

Supplementary material

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CYTOKINES AS PREDICTORS OF COVID-19 SEVERITY – EVIDENCE FORM A META-ANALYSIS

Supplementary digital file

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Characteristics of a meta-analysis conducting process

This trial was conducted in accordance with the MOOSE guidelines for reporting of systematic reviews and meta-analyses of observational studies. No institutional review board approval was required because all study data had been published previously and this study did not include individual patient data.

Search strategy

All candidate studies were initially identified by conducting a systematic review of online databases, namely MEDLINE, Web of Science, Embase, PubMed (non-MEDLINE records only), Cochrane Library, EBSCO CINAHL Complete, medRxiv and bioRxiv from databases inception until 27 October 2020. We used the following search terms: “COVID-19” OR “COVID” OR “SARS-CoV-2” OR “Coronavirus” AND “cytokin*” OR “interleukin*” OR “IL”.

Selection criteria/eligibility

Patients, 18 years of age or older, diagnosed with COVID-19 were eligible for inclusion. We restricted data to studies published in English language.

Data extraction

Three authors (L.S., D.K., M.J.J.) will independently conduct data abstraction using a data extraction form developed by all the review authors. The data extraction form contains study authors, year of publication, country, study design, number of participants, age, sex, type of cytokine, and cytokines levels.

Quality assessment

Two reviewers (L.S. and M.J.J.) independently extracted individual study data and evaluated studies for risk of bias using a previously piloted standardized form and the Newcastle-Ottawa scale [1].

Statistical analysis

Data synthesis and statistical meta-analysis (when possible) were carried out using Cochrane Review Manager software v.5.4 (The Cochrane Collaboration, Oxford, Copenhagen, Denmark). Outcomes were summarized using the Mantel-Haenszel Risk Ratios (RRs) or Mean Differences (MDs). All results are presented with their 95% confidence interval (CI). When the continuous outcome was reported in a study as median, range, and interquartile range, we estimated means and standard deviations using the formula described by Hozo et al. [2]. Heterogeneity was assessed statistically using I^2 (no heterogeneity, $I^2 = 0-25\%$; moderate heterogeneity, $I^2 = 25-50\%$; large heterogeneity, $I^2 = 50-75\%$; extreme heterogeneity, $I^2 = 75-100\%$) [3]. The random effects model was used for $I^2 > 50\%$; otherwise, the fixed effects model was employed. $P < 0.05$ was taken to indicate statistical significance. Statistical testing was 2 tailed.

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Supplementary Table 1. Characteristics of included studies reporting cytokines in severe and non-severe groups

Study	Country	Study design	SEVERE GROUP			NON-SEVERE GROUP		
			No.	Age	Sex, male	No.	Age	Sex, male
Cai Q. et al. 2020	China	Retrospective cohort study	58	61.8 ± 2.9	39 (67.2)	240	42.3 ± 4.2	106
Chen L.D. et al. 2020	China	Retrospective cohort study	25	60.7 ± 15.2	15 (60.0)	69	51.4 ± 15.8	34 (49.3)
Chen R. et al.	China	Retrospective cohort study	203	58.9 ± 13.3	131 (64.5)	345	67.3 ± 12.1	182 (52.8)
Chen X. et al. 2020	China	Retrospective cohort study	27	73.8 ± 15.4	24 (88.9)	21	52.8 ± 14.2	13 (61.9)
Gao Y. et al. 2020	China	Retrospective cohort study	15	45.2 ± 7.7	9 (60.0)	28	43 ± 14.0	17 (60.7)
Guirao J.J. et al. 2020	Spain	Retrospective cohort study	6	64.5 ± 2.3	5 (83.3)	44	63.4 ± 4.51	36 (81.1)
Gunder R. et al. 2020	Turkey	Retrospective cohort study	50	62.2 ± 11.9	33 (66.0)	172	47.7 ± 16.1	99 (57.6)
Huang H. et al. 2020	China	Retrospective cohort study	21	61.4 ± 16.4	12 (57.1)	43	41.2 ± 15.7	25 (58.1)
Li S. et al. 2020	China	Retrospective cohort study	26	59.0 ± 8.7	14 (53.8)	43	40.0 ± 6.9	26 (60.5)
Li T. et al. 2020	China	Retrospective study	105	71.3 ± 4.6	67 (63.8)	207	67.1 ± 5.4	120 (58.0)
Liao D. et al. 2020	China	Retrospective cohort study	231	67.8 ± 3.0	137 (59.3)	149	55.3 ± 4.3	69 (46.3)
Liu F. et al. 2020	China	Retrospective cohort study	33	76.8 ± 6.3	8 (24.2)	107	61.3 ± 4.9	41 (38.3)

Liu J. et al. 2020	China	Retrospective cohort study	13	59.7 ± 10.1	7 (53.8)	27	43.2 ± 12.3	8 (29.6)
Liu L. (a) et al. 2020	China	Retrospective single center	92	62.8 ± 2.8	62 (67.4)	202	50.8 ± 4.7	100 (49.5)
Liu L. (b) et al. 2020	China	Cohort study	7	52 ± 4.6	4 (57.1)	44	42.5 ± 4.6	28 (63.7)
Liu T. et al. 2020	China	Retrospective study	69	56.3 ± 10	33 (47.8)	11	36.5 ± 9.3	1 (9.1)
Lv Z. et al. 2020	China	Retrospective cohort study	239	61.1 ± 10.4	117 (49.0)	115	56.0 ± 16.2	58 (50.4)
Qin C. et al. 2020	China	Retrospective study	286	60.5 ± 3	155 (54.2)	166	52.3 ± 6	80 (48.2)
Sheng L. et al. 2020	China	Retrospective study	130	72.4 ± 5.7	NS	102	63 ± 3	NS
Sun Y. et al. 2020	China	Cohort study	19	59.4 ± 13.7	NS	44	42.3 ± 19.6	NS
Tian R et al. 2020	China	Retrospective single center	45	63.8 ± 4.3	26 (57.8)	45	63.8 ± 3.2	22 (50.0)
Xie Y. et al. 2020	China	Retrospective study	24	71.9 ± 6.8	13 (54.2)	38	60.1 ± 7.5	14 (36.8)
Xu X. et al. 2020	China	Retrospective single center	41	63.2 ± 14.4	15 (36.6)	47	52.49 ± 14.62	21 (44.7)
Xu Y. et al. 2020	China	Retrospective, multi-center case series	25	67.8 ± 5.3	13 (52.0)	44	48.5 ± 6.9	22 (50.0)
Yang Y. et al. 2020	China	Retrospective single center	34	60.8 ± 9.2	22 (64.7)	19	50.5 ± 16.2	9 (47.4)
Yuan J. et al. 2020	China	Retrospective single center	11	56.8 ± 9.2	5 (45.5)	83	37.9 ± 22	37 (44.6)
Zeng Z. et al. 2020	China	Retrospective study	224	62.7 ± 4.8	121 (54.0)	93	58.1 ± 3.8	41 (44.1)

Zhang Q. et al. 2020	China	Retrospective single center	27	70.8 ± 6.6	18 (66.7)	47	60.8 ± 3.7	18 (38.3)
Zhu Z. et al. 2020	China	Retrospective study	16	57.5 ± 11.7	9	111	50.0 ± 15.5	73

Legend: NS = Not specified.

Supplementary table 2. Summary of cytokines levels in severe vs. non-severe groups.

Cytokine type	No. of studies	MD (95%CI)	P - value	I² statistic
Tumor necrosis factor, TNF	8	0.74 [0.22, 1.26]	0.005	99%
Interleukin-1 β	3	0.12 [-0.15, 0.39]	0.38	91%
Interleukin-2R	8	206.97 [161.49, 252.44]	<0.001	100%
Interleukin-4	4	0.21 [-0.08, 0.50]	0.16	95%
Interleukin-6	24	21.90 [17.64, 26.16]	<0.001	99%
Interleukin-8	5	5.91 [4.03, 7.80]	<0.001	95%
Interleukin-10	7	1.51 [1.00, 2.02]	<0.001	97%
Interleukin-17	1	-0.40 [-0.74, -0.06]	0.02	NA
Interferon- γ	4	0.17 [-0.34, 0.69]	0.51	92%

Legend: CI = Confidence interval; MD = Mean difference; NA = Not applicable.

Supplementary Table 3. Characteristics of included studies reporting cytokines in ICU and non-ICU groups

Study	Country	Study design	ICU GROUP			NON-ICU GROUP		
			No.	Age	Sex, male	No.	Age	Sex, male
Guirao J.J. et al. 2020	Spain	Cohort study	8	62.1 ± 2.8	7 (87.5)	42	63.8 ± 1.8	34 (80.9)
Liu S-p. et al. 2020	China	Retrospective study	41	63 ± 13	28 (71.8)	214	61 ± 11.3	108 (50.9)
Maeda T. et al. 2020	USA	Single-center Retrospective study	57	67 ± 5.2	31 (54.4)	167	64.5 ± 4.3	96 (57.5)
Monaldi M.V. et al. 2020	Italy	Observational study	10	73 ± 7.4	8 (80.0)	18	47 ± 12.6	8 (44.4)

Supplementary table 4. Summary of cytokines levels in severe vs. non-severe groups.

Cytokine type	No. of studies	MD (95%CI)	P - value	I ² statistic
Tumor necrosis factor, TNF	1	-7.92 [-11.92, -3.93]	<0.001	NA
Interleukin-6	4	85.75 [30.01, 141.49]	<0.001	90%
Interleukin-8	1	-10.30 [-34.71, 14.11]	0.41	NA
Interleukin-10	1	8.62 [3.45, 13.80]	0.001	NA

Legend: CI = Confidence interval; MD = Mean difference; NA = Not applicable.

Supplementary Table 5. Characteristics of included studies reporting cytokines in survivors vs. non-survivors grupus.

Study	Country	Study design	Non-Survivors GROUP			Survivors GROUP		
			No.	Age	Sex, male	No.	Age	Sex, male
Almaghlouth N.K. et al. 2020	USA	Cohort study	7	NS	2 (28.6)	73	NS	43 (58.9)
Chen R. et al.	China	Retrospective study	103	66.9 ± 12.1	69 (67.0)	445	53.5 ± 13.9	244 (54.8)
Chen T.L. et al.	China	Case series	19	77	16 (84.2)	36	72	18 (50.0)
Garcia P.D.W. et al. 2020	Italy	Cohort study	97	70.5 ± 2.7	69 (71.1)	301	62 ± 2.7	231 (76.7)
Guirao J.J. et al. 2020	Spain	Cohort study	14	69.0 ± 3.1	11 (78.6)	36	61.4 ± 1.7	30 (83.3)
Laguna-Goya R. et al. 2020	Spain	Prospective cohort	36	64.8 ± 3.8	25 (69.4)	465	51.5 ± 2.3	292 (62.9)
Luo M. et al. 2020	China	Multicenter retrospective cohort	201	69.5 ± 2.7	133 (66.2)	817	56.5 ± 3.3	388 (47.5)
Sheng L. et al. 2020	China	Retrospective study	88	74.8 ± 2.2	NS	42	67.5 ± 7.5	NS

Legend: NS = Not specified.

Supplementary table 6. Summary of cytokines levels in survivors vs. non-survivors groups.

Cytokine type	No. of studies	MD (95%CI)	P - value	I ² statistic
Tumor necrosis factor, TNF	1	-4.35 [-4.58, -4.11]	<0.001	NA
Interleukin-2R	2	-548.08 [--577.12, -519.04]	<0.001	99%
Interleukin-6	8	-2.57 [-2.79, -2.36]	<0.001	100%
Interleukin-8	1	-20.43 [-21.35, -19.51]	<0.001	NA

Interleukin-10	1	-4.35 [-4.58, -4.11]	<0.001	NA
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Legend: CI = Confidence interval; MD = Mean difference; NA = Not applicable.

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