened inflammatory response, and the stimulation of the cytokine storm could all be explained by the consumption of CD^{4+} and CD^{8+} T cells [19].

Chang and colleagues conducted a systematic review investigating the associations between serum interleukins (IL-1β, IL-2, IL-4, IL-6, IL-8, and IL-10) and COVID-19 severity reported elevated levels of IL-6, IL-8, and IL-10 were associated with COVID-19 severity. In contrast, elevated levels of IL-1β, IL-6, and IL-8 were associated with poor COVID-19 prognosis [3]. No significant difference was found in IL-1β, IL-2, and IL-4 levels between severe and non-severe COVID-19 patients [3]. As the effector and inducer of this immunological mechanism, IL-4, the primary cytokine of the Th2 immune response, is crucial to the Th2 pathway. IL-4 and IL-13 are both primarily linked to fibrogenic inflammatory remodelling, whereas Th1 cells produce gamma interferon (IFN-) and IL-2 to inhibit fibrosis [20].

Some works of literature have reported significant associations between IL-6, IL-10, and IL-13; however, there exists a paucity of evidence on the existence of a significant association between IL-4 plasma concentrations and COVID-19 severity [20–23]. Therefore, it becomes crucial to compare the IL-4 load in the sera of patients with COVID-19 with those of healthy and recovered individuals to further understand the cellular mechanism behind the pathogenicity of COVID-19. Thus, this systematic review and meta-analysis aimed to determine the correlation between IL-4 concentrations and COVID-19 severity.

METHODS

This study was designed as a systematic review and meta-analysis and was performed according to the recommendations of the Cochrane Collaboration Group [24] and the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [25].

Search strategy and study selection

Two authors (M.M. and M.P.) independently performed the literature search. PubMed Central, Scopus, EMBASE and Cochrane Collaboration Library were used for a comprehensive search of relevant studies from January 2020 to September 10, 2022. We used the following search terms: "Interleukin-4" OR "IL-4" AND "SARS-CoV-2" OR "novel coronavirus" OR "COVID-19". Additionally, the reference lists of included papers were also manually searched for additional studies. Titles, abstracts, and full texts of articles identified from database search were imported into EndNote X9 (Clarivate Analytics, Philadelphia, USA).

Inclusion and exclusion criteria

The adopted inclusion criteria were as follows: (1) original articles; (2) COVID-19 patients in different clinical conditions: mild, moderate, severe or critical; (3) COVID-19 patients who survived hospital discharge or died on admission; (4) all types of observational studies: cohort, cross-sectional, case-control, longitudinal; (5) full-text articles published in English. Exclusion criteria were as follows: (1) studies, which did not meet the above criteria, (2) letters, posters, editorials, review articles and meta-analyses.

Data extraction

The data extraction exercise was conducted by two authors (M.P. and M.M.), and disagreements concerning the selection criteria were discussed and resolved by consensus, including six authors (A.A.A., O.S.I., F.C., M.B., M.A.-J. and L.S). Data were extracted from the included studies using a predefined form.

Quality assessment

Three authors (M.M., A.N. and M.P.) independently completed the quality assessment. Any disagreements were also resolved by discussion with the third reviewer (L.S.). We used the Newcastle-Ottawa scale (NOS) to assess the methodological quality of observational studies with its design. According to the NOS criteria, the studies were rated low, moderate, and high quality in accordance with the scores, 0–3, 4–6 and 7–9, respectively. Additionally, we performed funnel plot tests for asymmetry to investigate potential publication bias if there were more than 10 trials in a single meta-analysis.

Statistical analysis

All the meta-analyses were performed using the STATA software (version 14, StataCorp LLC, College Station, TX, USA) and the RevMan software (version 5.4, The Cochrane Collaboration, Copenhagen, Denmark). Mean differences (MD) and 95% confidence intervals (CIs) were calculated to build forest plots of continuous data and evaluate differences in IL-4 concentrations between COVID-19 patients with severe *vs* non-severe groups or survivor *vs* non-survivor status during follow-up. P-values of <0.05 were considered to indicate statistical significance. In situations where IL-4 levels were reported as median with interquartile range, estimated means and standard deviations with the formula described by Hozo were used [26]. We evaluated heterogeneity between studies using the p-value of the Q-test and the I^2 statistic. I^2 of <50% was considered low or moderate heterogeneity, and a fixed-effects model was used. We additionally performed a sensitivity analysis to evaluate the influence of any given study on the pooled estimate.

RESULTS

Study characteristics

Based on the above-mentioned inclusion criteria, we identified 5,722 reports and screened their summaries for eligibility after removing duplicates. Overall, 1,394 articles were screened according to the titles and abstracts. Full-text screening was performed on 55 studies, and data for 39 studies [27–66] were extracted for this meta-analysis. A flow chart of the literature search and study selection is presented in Figure 1. Thirty-three studies reported the IL-4 values among severe vs. non-severe COVID-19 patients. Eight studies reported the correlation coefficient between IL-4 concentration and COVID-19 survivability.

The systematic review included articles published between 2020 and 2022, comprising 8,722 COVID-19 participants. The baseline characteristics of selected studies are presented in Table 1. The study quality assessed using the NOS scores was ≥7 for all included trials (Table 1).

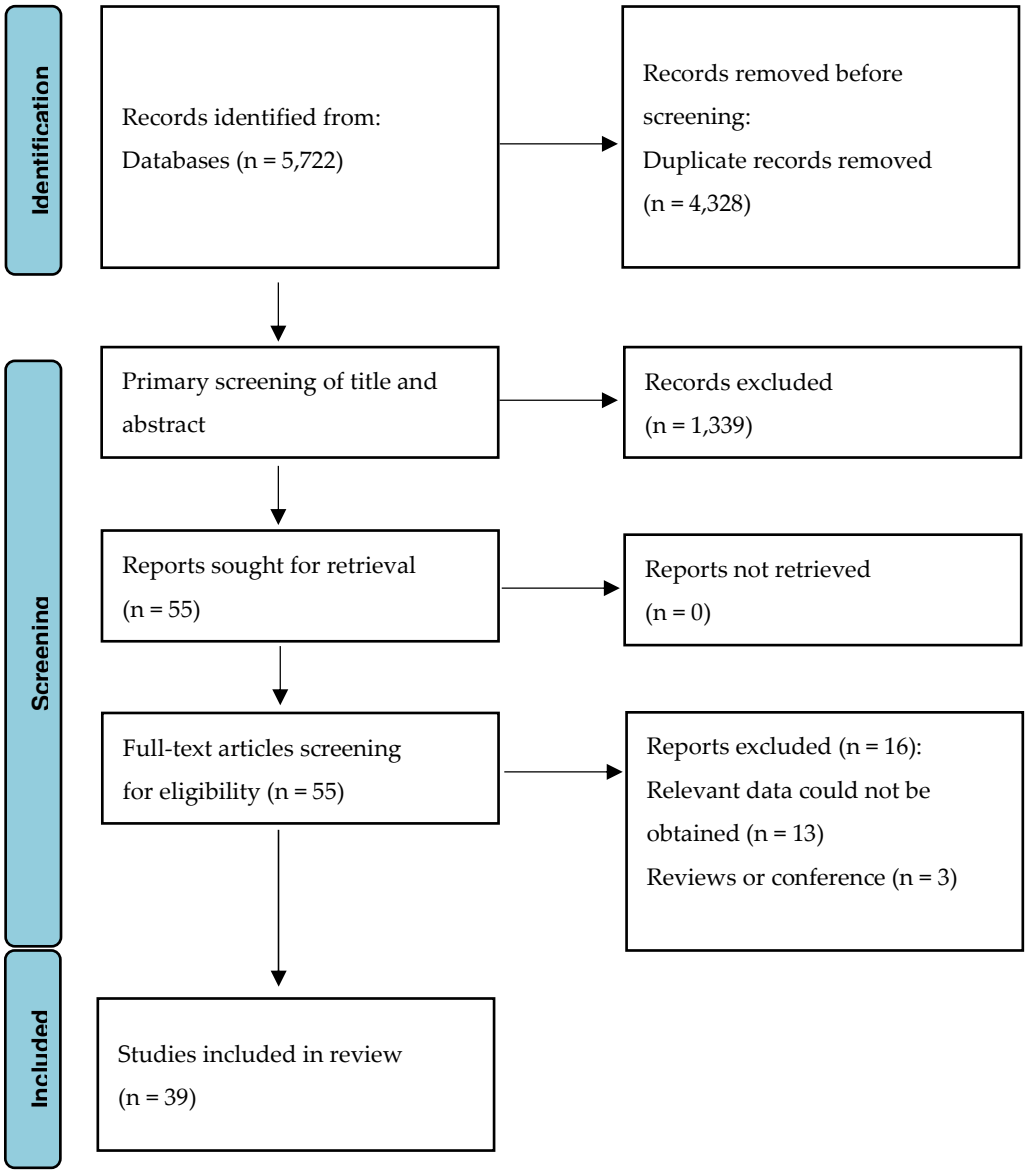

Figure 1. Flowchart detailing selection and screening of the studies included in this review.

Table 1. Baseline characteristics of included trials.

Study and year	*Country*	*Study group*	*No. of patients*	*Age (ys)*	*Sex, male*	*IL-4, pg/mL*	*NOS score*
Akinosoglou et al, 2022 [27]	Greece	Severe	9	61.5 ± 28	6 (66.7%)	4.9 ± 24.9	7
		Non-severe	18	63.0 ± 19	9 (50.0%)	0.0 ± 17.8	
Belaid et al, 2022 [28]	Algeria	Severe	26	66.8 ± 12.3	21 (80.8%)	0.67 ± 0.38	8
		Non-severe	31	53.7 ±14.4	19 (61.3%)	1.05 ± 0.38	
		Survival	42	NS	NS	1.01 ± 0.37	
		Death	15	NS	NS	0.64 ± 0.35	
Cabaro et al, 2021 [29]	Italy	Severe	19	67.5 ± 4.0	15 (78.9%)	3.44 ± 0.58	9
		Non-severe	46	57.8 ± 5.8	27 (58.7%)	3.59 ± 0.79	
Chi et al, 2020 [30]	China	Severe	8	54.0 ±12.3	5 (62.5%)	0.09 ± 0.95	8
		Non-severe	58	41.8 ± 14,5	32 (55.2%)	9.35 ± 1.16	
Gadotti et al, 2020 [31]	Brazil	Survival	38	56.8 ± 7.3	23 (60.5%)	1.65 ± 0.15	8
		Death	18	66.3 ± 5.3	16 (88.9%)	1.53 ± 0.18	
Gao et al, 2021 [32]	China	Severe	32	54.3 ± 11.4	20 (62.5%)	1.3 ± 1.0	9
		Non-severe	135	48.1 ± 13.7	51 (37.8%)	1.6 ± 0.9	
Gil-Etayo et al, 2021 [33]	Spain	Survival	46	53 ± 4.5	30 (65.2%)	2.44 ± 1.25	7
		Death	9	87 ± 2.8	7 (77.8%)	96.33 ± 109.65	
He et al, 2020 [34]	China	Severe	33	43.6 ± 10.4	18 (54.5%)	1.52 ± 0.91	8
		Non-severe	60	36.3 ± 8.0	31 (51.7%)	1.67 ± 1.06	
He et al, 2020 [35]	China	Severe	69	62.0 ± 5.5	37 (53.6%)	4.30 ± 0.27	9
		Non-severe	135	42,5 ± 3.7	42 (31.1%)	3.76 ± 0.03	
Hu et al, 2020 [36]	China	Severe	13	61.5 ± 2.5	8 (61.5%)	1.03 ± 0.29	8
		Non-severe	63	48.2 ± 1.1	26 (41.3%)	1.30 ± 0.23	
Jin et al, 2021 [37]	China	Severe	40	55.5 ± 15	19 (47.5%)	2.95 ± 2.44	9
		Non-severe	106	43.8 ± 12.8	58 (54.7%)	2.24 ± 0.98	
Lai et al, 2022 [38]	China	Survival	2,343	58.0 ± 3.3	1.072 (45.8%)	2.50 ± 0.30	8
		Death	212	69.5 ± 2.7	150 (70.8%)	2.12 ± 0.18	
Li et al, 2020 [39]	China	Survival	1,327	54.0 ± 4.0	643 (48.5%)	3.0 ± 0.33	8
		Death	122	69.8 ± 2.5	90 (73.8%)	2.5 ± 0.33	
Liao, 2020 [40]	China	Severe	231	67.7 ± 3.0	137 (59.3%)	2.16 ± 0.19	9
		Non-severe	149	55.3 ± 4.3	69 (46.3%)	2.05 ± 0.15	
Ling et al, 2021 [41]	China	Severe	17	64.0 ± 3.5	11 (64.7%)	2.15 ± 1.30	8
		Non-severe	15	47.5 ± 8.5	4 (26.7%)	4.72 ± 2.55	

Liu et al, 2020 [42]	China	Severe	92	62.8 ± 2.8	62 (67.4%)	1.30 ± 0.22	8
		Non-severe	202	50.8 ± 4.7	100 (49.5%)	1.48 ± 0.25	
Liu et al, 2021 [43]	China	Severe	57	64.7 ± 3.8	33 (58.8%)	2.71 ± 0.75	9
		Non-severe	10	44.4 ± 7.6	6 (60.0%)	2.9 ± 0.61	
Lv et al, 2020 [44]	China	Severe	239	61.1 ± 10.4	117 (49.0%)	3.51 ± 1.76	9
		Non-severe	115	56.0 ± 9.3	58 (50.4%)	4.61 ± 12.11	
Meng et al, 2021 [45]	China	Severe	27	51.8 ± 5.8	17 (63.0%)	2.68 ± 1.65	8
		Non-severe	71	44.0 ± 3.0	38 (53.5%)	2.07 ± 1.0	
Nie et al, 2020 [46]	China	Severe	25	57.5 ± 5.0	13 (52.0%)	4.45 ± 0.29	8
		Non-severe	72	39.5 ± 4.3	21 (29.1%)	4.2 ± 0.34	
Ozger et al, 2021 [47]	Turkey	Survival	29	58.1 ± 7.4	20 (69.0%)	0.93 ± 0.33	8
		Death	8	78.9 ± 5.7	4 (50.0%)	0.75 ± 0.27	
Queiroz et al, 2022 [48]	Brazil	Severe	91	NS	51 (56.0%)	8.04 ± 5.72	7
		Non-severe	226	NS	95 (42.0%)	9.31 ± 5.72	
Qun et al, 2020 [49]	Cbina	Severe	40	67.9 ± 16.9	25 (62.5%)	2.07 ± 1.01	8
		Non-severe	190	59.4 ± 13.4	73 (38.4%)	2.03 ± 1.18	
Ren et al, 2021 [50]	China	Severe	59	NS	NS	1.68 ± 0.23	7
		Non-severe	21	NS	NS	1.68 ± 0.23	
Rutkowska et al, 2021 [51]	Poland	Severe	15	59.1 ± 12.0	14 (93.3%)	0.13 ± 0.25	7
		Critical	23	54.9 ± 14.4	8 (34.8%)	0.18 ± 0.18	
Shi et al, 2020 [52]	China	Severe	29	NS	21 (72.4%)	1.14 ± 0.3	8
		Non-severe	119	NS	71 (59.7%)	0.70 ± 0.29	
Song et al, 2020 [53]	China	Severe	42	55.8 ± 4.1	30 (71.4%)	1.7 ± 0.24	8
		Non-severe	31	48.0 ± 5.5	16 (51.6%)	1.65 ± 0.27	
Wan et al, 2020 [54]	China	Severe	21	61.2 ± 15.5	NS	1.83 ± 0.19	7
		Non-severe	102	43.0 ± 13.1	NS	1.69 ± 0.07	
Wang et al, 2021 [55]	China	Severe	100	63.0 ± 4.9	63 (63.0%)	0.39 ± 0.26	8
		Non-severe	111	46.5 ± 4.0	38 (34.2%)	0.83 ± 0.08	
Wei et al, 2020 [56]	China	Severe	121	69.9 ± 12.6	71 (58.7%)	3.46 ± 8.92	9
		Non-severe	131	60.1 ± 12.4	59 (45.0%)	2.60 ± 1.00	
Wu et al, 2020 [57]	China	Severe	39	62.5 ± 4.5	27 (69.2%)	0.16 ± 0.24	8
		Non-severe	32	54.0 ± 7.0	18 (56.2%)	0.27 ± 0.23	
Yang et al, 2020 [58]	China	Severe	24	57.9 ± 11.8	18 (75.0%)	1.75 ± 0.89	8
		Non-severe	69	42.1 ± 18.6	38 (55.1%)	2.67 ± 1.94	
Yin et al, 2021 [59]	China	Severe	11	NS	5 (45.5%)	3.40 ± 1.10	7
		Non-severe	26	NS	13 (50.0%)	3.80 ± 1.80	
Yuan et al, 2020 [60]	China	Severe	56	68.3 ± 5.4	26 (46.4%)	2.94 ± 0.58	8
		Non-severe	61	63.3 ± 4.3	30 (49.2%)	2.93 ± 0.55	
Zhang et al, 2020 [61]	China	Severe	14	61.7 ± 9.2	5 (35.7%)	1.03 ± 0.37	8
		Non-severe	29	44.3 ± 15.8	17 (58.6%)	0.79 ± 0.39	
Zhang et al, 2020 [62]	China	Survival	93	37.5 ± 2.8	32 (34.4%)	1.95 ± 0.12	8
		Death	18	62.5 ± 8.3	14 (77.8%)	1.97 ± 0.27	

Zhang et al, 2020 [63]	Italy	Severe	67	NS	NS	3.29 ± 0.32	7
		Non-severe	81	NS	NS	3.44 ± 0.42	
Zheng et al, 2020 [64]	China	Severe	74	56.9 ± 3.1	49 (66.2%)	0.85 ± 0.03	7
		Non-severe	22	47 ± 5.6	9 (40.9%)	0.90 ± 0.20	
Zhu et al, 2020 [65]	China	Severe	16	57.5 ± 11.7	9 (56.3%)	1.99 ± 0.47	8
		Non-severe	111	49.9 ± 15.5	73 (65.8%)	1.93 ± 0.19	
Zhu et al, 2021 [66]	China	Severe	17	56.8 ± 11.6	8 (47.1%)	1.92 ± 0.50	9
		Non-severe	125	48.0 ± 16.6	47 (37.6%)	1.84 ± 0.22	

Note:NS = Not specified

Thirty-three studies reported IL-4 levels among patients with severe vs. non-severe COVID-19 patients. Pooled analysis showed that levels of IL-4 among those groups varied and amounted to 2.72 ± 3.76 pg/mL vs. 3.08 ± 4.14 pg/mL (MD = -0.26; 95%CI: -0.43 to -0.10; p=0.002; Figure 2).

Eight studies reported levels of IL-4 among COVID-19 patients who survived vs. deceased. IL-4 levels among patients who survived were 2.61 ± 0.49 pg/mL and were statistically significantly lower than in the deceased group (3.44 ± 16.4 pg/mL; MD = 0.22; 95%CI: 0.08 to 0.37; p=0.002; Figure 3).

In addition, based on the available articles, we averaged the data on IL-4 levels and obtained IL-4 levels at 2.55 ± 0.4 pg/mL in the asymptomatic COVID-19 patients' group, 2.89 ± 5.16 pg/mL among mild COVID-19 patients' group, 2.76 ± 1.98 pg/mL in the moderate COVID-19 patients' group, 2.68 ± 3.33 pg/mL in the severe COVID-19 patients' group and 2.63 ± 5.85 pg/mL in the critical COVID-19 patients' group (Figure 4).

Sensitivity analysis based on the leave-one-out analysis showed that a single trial did not influence the pooled results. The above dependence applied to all comparisons included in the meta-analysis.

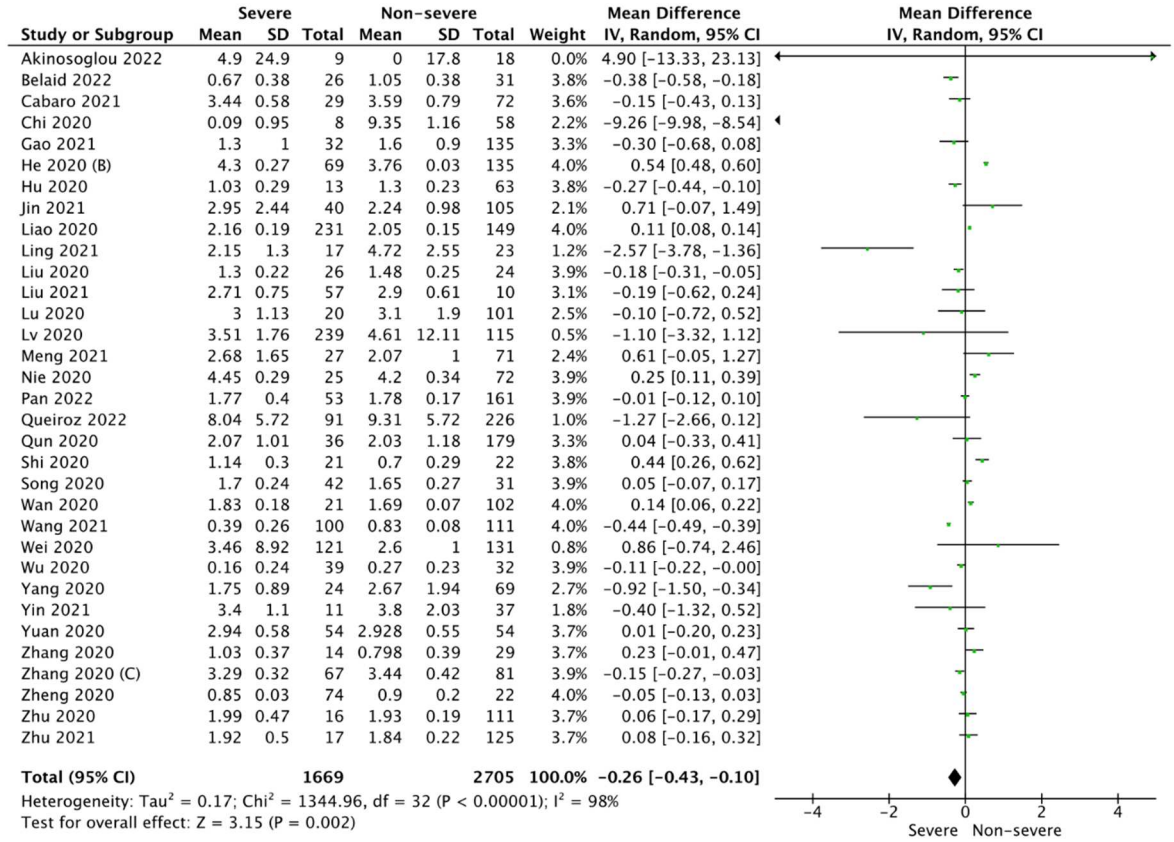

Figure 2. Forest plot of interleukin 4 levels among severe vs. non-severe COVID-19 patients. The center of each square represents the mean differences for individual trials, and the corresponding horizontal line stands for a 95% confidence interval. The diamonds represent pooled results.

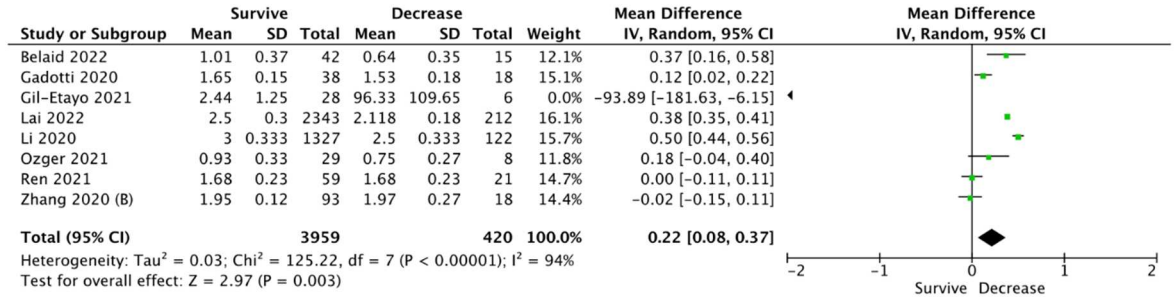

Figure 3. Forest plot of interleukin 4 levels among COVID-19 patients who survive vs. decrease. The center of each square represents the mean differences for individual trials, and the corresponding horizontal line stands for a 95% confidence interval. The diamonds represent pooled results.

DISCUSSION

This systematic review and meta-analysis found that COVID-19 alters IL-4 plasma concentration levels in COVID-19-positive individuals, regardless of symptomatology. We observed no remarkable difference in the plasma concentration of IL-4 in severe and non-severe COVID-19-positive cases. However, IL-4 levels were significantly lower among COVID-19 survivors compared to the deceased. It is also interesting to note that IL-4 plasma concentration was lowest in both severe and non-severe COVID-19 groups compared to the concentration of other cytokines [33]. These

findings are similar to the results of a clinical trial conducted among healthy, moderate, and severe COVID-19 patients enrolled from three public hospitals in the Erbil city, Kurdistan, Iraq where the recovery group had lower levels of IL-4 compared to the severe COVID-19 group [67]. Notably, treatment with antiviral medications did not effectively lower IL-4 concentration among COVID-19 cases presenting with mild symptoms [67], thus increasingly placing the individuals at risk for poor prognosis and likely mortality.

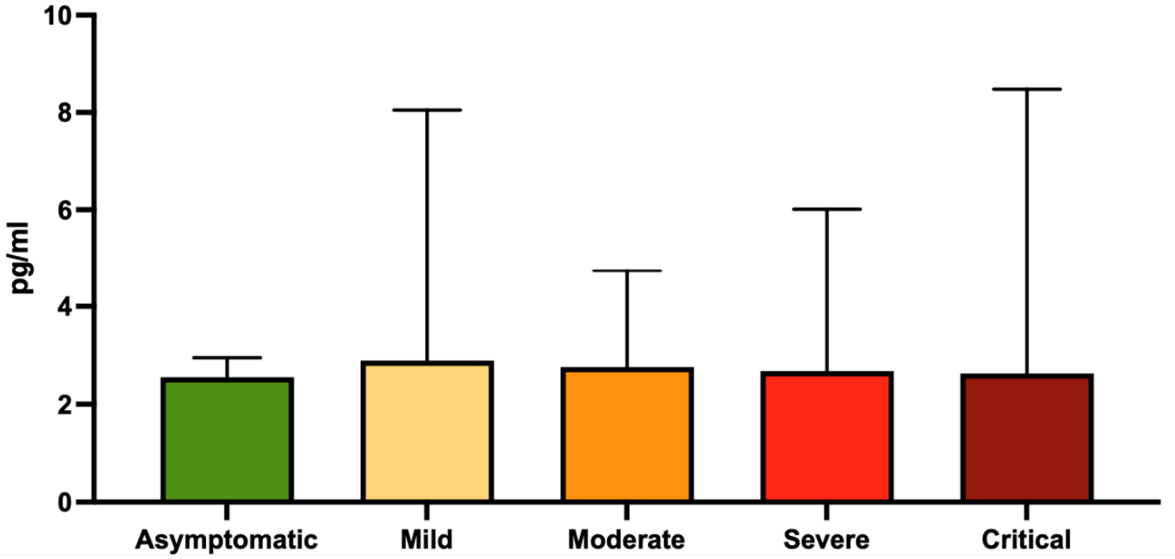

Figure 4. Mean interleukin 4 levels amond differen COVID-19 severity groups.

From this study, we identified that a large fraction of males had poor COVID-19 outcomes overall. In COVID-19 infection, male sex was found to be a risk factor for severe and critical illness and greater mortality [68–70]. Understanding the gender differences in COVID-19 outcomes is crucial for clinical care and remission strategies [68,71]. It is important to note that IL-4 has been demonstrated to activate various signalling pathways crucial for controlling cell growth. IL-1 activation inhibits several crucial cytokines that may be released by proinflammatory monocytes, preventing macrophages from becoming cytotoxic and even creating nitric oxide [72,73]. TNF-, IL-1, and PGE-2 are other inflammatory cytokines that are inhibited by the release and activation of IL-4, ultimately stimulating the IL-4 receptor [7]. LDL oxidation, which reduces inflammation, is also increased.

On the other hand, IL-4 can effectively activate JAK-STAT, causing infertility issues in men as one of its adverse effects. It has also been demonstrated that Th2 cells can activate this interleukin, stimulating the STAT signalling pathway to cause apoptosis [74]. However, if Th2 levels were increased, patients should undergo intensive treatment as SARS-CoV-2 has been observed to dramatically enhance Th2, Th1/Th17 cells, and antibody production in the body of patients with COVID-19 [71].

This study found that COVID-19-positive cases in severe and critical conditions belonged to older age groups compared to those in less severe conditions. Also, people who died due to COVID-19-related causes were older than the survived cohort. Literature suggests a higher prevalence of systemic pro-inflammatory cytokines and a reduced prevalence of systemic anti-inflammatory cytokines as people age [74,75]. As a result, "inflamme-aging"—a chronic inflammatory condition—

may develop in older subjects [74,75]. Numerous investigations have shown that older adults had higher levels of the inflammatory proteins IL-6, IL-1, tumor necrosis factor (TNF), and C-reactive protein (CRP) [76,77]. The precise cause of the cytokine storm in elderly persons with severe COVID-19 infection is not yet known [78]. The likelihood of a cytokine storm and subsequent acute respiratory distress syndrome in some elderly patients with severe COVID-19 infection, however, is probably significantly influenced by disruption of the cytokine homeostasis in the "inflamme-aging" phenomena [79]. The inflammatory phenotype of senescent cell activity, particularly in adipose tissue, immune-senescence, and lack of vitamin D content, as well as age-related pathophysiologic processes, are associated with the "cytokine storm" phenomenon in elderly patients with severe COVID-19 infection [80–84]. These processes include altered angiotensin-converting enzyme 2 (ACE2) receptor expression, excess ROS production, and altered autophagy [85,86].

Strengths and limitations

A solid point of our study is the comprehensive inclusion of all previous research on the subject of IL-4 in the disease, which is COVID-19, as well as a detailed analysis of all related factors, thus providing current evidence required for improving the management of COVID-19-positive patients. However, there are some limitations to the study. The considerable heterogeneity of the studies included in the meta-analysis and the observational character of the studies are the first and most significant limitations (retrospective analysis). Another drawback might be that some drugs affect the amounts of circulating biomarkers and influence the prognosis for COVID-19. As a result, it is important to reconsider the same biomarkers in light of the current treatments. Another problem is the small patient populations in the studies that made up the meta-analysis.

CONCLUSION

This detailed systematic review and meta-analysis revealed that the plasma concentration of IL-4 is a potential risk factor for COVID-19 severity and mortality. Specifically, old age and male gender were associated with high IL-4 levels. Lung damage could result from the change in IL-4 concentration, thus placing critical and severe COVID-19 cases at a very high risk of dying, thereby reducing their quality of life. Therefore, strategies such as using monoclonal antibodies to inhibit Th2 cytokines could be explored in developing an effective treatment regimen for COVID-19 patients.

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References

1. Ragab D, Eldin HS, Taeimah M, Khattab R, Salem R. The COVID-19 Cytokine Storm; What We Know So Far. Front Immunol. 2020;11:1446.
2. Hojyo S, Uchida M, Tanaka K, Hasebe R, Tanaka Y, Murakami M, et al. How COVID-19 induces cytokine storm with high mortality. Inflamm Regen. 2020;40(1):37.
3. Chang Y, Bai M, You Q. Associations between Serum Interleukins (IL-1β, IL-2, IL-4, IL-6, IL-8, and IL-10) and Disease Severity of COVID-19: A Systematic Review and Meta-Analysis. Biomed Res Int. 2022; 2755246.
4. Chen L, Deng H, Cui H, Fang J, Zuo Z, Deng J, et al. Inflammatory responses and inflammation-associated diseases in organs. Oncotarget. 2017; 9(6):7204–7218.
5. Katipoğlu B, Sönmez LO, Vatansev H, Yüce N, Sabak M, Szarpak L, et al. Can hematological and biochemical parameters fasten the diagnosis of COVID-19 in emergency departments? Disaster Emerg Med J. 2020; 5(4):175–181.
6. Fialek B, Yanvarova O, Pruc M, Gasecka A, Skrobucha A, Boszko M, et al. Systematic review and meta-analysis of serum amyloid a prognostic value in patients with COVID-19. Disaster Emerg Med J. 2022; 7(2):107–113.
7. Kany S, Vollrath JT, Relja B. Cytokines in Inflammatory Disease. Int J Mol Sci. 2019;20(23):6008.
8. Costela-Ruiz VJ, Illescas-Montes R, Puerta-Puerta JM, Ruiz C, Melguizo-Rodríguez L. SARS-CoV-2 infection: The role of cytokines in COVID-19 disease. Cytokine Growth Factor Rev. 2020;54:62–75.
9. Yaman E, Demirel B, Yilmaz A, Avci S, Szarpak L. Retrospective evaluation of laboratory findings of suspected paediatric COVID-19 patients with positive and negative RT-PCR. Disaster Emerg Med J. 2021;6(3):97–103.
10. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. 2020; 395(10229):1033–1034.
11. Szarpak Ł, Nowak B, Kosior D, Zaczynski A, Filipiak KJ, Jaguszewski MJ. Cytokines as predictors of COVID-19 severity: evidence from a meta-analysis. Pol Arch Intern Med. 2021;131(1):98-99.
12. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497–506.
13. Chirico F, Nucera G, Ilesanmi OS, Afolabi AA, Pruc M, Szarpak Ł. Identifying asymptomatic cases during the mass COVID-19 vaccination campaign: insights and implications for policy makers. Future Virol. 2021;17(2):141–144.
14. Szarpak Ł, Nucera G, Pruc M, Ilesanmi OS, Afolabi AA, Chirico F. Point-of-care testing as the future of pre-hospital emergency medicine: an overview. Signa Vitae. 2021;18(3):153–157.
15. Chirico F, Nowrouzi-Kia B. Post-COVID-19 Syndrome and new challenges posed by climate change require an interdisciplinary approach: The role of occupational health services. J Health Soc Sci. 2022; 7(2):132–136.
16. Sánchez-de Prada L, Gorgojo-Galindo Ó, Fierro I, Martínez-García AM, de Quintana GS, Gutiérrez-Bustillo R, et al. Time evolution of cytokine profiles associated with mortality in COVID-19 hospitalized patients. Front Immunol. 2022; 13:946730.
17. Skevaki C, Fragkou PC, Cheng C, Xie M, Renz H. Laboratory characteristics of patients infected with the novel SARS-CoV-2 virus. J Infect. 2020; 81(2):205–212.
18. Han H, Ma Q, Li C, Liu R, Zhao L, Wang W, et al. Profiling serum cytokines in COVID-19 patients

reveals IL-6 and IL-10 are disease severity predictors. Emerg Microbes Infect. 2020; 9(1):1123–1130.

19. Nidadavolu LS, Walston JD. Underlying Vulnerabilities to the Cytokine Storm and Adverse COVID-19 Outcomes in the Aging Immune System. J Gerontol A Biol Sci Med Sci. 2021; 76(3):e13-e18.
20. Vaz de Paula CB, de Azevedo MLV, Nagashima S, Martins APC, Malaquias MAS, Miggiolaro AFRDS, et al. IL-4/IL-13 remodeling pathway of COVID-19 lung injury. Sci Rep. 2020; 10(1):18689.
21. Darif D, Hammi I, Kihel A, El Idrissi Saik I, Guessous F, Akarid K. The pro-inflammatory cytokines in COVID-19 pathogenesis: What goes wrong? Microb Pathog. 2021; 153:104799.
22. Liu QQ, Cheng A, Wang Y, Li H, Hu L, Zhao X, et al. Cytokines and their relationship with the severity and prognosis of coronavirus disease 2019 (COVID-19): a retrospective cohort study. BMJ Open. 2020; 10:e041471.
23. Tapela K, Oyawoye F, Ochieng'Olwal C, Opurun PC, Amponsah JA, Lumor Segedzi KA, et al. Probing SARS-CoV-2-positive plasma to identify potential factors correlating with mild COVID-19 in Ghana, West Africa. BMC Med. 2022;20:370.
24. Higgins JPT, Thomas J, eds. Cochrane handbook for systematic reviews of interventions version 6.0 [updated 2019 Jul]. Cochrane; 2019 [cited 2022 Sep 10]. Available from: www.training.cochrane.org/handbook.
25. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Rev Esp Cardiol (Engl Ed). 2021; 74(9):790–799.
26. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol. 2005;5:13.
27. Akinosoglou K, Delastic AL, Dimakopoulou V, Marangos M, Gogos C. Elements of Th1/Th2 response and disease severity in COVID-19 patients: A short report. J Med Virol. 2022;94(1):404–406.
28. Belaid B, Lamara Mahammad L, Mihi B, Rahali SY, Djidjeli A, et al. T cell counts and IL-6 concentration in blood of North African COVID-19 patients are two independent prognostic factors for severe disease and death. J Leukoc Biol. 2022;111(1):269–281.
29. Cabaro S, D'Esposito V, Di Matola T, Sale S, Cennamo M, Terracciano D, et al. Cytokine signature and COVID-19 prediction models in the two waves of pandemics. Sci Rep. 2021;11(1):20793.
30. Chi Y, Ge Y, Wu B, Zhang W, Wu T, Wen T, et al. Serum Cytokine and Chemokine Profile in Relation to the Severity of Coronavirus Disease 2019 in China. Infect Dis. 2020;222(5):746–754.
31. Gadotti AC, de Castro Deus M, Telles JP, Wind R, Goes M, Garcia Charello Ossoski R, et al. IFN-γ is an independent risk factor associated with mortality in patients with moderate and severe COVID-19 infection. Virus Res. 2020;289:198171.
32. Gao Y, Li T, Han M, Li X, Wu D, Xu Y, et al. Diagnostic utility of clinical laboratory data determinations for patients with the severe COVID-19. J Med Virol. 2020;92(7):791–796.
33. Gil-Etayo FJ, Suàrez-Fernández P, Cabrera-Marante O, Arroyo D, Garcinuño S, Naranjo L, et al. T-Helper Cell Subset Response Is a Determining Factor in COVID-19 Progression. Front Cell Infect Microbiol. 2021;11:624483.
34. He S, Zhou C, Lu D, Yang H, Xu H, Wu G, et al. Relationship between chest CT manifestations and immune response in COVID-19 patients. Int J Infect Dis. 2020;98:125–129.
35. He R, Lu Z, Zhang L, Fan T, Xiong R, Shen X, et al. The clinical course and its correlated immune status in COVID-19 pneumonia. J Clin Virol. 2020;127:104361.

36. Hu ZJ, Xu J, Yin JM, Li L, Zhang LL, Zhou Z, et al. Lower Circulating Interferon-Gamma Is a Risk Factor for Lung Fibrosis in COVID-19 Patients. Front Immunol. 2020;11:585647.
37. Jin XH, Zhou HL, Chen LL, Wang GF, Han QY, Zhang JG, et al. Peripheral immunological features of COVID-19 patients in Taizhou, China: A retrospective study. Clin Immunol. 2021;222:108642.
38. Lai X, Deng S, Hu L, Chen R, Chen M, Liang M, et al. J-shaped associations and joint effects of fasting glucose with inflammation and cytokines on COVID-19 mortality. Int J Infect Dis. 2022;122:285–294.
39. Li Q, Cao Y, Chen L, Wu D, Yu J, Wang H, et al. Hematological features of persons with COVID-19. Leukemia. 2020;34:2163–2172.
40. Liao D, Zhou F, Luo L, Xu M, Wang H, Xia J, et al. Haematological characteristics and risk factors in the classification and prognosis evaluation of COVID-19: a retrospective cohort study. Lancet Haematol. 2020;7(9):e671–e678.
41. Ling L, Chen Z, Lui G, Wong CK, Wong WT, Ng RWY, et al. Longitudinal Cytokine Profile in Patients With Mild to Critical COVID-19. Front Immunol. 2021;12:763292.
42. Liu L, ZhengY, Cai L, Wu W, Tang S, Ding Y, et al. Neutrophil-to-lymphocyte ratio, a critical predictor for assessment of disease severity in patients with COVID-19. Int J Lab Hematol. 2021;43(2):329–335.
43. Liu Y, Tan W, Chen H, Zhu Y, Wan L, Jiang K, et al. Dynamic changes in lymphocyte subsets and parallel cytokine levels in patients with severe and critical COVID-19. BMC Infectious Diseases 2021; 21:79.
44. Lv Z, Cheng S, Le J, Huang J, Feng L, Zhang B, et al. Clinical characteristics and co-infections of 354 hospitalized patients with COVID-19 in Wuhan, China: a retrospective cohort study. Microbes Infect. 2020;22(4-5):195-199.
45. Meng Z, Wang M, Zhao Z, Zhou Y, Wu Y, Guo S, et al. Development and Validation of a Predictive Model for Severe COVID-19: A Case-Control Study in China. Front Med (Lausanne). 2021; 8:663145.
46. Nie S, Zhao X, Zhao K, Zhang Z, Zhang Z, Zhang Z. Metabolic disturbances and inflammatory dysfunction predict severity of coronavirus disease 2019 (COVID-19): a retrospective study. medRxiv 2020. Doi: 10.1101/2020.03.24.20042283.
47. Ozger HS, Karakus R, Kuscu EN, Bagruacuj UE, Oruklu N, Yaman M, et al. Serial measurement of cytokines strongly predict COVID-19 outcome. PLoS One. 2021;16(12):e0260623.
48. Queiroz MAF, Neves PFMD, Lima SS, da Costa Lpes J, da Silva Torres MK, Cayres Vallinoto IMV, et al. Cytokine Profiles Associated With Acute COVID-19 and Long COVID-19 Syndrome. Front Cell Infect Microbiol. 2022; 12:922422.
49. Qun S, Wang Y, Chen J, Huang X, Guo H, Lu Z, et al. Neutrophil-to-Lymphocyte Ratios Are Closely Associated With the Severity and Course of Non-mild COVID-19. Front Immunol. 2020;11:2160.
50. Ren P, Zhu C, He Y, Jiang H, Chen J. Analysis of the dynamic relationship between immune profiles and the clinical features of patients with COVID-19. Ann Transl Med. 2021; 9(14):1118.
51. Rutkowska E, Kwiecień I, Żabicka M, Maliborski A, Raniszewska A, Kłos K, et al. Cytokines and Leukocytes Subpopulations Profile in SARS-CoV-2 Patients Depending on the CT Score Severity. Viruses. 2021;13(5):880.
52. Shi H, He L, Sun W, Xu J, Wang M, Chen X, et al. Clinical characteristics and prognostic factors of 148 COVID-19 cases in a secondary epidemic area (4/7/2020). SSRN. doi:10.2139/ssrn.3572911. Available from: https://ssrn.com/abstract=3572911.

53. Song CY, Xu J, He JQ, Lu YQ. COVID-19 early warning score: a multi-parameter screening tool to identify highly suspected patients. medRxiv. 2020. Doi: 10.1101/2020.03.05.20031906.
54. Wan S, Yi Q, Fan S, Lv J, Zhang X, Guo L, et al. Relationships among lymphocyte subsets, cytokines, and the pulmonary inflammation index in coronavirus (COVID-19) infected patients. Br J Haematol. 2020;189(3):428-437.
55. Wang M, Fan Y, Chai Y, Cheng W, Wang K, Cao J, et al. Association of Clinical and Immunological Characteristics With Disease Severity and Outcomes in 211 Patients With COVID-19 in Wuhan, China. Front Cell Infect Microbiol. 2021;11:667487.
56. Wei X, Su J, Yang K, Wei J, Wan H, Cao X, et al. Elevations of serum cancer biomarkers correlate with severity of COVID-19. J Med Virol. 2020; 92(10):2036-2041.
57. Wu Y, Huang X, Sun J, Xie T, Lei Y, Muhammad J, et al. Clinical Characteristics and Immune Injury Mechanisms in 71 Patients with COVID-19. mSphere. 2020; 5(4):e00362-20.
58. Yang AP, Li HM, Tao WQ, Yang XJ, Wang M, Yang WJ, et al. Infection with SARS-CoV-2 causes abnormal laboratory results of multiple organs in patients. Aging (Albany NY). 2020; 12(11):10059–10069.
59. Yin SW, Zhou Z, Wang JL, Deng YF, Jiang H, Qiu Y. Viral loads, lymphocyte subsets and cytokines in asymptomatic, mildly and critical symptomatic patients with SARS-CoV-2 infection: a retrospective study. Virol J. 2021;18:126.
60. Yuan X, Huang W, Ye B, Chen C, Huang R, Wu F, et al. Changes of hematological and immunological parameters in COVID-19 patients. Int J Hematol. 2020;112:553–559.
61. Zhang H, Wang X, Fu Z, Luo M, Zhang Z, Zhang K, et al. Potential Factors for Prediction of Disease Severity of COVID-19 Patients. medRxiv. 2020. Doi: 0.1101/2020.03.20.20039818.
62. Zhang J, Yu M, Tong S, Liu LY, Tang LV. Predictive factors for disease progression in hospitalized patients with T coronavirus disease 2019 in Wuhan, China. J Clin Virol. 2020;127:104392.
63. Zhang B, Zhou X, Zhu C, Song Y, Feng F, Qiu Y, et al. Immune Phenotyping Based on the Neutrophil-to-Lymphocyte Ratio and IgG Level Predicts Disease Severity and Outcome for Patients With COVID-19. Front Mol Biosci. 2020;7:157.
64. Zheng S, Fan J, Yu F, Feng B, Lou B, Zou Q, et al. Viral load dynamics and disease severity in patients infected with SARS-CoV-2 in Zhejiang province, China, January-March 2020: retrospective cohort study. BMJ. 2020;369:m1443.
65. Zhu Z, Cai T, Fan L, Lou K, Hua X, Huang Z, et al. Clinical value of immune-inflammatory parameters to assess the severity of coronavirus disease 2019. Int J Infect Dis. 2020;95:332-339.
66. Zhu Z, Yang Y, Fan L, Ye S, Lou K, Hua X, et al. Low serum level of apolipoprotein A1 may predict the severity of COVID-19: A retrospective study. J Clin Lab Anal. 2021;35(8):e23911.
67. Merza MY, Hwaiz RA, Hamad BK, Mohammad KA, Hama HA, Karim AY. Analysis of cytokines in SARS-CoV-2 or COVID-19 patients in Erbil city, Kurdistan Region of Iraq. PLoS ONE. 2021;16(4): e0250330.
68. Hu H, Pan H, Li R, He K, Zhang H, Liu L. 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. Front Pharmacol. 2022;13:802228.
69. Takahashi T, Ellingson MK, Wong P, Israelow B, Lucas C, Klein J, et al. Sex Differences in Immune Responses that Underlie COVID-19 Disease Outcomes. Nature. 2020;588(7837):315–320.

70. Zeng Z, Yu H, Chen H, Qi W, Chen L, Chen G, et al. Longitudinal Changes of Inflammatory Parameters and Their Correlation with Disease Severity and Outcomes in Patients with COVID-19 from Wuhan, China. Crit Care. 2020;24(1):525.
71. Renu K, Prasanna PL, Valsala GA. Coronaviruses pathogenesis, comorbidities, and multi-organ damage: a review. Life Sci. 2020;255:117839.
72. Hasanvand, A. COVID-19 and the role of cytokines in this disease. COVID-19 and the role of cytokines in this disease. Inflammopharmacology. 2022;30:789–798.
73. Wu C, Liu Y, Yang Y, Zhang P, Zhong W, Wang Y, et al. Analysis of therapeutic targets for SARS-CoV-2 and discovery of potential drugs by computational methods. Acta Pharm Sin B. 2020;10(5):766–788.
74. Schoeman D, Fielding BC. Coronavirus envelope protein: current knowledge. Virol J. 2019;16(1):69.
75. Sanada F, Taniyama Y, Muratsu J, Otsu R, Shimizu H, Rakugi H, et al. Source of chronic inflammation in aging. Front Cardiovasc Med. 2018;5:12.
76. Ferrucci L, Fabbri E. Inflammageing: chronic inflammation in ageing, cardiovascular disease, and frailty. Nat Rev Cardiol. 2018;15(9):505–522.
77. Koelman L, Pivovarova-Ramich O, Pfeiffer AF, Grune T, Aleksandrova K. Cytokines for evaluation of chronic inflammatory status in ageing research: reliability and phenotypic characterization. Immun Ageing. 2019;16(1):11.
78. Olszewska-Parasiewicz J, Szarpak Ł, Rogula S, Gąsecka A, Szymańska U, Kwiatkowska M, et al. Statins in COVID-19 Therapy. Life (Basel). 2021 Jun 16;11(6):565.
79. Meftahi GH, Jangravi Z, Sahraei H, Bahari Z. The possible pathophysiology mechanism of cytokine storm in elderly adults with COVID-19 infection: the contribution of "inflame-aging". Inflamm Res. 2020;69(9):825–839.
80. Stojanović SD, Fiedler J, Bauersachs J, Thum T, Sedding DG. Senescence-induced inflammation: an important player and key therapeutic target in atherosclerosis. Eur Heart J. 2020; 41(31):2983–2996.
81. Szarpak L, Filipiak KJ, Gasecka A, Gawel W, Koziel D, Jaguszewski MJ, et al. Vitamin D supplementation to treat SARS-CoV-2 positive patients. Evidence from meta-analysis. Cardiol J. 2022;29(2):188–196.
82. Cao Y, Li L, Feng Z, Wan S, Huang P, Sun X, et al. Comparative genetic analysis of the novel coronavirus (2019-nCoV/SARS-CoV-2) receptor ACE2 in different populations. Cell Discov. 2020; 6(1):1–4.
83. Tian S, Xiong Y, Liu H, Niu L, Guo J, Liao M, et al. Pathological study of the 2019 novel coronavirus disease (COVID-19) through postmortem core biopsies. Mod Pathol. 2020; e20462:1–8.
84. Szarpak L, Rafique Z, Gasecka A, Chirico F, Gawel W, Hernik J, et al. A systematic review and meta-analysis of effect of vitamin D levels on the incidence of COVID-19. Cardiol J. 2021;28(5):647–654.
85. Jain V, Yuan J-M. Predictive symptoms and comorbidities for severe COVID-19 and intensive care unit admission: a systematic review and meta-analysis. Int J Public Health. 2020; 65:533–546.
86. Pietrobon AJ, Teixeira FME, Sato MN. Immunosenescence and Inflammaging: Risk Factors of Severe COVID-19 in Older People. Front Immunol. 2020;11:579220.