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Systematic Review in Immunology

A comprehensive review and meta-analysis of the relationships between interleukin-7 levels and COVID-19 severity

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Abstract

Introduction: As the major mechanism for coronavirus disease 2019, cytokine storm-mediated organ harm continues to dominate current understanding. Despite the first hyper-inflammatory phase, emerging data show that virus-induced poor host immunity may be the true cause of mortality in many individuals. Interleukin 7 (IL-7) is an interleukin that participates in the COVID-19 cytokine storm and regulates the immune system. Its role in COVID-19 cytokine storms is thought to be related to its ability to stimulate the formation and activation of immune cells such as T cells and B cells. This meta-analysis aims to determine the relationship, if any, between interleukin-7 and COVID-19 severity.

Methods: This study was planned as a systematic review and meta-analysis and followed the PRISMA guidelines. Four main electronic databases (Web of Science, PubMed, Scopus, and the Cochrane Central Register of Controlled Trials) were searched from January 1st, 2020 to September 2nd, 2022, to find papers investigating the prognostic significance of interleukin-7 in COVID-19-hospitalized adults. Google Scholar was used in addition to the online database search. A random effects model was used to calculate mean differences and 95% confidence interval (CIs) as well as the I2 statistics for heterogeneity analysis.

Results: Seven papers were chosen for meta-analysis findings synthesis. All six trials reported interleukin-7 levels among severe and non-severe COVID-19 patients. Pooled analysis showed that IL-7 levels in the severe group were 62.79±81.03 pg/mL, compared to 33.39±56.54 pg/mL for the non-severe group (SMD = -0.17; 95%CI: -0.93 to 0.60; p=0.67).

Discussion: Available evidence suggests that elevated levels of IL-7 were not associated with the disease severity of COVID-19. While IL-7 levels alone may not have a substantial impact on COVID-19 severity, the interaction between IL-7 and other cytokines, immune cells, and variables such as viral load and genetics should be investigated further.

Take-home message: This meta-analysis found that there was no strong link between levels of interleukin-7 and the severity of COVID-19. However, further research is needed to explore the interaction between IL-7 and other factors such as cytokines, immune cells, viral load, and genetics in order to better understand the role of IL-7 in COVID-19 pathogenesis.

Keywords: interleukin 7; IL-7; SARS-CoV-2; COVID-19; severity; cytokine storm; meta-analysis.

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INTRODUCTION

COVID-19 is a highly contagious illness caused by the new coronavirus SARS-CoV-2 that arose in late 2019 in Wuhan, China, and has since spread rapidly throughout the world [1–4]. Worldwide, it has caused 672,363,743 confirmed cases, including 6,849,462 deaths [5,6].

A cytokine storm has been found to play a role in the development of severe illness and multi-organ failure in the setting of COVID-19 [7–9]. The virus is hypothesized to cause an overactive immunological response, resulting in the uncontrolled production of cytokines and consequent immune system overstimulation [10–12]. Depending on which organs are damaged, cytokine storm symptoms in COVID-19 might include fever, weariness, muscle and joint discomfort, and a variety of additional symptoms [13]. A cytokine storm can cause respiratory failure, shock, and death in extreme situations [14].

Certain groups, such as older adults and persons with underlying health issues such as heart disease, diabetes, and lung illness, are at a higher risk of experiencing a cytokine storm [15–17]. On the other hand, cytokine storms can happen to people of any age and without any underlying health problems.

Interleukin 7 (IL-7) is an example of an interleukin that is involved in the COVID-19 cytokine storm. IL-7 is a cytokine that has a function in immune system regulation [18,19]. Its participation in cytokine storms in COVID-19 is considered to be connected to its capacity to increase the generation and activation of immune cells such as T cells and B cells (Figure 1). It is thought that IL-7 may interact with other cytokines, such as IL-2 and IFN-α, to boost the immune response and stimulate the production of pro-inflammatory cytokines, which cause inflammation [20]. This can lead to an excessive immune response, which aids in the formation of a cytokine storm. There is some evidence that IL-7 levels are related to the severity of COVID-19, an illness caused by the new coronavirus SARS-CoV-2 [21–23].

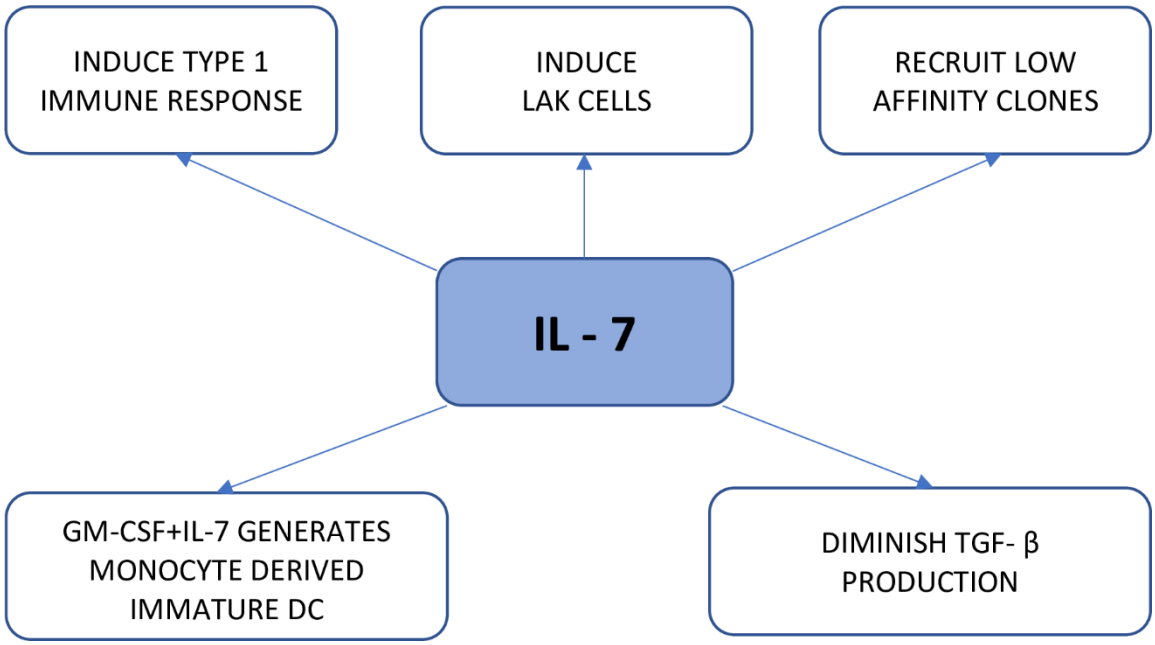

Figure 1. IL-7 signaling.

The aim of this meta-analysis is to systematically review and synthesize the available evidence on the role of interleukin-7 (IL-7) as a predictor of COVID-19 severity.

METHODS

This systematic review and meta-analysis were conducted in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement [24].

Search strategy

Four independent reviewers (M.P., A.H., A.B., and M.M.) searched four main electronic databases (Web of Science, PubMed, Scopus, and the Cochrane Central Register of Controlled Trials) from January 1st, 2020 to September 2nd, 2022, to find papers investigating the prognostic significance of interleukin-7 in COVID-19-hospitalized adults. Google Scholar was used in addition to the online database search. For each source, a unique and suitable search approach was used. We were using the following search terms: "interleukin 7" OR "IL-7" AND "SARS-CoV-2" OR "COVID-19" OR "novel coronavirus". The EndNote application was used to handle the search results (version X7; Thomson Reuters). References for related papers were also examined.

Study selection

Original studies that reported IL-7 levels in COVID-19 patients on at least one or more of the following outcomes, like COVID-19 severity, were included. Original English-language articles were included. The exclusion criteria for the meta-analysis were as follows: (1) studies containing pediatric patients' data; (2) case reports, editorials, conference papers, and reviews; (3) studies published in languages other than English; and (4) studies without the research parameters needed for meta-analysis.

Two reviewers (M.M. and M.P.) independently looked at the search criteria and compared the titles and abstracts of the papers found by the databases. Following that, the same reviewers obtained the complete texts of all potentially pertinent papers and independently evaluated them. If there was a disagreement about which literature articles to choose, it was talked out with another reviewer (A.N.).

Data extraction

Two investigators (M.M. and M.P.) worked separately to choose studies that matched the aforementioned inclusion criteria. Data extraction disagreements were resolved by conversation with another reviewer (A.N.). A prepared form was used to collect the data. The data retrieved comprised publication characteristics (for example, first author name, year of publication, research design), population data (for example, number of participants, age, male sex), and IL-7 levels in designated groups (COVID-19 positive and negative patients; mild and moderate COVID-19 severity groups; severe and non-severe COVID-19).

Quality and risk of bias assessment

Five reviewers (M.M., A.B., A.H., M.P., and Y.S.) independently assessed the risk of bias in the individual studies. Inconsistencies were resolved through the consensus of all researchers involved in the data extraction process. We used the Newcastle-Ottawa scale (NOS) [25] to measure the methodological quality of observational studies based on their design. The NOS score was divided into three levels: low, moderate, and high quality. The NOS values were 0–5, 6-7, and 8–9. If there are more than 10 studies in a single analysis, we do funnel plot analyses for asymmetry to explore probable publication bias.

Statistical analysis

This meta-analysis was carried out according to the Cochrane Handbook. We use RevMan software (ver. 5.4, Cochrane Collaboration, UK) to analyze data. We utilized standardized mean differences (SMDs) as the impact metric with 95% confidence intervals to assess IL-7 levels (CIs). When IL-7 values were presented as medians with an interquartile range, Hozo's algorithm was used

to calculate approximate means and standard deviations [26]. Heterogeneity was quantified using Cochran's Q statistics and Higgins' index (I^2), with 25%, 50%, and 75% indicating moderate, substantial, and significant heterogeneity [24]. A random effects model was employed for all analyses; a fixed effects model was only used where specified in the results section for datasets with very low heterogeneity. To give quantitative proof, the Egger's test was performed. The significance level was set at P 0.05.

RESULTS

Figure 2 depicts an overview of the systematic review search results. By scanning four major databases, we found 1,217 studies. 717 records were reviewed after duplicates were removed. Following an examination of the titles and abstracts, 476 were eliminated. The study eligibility of the retained papers was determined. 18 trials were eliminated due to a lack of categorization based on severity/mortality, reporting on only severe cases, and overlapping research periods. Finally, seven papers were chosen for synthesis of the meta-analysis findings [21-23,28-31].

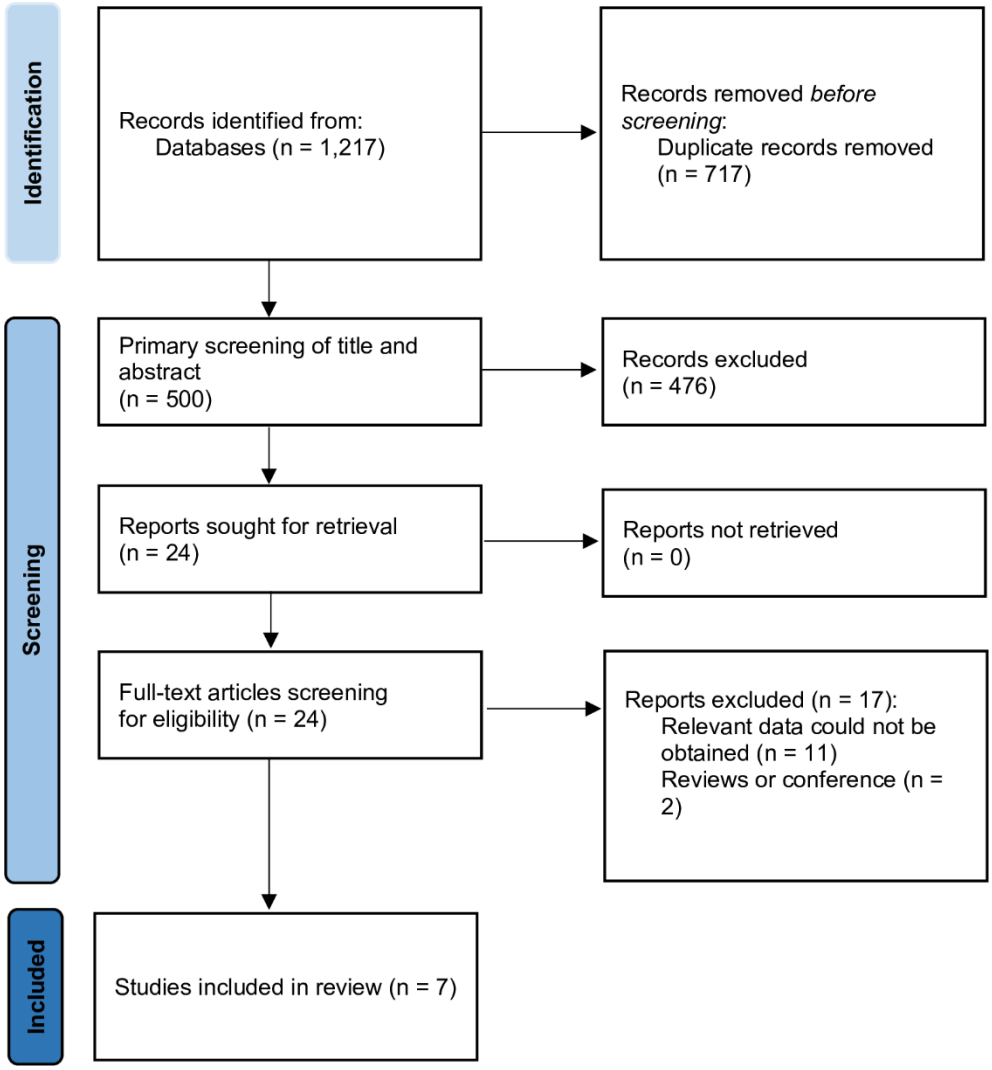

Figure 2. Flowchart detailing selection and screening of the studies included in this review.

Table 1 shows the characteristics of the trials included in the meta-analysis. There were 492 patients in the six studies that were included. Patients with severe COVID-19 had a mean age of

64.1±7.2 years, compared to 52.3±12.2 years for patients with non-severe COVID-19. Three of these studies were carried out in China, one each in the UK, Italy, Russia, and Brazil.

Table 1. Baseline characteristics of included trials.

Study	Country	Study design	Research group	No. of patients	Age	Sex, male	Comorbidities		NOS
							DM	Hypertension	
Arulkumaran et al., 2021 [28]	UK	Single-Center Cohort Trial	Severe	42	65.3 ± 5.8	31 (73.8%)	9 (21.4%)	15 (35.7%)	8
			Non-severe	44	58.3 ± 5.8	24 (54.5%)	9 (20.5%)	15 (34.1%)	
Cabaro et al., 2021 [21]	Italy	Single-Center Cohort Trial	Severe	19	67.5 ± 4.0	15 (78.9%)	NS	NS	7
			Non-severe	46	57.8 ± 5.8	27 (58.7%)	NS	NS	
Chi et al. 2020 [29]	China	Cohort trial	Severe	8	54.00 ± 12.38	5 (62.5%)	0 (0.0%)	4 (80.0%)	8
			Non-severe	58	41.76 ± 14.54	32 (55.2%)	4 (12.5%)	6 (18.8%)	
Hu et al., 2020 [30]	China	Cohort trial	Severe	13	61.5 ± 2.5	8 (61.5%)	1 (7.7%)	6 (46.2%)	8
			Non-severe	63	48.2 ± 1.1	26 (41.3%)	7 (11.1%)	11 (17.5%)	
Kalinina et al., 2022 [23]	Russia	Single-Center Cohort Trial	Severe	32	59.0 (49.5;65.0)	14 (43.8%)	NS	NS	8
			Non-severe	41	61.0 (52.0;69.0)	19 (46.3%)	NS	NS	
Ling et al., 2021 [31]	China	Prospective observational study	Severe	17	64.0 ± 3.5	11 (64.7%)	NS	NS	7
			Non-severe	15	47.5 ± 8.5	4 (26.7%)	NS	NS	
Moll-Bernardes et al., 2021 [22]	Brazil	Multicenter, randomized, phase IV, clinical trial	Severe	13	NS	11 (10.0%)	10 (24.4%)	NS	8
			Non-severe	154	NS	99 (90.0%)	31 (75.6%)	NS	

Legend: DM = diabetes mellitus; NS = not specified; NOS = Newcastle Ottawa scale.

All seven trials reported interleukin-7 levels among severe and non-severe COVID-19 patients. Pooled analysis showed that IL-7 levels in the severe group was 62.79±81.03 pg/mL, compared to 33.39±56.54 pg/mL for the non-severe group (SMD = -0.17; 95%CI: -0.93 to 0.60; p=0.67; Figure 3).

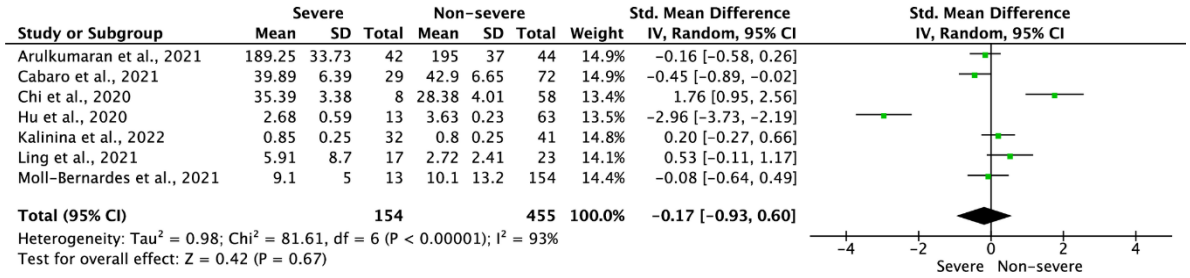

Figure 3. Forest plot of interleukin 7 levels among severe vs. non-severe COVID-19 patients. The center of each square represents the mean differences for individual trials, and the corresponding horizontal line stands for a 95% confidence interval. The diamonds represent pooled results.

DISCUSSION

There is evidence that the cytokine known as interleukin-7 has a role in both the formation and maintenance of the immune system. T lymphocytes depend on it for their development, maintenance, and activation, and it plays a part in all three processes. With the beginning of the COVID-19 epidemic in recent years, researchers have been concentrating their efforts on determining the role that interleukins, namely IL-7, play in the severity of the illness. So far, the findings have been inconclusive. There was also no correlation found in the findings of the meta-analysis between the amount of interleukin-7 that was present and the severity of COVID-19. According to the findings, there was not a significant difference in the levels of IL-7 between the two groups. The severe group had an average IL-7 level of 62.7±81.03 pg/mL, while the non-severe group had a level of 33.3±56.54 pg/mL. The standardized mean difference (SMD) was -0.17, and the p-value for the experiment was 0.67. The 95% confidence interval ranged from -0.93 to 0.60, and the SMD was -0.17.

Even though there wasn't a big difference between the levels of IL-7 in patients with severe and non-severe COVID-19, IL-7 is still being looked at as a possible therapeutic target for severe COVID-19. IL-7 inhibitors are being looked into as a possible treatment for people with severe COVID-19 because they can control the immune response and reduce inflammation [32,33]. IL-7 is important for immune cell survival, proliferation, and differentiation. The immune response in COVID-19 individuals can be dysregulated, resulting in severe inflammation and harm to the lungs and other organs. This dysregulated immune response is likely to add to the disease's severity. IL-7 inhibitors have been shown to reduce inflammation and improve immune function in a number of diseases and conditions, such as autoimmune diseases and cancer [34–37]. These inhibitors have been determined to be safe and to have few adverse effects. As a result, they are a viable therapy option for individuals with severe COVID-19 who may have pre-existing health issues that restrict their capacity to tolerate more harsh therapies. IL-7 inhibitors can be used alone or with other drugs like antivirals or drugs that change how the immune system works. Using IL-7 inhibitors along with other medicines may be a more complete way to treat COVID-19 because it addresses different parts of the disease. However, it is important to remember, though, that IL-7 inhibitors are still in the early stages of clinical testing for COVID-19, and more research is needed to figure out how safe and effective they are.

To fight COVID-19 well, it is important to know how interleukins and other types of cytokines work together inside the immune system [38,39]. Other cytokines, like interleukin 4 (IL-4),

interleukin-10 (IL-10) and interleukin-12 (IL-12), are also very important in the immune response to COVID-19 [22,40,41]. These cytokines are in addition to IL-6 and TNF, which play major roles. IL-10 is an anti-inflammatory cytokine that has the ability to downregulate the immune response, whereas IL-12 has the ability to boost the synthesis of interferon-gamma (IFN-gamma), which can assist in the elimination of the virus. For an effective immune response, maintaining a healthy equilibrium between these cytokines is essential, and it is necessary to have a solid grasp of how IL-7 fits into this dynamic. In addition, a number of recent studies have suggested that IL-7 may play a role in the long-term immune response to COVID-19. This is due to the fact that it has been demonstrated to enhance the development of memory T cells, which have the potential to provide protection against the virus for an extended period of time. However, further study is required in order to get a complete understanding of the intricate interactions that occur between interleukins and other cytokines in the immune system and their part in the severity of COVID-19 [14,42,43].

In addition to the role of interleukins in the immune response, other factors such as viral load and genetics may also play a role in COVID-19 severity [14,44,45]. The virus can replicate quickly in the body, leading to a high viral load, which is associated with more severe disease [46,47]. On the other hand, some individuals may be genetically predisposed to a more severe outcome, potentially due to variations in immune response genes [48,49]. Recent research by Fricke-Galindo has found certain genetic variants that, if present, may make it more likely for a person to have disastrous COVID-19 effects [48]. For instance, two genome-wide association studies (GWAS) have found that loci on chromosomes 3p21.31 and 9q34.2 are linked with the severity of COVID-19 [50]. These loci contain a number of genes that are important to the function of the immune system, including CXCR6, CCR9, and ABO [51]. If these genes change, it could change how a person's immune system responds to the virus, which could lead to a more serious illness.

It is important to note that COVID-19 is a complex disease with multiple factors contributing to its severity [52–56]. Age, underlying health conditions, and genetic factors can all influence the course of the disease and the likelihood of severe outcomes [57–63]. Additionally, the role of the immune response in COVID-19 is not fully understood and is the subject of ongoing research.

CONCLUSION

While IL-7 levels alone may not have a substantial impact on COVID-19 severity, the interaction between IL-7 and other cytokines, immune cells, and variables such as viral load and genetics should be investigated further. More complete knowledge of the immune response to SARS-CoV-2 will give critical insights into the development of effective COVID-19 therapies. Until then, it's critical to keep an eye on the condition and perform a further study to better understand the complicated interaction between interleukins and COVID-19 severity.

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