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Elevated interleukin levels are associated with higher severity and mortality in COVID 19 – A systematic review, meta-analysis, and meta-regression

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ABSTRACT

Background and aims: COVID 19 pneumonia commonly leads to ARDS. The occurrence of ARDS in COVID 19 patients is thought to occur secondary to an exaggerated immunologic response. In this meta-analysis, we aim to comprehensively study the various levels of immunological parameters in patients with COVID 19.

Materials and methods: We performed a systematic literature search from PubMed, EuropePMC, SCOPUS, Cochrane Central Database, and medRxiv with the search terms, "COVID-19" and "Interleukin". The outcome of interest was prognosis in COVID 19 patients.

Results: We performed meta analysis of 16 studies. Higher counts of CD4 and CD8 with Lower Levels of TNF-a, IL2R, IL6, IL8 were observed on patients with good prognosis compared to patients with poor prognosis; −0.57 (pg/mL) (−1.10, −0.04, p = 0.04), (I^2 91%, p < 0.001); −579.84 (U/mL) (−930.11, −229.57, p < 0.001), (I^2 96%, p < 0.001); −1.49 (pg/mL) (−1.97, −1.01, p < 0.001), (I^2 94%, p < 0.001); −0.80 (pg/mL) (−1.21, −0.40, p < 0.001), (I2 79%, p < 0.001); −2.51 (pg/mL) (−3.64, −1.38, p < 0.00001), (I^2 98%, p < 0.001) respectively. Meta-regression showed age and hypertension (coefficient: 1.99, and −1.57, p = 0.005, and 0.006) significantly influenced association between IL-6 and poor outcome.

Conclusion: Elevated immune response to coronavirus occurs in COVID 19 patients. Higher counts of CD4 and CD8 were seen in patients with good prognosis compared to patients with poor prognosis, with Lower levels of TNF-a, IL2R, IL6, IL8, were observed in patients with good prognosis compared to patients with poor prognosis.

1. Introduction

Coronavirus disease 2019 (COVID 19) is a severe acute respiratory syndrome caused by the Severe Acute Respiratory Syndrome Coronavirus 2 [1]. Although most of the patients may be asymptomatic or only display mild symptoms, a significant portion of the patients, especially those with comorbidities, experience severe symptoms [2–7].

COVID 19 pneumonia commonly leads to adult respiratory distress syndrome (ARDS), which is the most common cause of

Abbreviations: ARDS, adult respiratory distress syndrome; COVID 19, coronavirus disease 2019; CAP, community-acquired pneumonia; TNF-a, tumour necrosis factor-a; sHLH, secondary hemophagocytic lymphohistiocytosis; SRF, sudden respiratory failure; IL, interleukin.

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death from this disease. The occurrence of ARDS in COVID 19 patients is thought to occur secondary to an exaggerated immunologic response, which leads to a Cytokine release syndrome (CRS), commonly known as "cytokine storm", causing multi-organ failure [8]. CRS primarily occurs in patients receiving immunotherapy, such as granulocyte-monocyte colony-stimulating factors. However, CRS can develop in association with severe viral infection, such as COVID 19. CRS is triggered by the release of Interferon-gamma (IFN) from activated T Cells, which produces excessive interleukin (IL) 6, tumor necrosis factor alpha (TNF-a) and IL-10 [9,10].

One study observed severe respiratory failure with sudden clinical deterioration approximately 7–8 days after onset of symptoms in COVID 19 pneumonia, this phenomenon is thought to be driven by a specific pattern of immune dysfunction [11].

In this meta-analysis, we aim to comprehensively study the various levels of immunological parameters in patients with COVID 19.

2. Methods

2.1. Search and selection criteria

Systematic search of the literature was performed using PubMed, EuropePMC, SCOPUS, Cochrane Central Database, and medRxiv for preprint studies with the search terms, "COVID-19" and "Interleukin". The inclusion criterion for the studies in this meta-analysis was are all studies that reported interleukin (IL) levels in patients with COVID 19. We excluded all case reports, case series, and cross-sectional studies. The outcome of interest was poor prognosis in COVID 19 patients, defined by the incidence of severe COVID 19 (patients with (1) shortness of breath with respiratory rate >30 times/minute, resting oxygen saturation <93%, or PaO2/FiO2 ratio <300 mmHg), ARDS/need for ICU care (Critically ill patients which experience respiratory failure requiring mechanical ventilation, patients experiencing shock, or multiple organ failure requiring admission to intensive care units), and mortality.

2.2. Data extraction

Data extraction was carried out by E.Y R.P, I.H, and M.A.H using a standardized form reporting the author name, year of publication, study design, and sample size.

2.3. Statistical analysis

We performed a meta-analysis using RevMan Version 5.3 (Cochrane Collaboration). Mean difference and standardized mean difference with standard deviation were used to measure continuous data.

In this meta-analysis, we performed the analysis of mean difference on CD4 count, CD8 count, serum TNF a level, serum IFN level, serum IL2R level, serum IL4 level, serum IL6 level, serum IL8 level, serum IL10 level, serum complement 3 level, and serum complement 4 level between patients with good and poor prognosis, analyses on IL1B and IL5 were not done due to insufficient data. Calculation of pooled 95% confidence interval was done using RevMan software. The heterogeneity index (I [2]) was used to assess heterogeneity in the studies included in this meta-analysis. Heterogeneity beyond 50% or $p < 0.05$ was set as the threshold for statistically significant heterogeneity. Generic Inverse Variance mode in RevMan with a fixed-effect model was used for this meta-analysis; the random effect model was used in analyses with significant heterogeneity. We used a two-tailed P-value with a statistical significance threshold of 0.05.

We performed sensitivity analyses on our meta analyses to test the statistical robustness of pooled results, to assess for significant change in pooled results by exclusion of studies, and to single out studies with high heterogeneity. Random-effects restricted maximum likelihood meta-regression was performed for the association between IL-6 and outcome.

3. Results

We obtained a total of 251 potential articles from our search; 31 duplicates were removed from our pool. The remaining 148 articles were screened by titles and abstracts; 72 potentially relevant articles were obtained. After screening full articles and abstracts and applying the inclusion and exclusion criteria, we excluded 56 studies for insufficient data regarding COVID 19 and the outcome of interest. Specifically, 42 did not include the outcome of interest, two were meta-analysis, two were systematic reviews, three were literature reviews, and one involved children. We included 16 studies in our qualitative synthesis and meta-analysis. There were 2277 patients with COVID 19 from the 16 studies (Fig. 1), (Tables 1 and 2) [12–15,15–25].

3.1. CD4 count at treatment

Five studies reported a statistically significant difference in CD4 count between COVID 19 patients with good and poor prognosis. Pooled mean differences of CD4 counts between good and poor prognosis yielded results of 174.78 (count/ul) (136.70, 212.86; $p < 0.001$) and high heterogeneity (I^2 73%; $p < 0.001$), with patients with good prognosis having higher CD4 counts than those with poor prognosis. Sensitivity analyses were performed and removal of the study by Wan S et al. and Cao et al. resulted in a pooled mean difference of CD4 counts of 139.38 (count/ul) (110.75,168.01; $p < 0.001$) and low heterogeneity (I^2 0%, $p = 0.76$)(Fig. 2A).

3.2. CD8 count at treatment

Five studies reported a statistically significant difference in CD8 count between COVID 19 patients with good and poor prognosis. The pooled mean difference of CD8 counts between patients between good and poor prognosis yielded results of 88.43 (count/ul) (54.54, 122.31, $p < 0.001$) high heterogeneity (I^2 86%, $p < 0.001$), with patients with good prognosis having higher CD8 counts than those with poor prognosis. Sensitivity analyses were performed, and removal of the study by Qin et al. resulted in a pooled mean difference of CD8 counts of 105.28 (count/ul) (92.01, −118.55, $p < 0.001$), with low heterogeneity (I [2] 9%, $p = 0.35$) (Fig. 2B).

3.3. Tumor necrosis factor (TNF)-a levels

Seven studies reported a statistically significant difference in TNF-a levels between COVID 19 patients with good and poor prognosis. The pooled standardized mean difference between the groups was −0.57 (pg/mL) (−1.10, −0.04, $p = 0.04$), with high heterogeneity (I^2 91%, $p < 0.001$); patients with good prognosis having lower TNF-a levels than those with poor prognosis. Sensitivity analyses were performed, and removal of the studies by Qin et al. and Wan et al. resulted in a pooled mean difference of −0.95(pg/mL) (−1.34, −0.56, $p < 0.01$), with high heterogeneity (I^2 58%, $p = 0.05$)(Fig. 3A).

3.4. IFN levels

Data regarding interferon-gamma in COVID patients were only available in two studies (Nie, 2020; Wan, 2020). The pooled mean

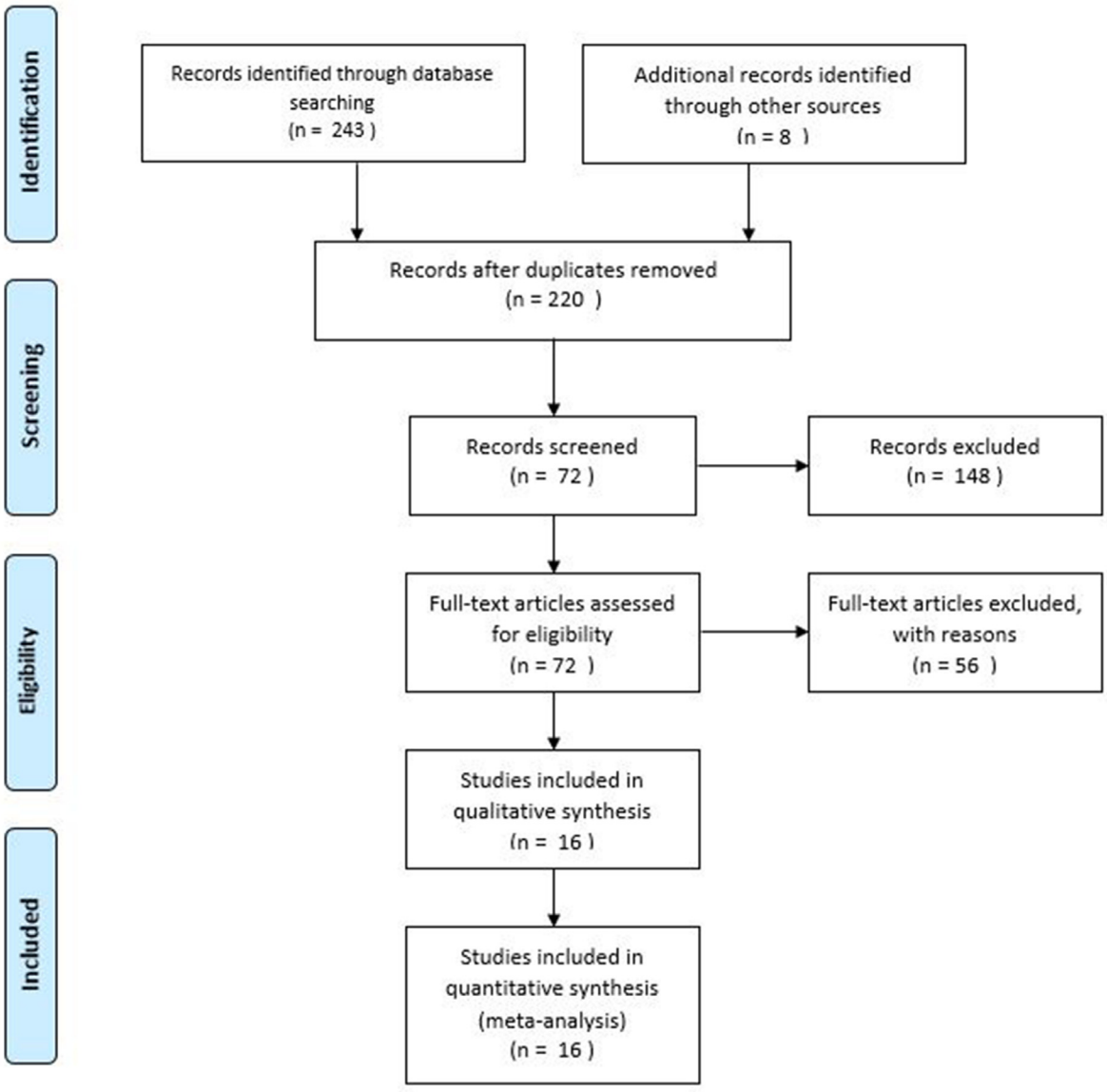

Fig. 1. PRISMA flowchart.

difference in IFN levels between patients with good and poor prognosis was insignificant at −1.19 (pg/mL) (−2.61, 0.24, p = 0.1), with high heterogeneity (I^2 93%, p < 0.001).

3.5. IL2R levels

Five studies reported a statistically significant difference in IL2R levels between COVID 19 patients with good and poor prognosis. The pooled mean difference in IL2R levels between the groups was −579.84 (U/mL) (−930.11, −229.57, p < 0.001), with high heterogeneity (I^2 96%, p < 0.001); patients with good prognosis had lower IL2R levels than those with poor prognosis. Sensitivity analyses were performed and removal of the study by Qin et al. resulted in a pooled mean difference of −672.93 (U/mL) (−779.81, −566.05, p < 0.001), with low heterogeneity (I^2 9%, p = 0.35) (Fig. 3B).

3.6. IL4 levels

Two studies reported a statistically significant difference in IL4 levels between COVID 19 patients with good and poor prognosis. The pooled mean difference in IL4 levels between the patients was −0.15 (pg/mL) (−0.23, −0.07, p < 0.001), with low heterogeneity (I^2 0%).

3.7. IL6 levels

Fourteen studies reported a statistically significant difference in IL6 levels between COVID 19 patients with good and poor prognosis. The pooled standardized mean difference in IL6 levels between the patients was −1.49 (pg/mL) (−1.97, −1.01, p < 0.001), high heterogeneity (I^2 94%, p < 0.001), patients with good prognosis had lower levels of IL6 than those with poor prognosis. Sensitivity analyses were performed and removal of the study by Wan et al. resulted in a pooled standardized mean difference of −1.14 (pg/mL) (−1.47, −0.81, p < 0.001), with high heterogeneity (I^2 87%,

Table 1
Characteristics of included studies.

Authors	Study Design	Samples	Non Outcome vs Outcome	CD4 (count/ul)	CD8 (count/ul)	TNF A (pg/mL)	IFN (pg/mL)
Qin et al.	Retrospective	452	166 vs 286	420.5 ± 207.8 vs 285.1 ± 168	201.9 ± 107.1 vs 154.7 ± 116.5	8.4 (6.9−10.4) vs 8.7 (7.1−11.6) p 0.037 CALCULATED MEAN = 8.4 ± 2.33 vs 8.7 ± 4.5	NA
Nie S et al., 2020	Retrospective	97	28vs 25	40(33−43) vs 33(25−42) (percentage, not count)	26(24−30) vs 20(16−25) Percentage, not count	2.85(2.51−3.35) vs 2.98(2.76−3.41) p0.438 CALCULATED MEAN = 2.85 ± 0.56 vs 2.98 ± 0.65	3.76(3.53−4.19) vs 3.99(3.61 −4.44) p0.177 CALCULATED MEAN = 3.76 ± 0.44 vs 3.99 ± 0.553
Chen G et al., 2020	Retrospective	21	10vs11	359.2 ± 118.7 vs 185.6 ± 101.4	272 ± 105 vs 124.3 ± 107.9	7.5 ± 1.6 vs 10.9 ± 3.0 p0.023	NA
Chen T et al.	Retrospective	274	161 vs 113	NA	NA	7.9 (6.7−9.6) vs 11.8 (8.6−17.6) (MEDIAN IQR) CALCULATED MEAN = 7.9 ± 1.93 vs 11.8 ± 6	NA
Li K et al.	Retrospective	102	87 vs 15 (death)			7.3(5.6−9.4) Vs 13.0(8.3−23.3) P0.006 CALCULATED MEAN = 7.3 ± 2.533 vs 13.0 ± 10	NA
Cai Q et al., 2020	prospective	298	240 vs 58 (Severe covid)			NA	NA
Wan S et al.	Prospective Cohort	123	102/21	451.3 ± 23.0 vs 263.2 ± 28.83	288.6 ± 14.23 vs 179 ± 23.87	(4.077 ± 1.588) vs (2.948 ± 0.443) 0.7486	(5.132 ± 0.841) vs (6.904 ± 1.247) 0.3533
Lei L et al., 2020	Retrospective	51	44 vs 7 (Severe)	NA	NA	NA	NA
Ma LK 2020	Observational Retrospective	84	(20/64)	NA	NA	NA	NA
Wu C et al., 2020	Retrospective Cohort	201	117 vs 84	371.00 (283.00−572.00) vs 234.00 (136.75−398.00) CALCULATED MEAN = 371 ± 192.667 vs 234 ± 174.1667	241.00 (159.00−323.00) vs 157.50 (76.00 −289.50) CALCULATED MEAN = 241 ± 109.333 vs 157.5 ± 142.333	NA	NA
Wu C et al. 2020	Retrospective Cohort	84	40/44	286.00 (132.00−449.50) vs 166.00 (128.50−312.50)	273.00 (88.00−316.00) vs 96.00 (67.00 −143.50)	NA	NA
Xu Y et al., 2020		69	44/25	NA	NA	NA	NA
Zhou F et al., 2020	Retrospective cohort	191	137/54	NA	NA	NA	NA
Cao M et al., 2020	Observational retrospective	198	179/19	468 (309.5−679.5) vs 198 (116.0−340.0) CD4/8 ratio 1.68 (1.23−2.32) vs 1.78 (1.29−2.15) CALCULATED MEAN = 468 ± 246.667 vs 198 ± 149.333	217 (176.0−415.0) vs 128 (65.0−182.0) CALCULATED MEAN = 217 ± 159.333 vs 128 ± 78	NA	NA
Liu J et al.	Prospective cohort	40	27/13	NA	NA	NA	NA
Chen X et al., 2020	Prospective Cohort	48	21/10	NA	NA	NA	NA
Chen X et al., 2020	Prospective Cohort	48	21/17	NA	NA	NA	NA
Wang F et al., 2020	Retrospective	28	14/14	NA	NA	9.1 (6.1−11.0) vs 17.1 (8.4−20.2) TNF CALCULATED MEAN 9.1 ± 3.2667 vs 17.1 ± 7.8667	NA

IL1B (pg/mL)	IL2R (U/mL)	IL4 (pg/mL)	IL5 (pg/mL)	IL6 (pg/mL)	IL8 (pg/mL)	IL 10 (pg/mL)	C3 (g/L)	C4 (g/L)	Outcome
5.0 (5.0–5.0) vs 5.0 (5.0 –5.0) p0.962	(IL2R) 663.5 (473.3–862.8) vs 757.0 (528.5–1136.3) p0.001 CALCULATED MEAN = 663.5 ± 259.667 vs 757.0 ± 405.2	NA	NA	13.3 (3.9–41.1) vs 25.2 (9.5–54.5) p0.001 CALCULATED MEAN = 13.3 ± 24.8 vs 25.2 ± 30	13.7 (8.9–21.0) vs 18.4 (11.3–28.4) p0.001 CALCULATED MEAN = 13.7 ± 8.0667 vs 18.4 ± 17.1	5.0 (5.0–7.0) vs 6.6 (5.0 –11.3) p0.001 CALCULATED MEAN = 5 ± 1.33 vs 6.6 ± 4.2	0.88 (0.77–1.00) vs 0.89 (0.77–1.00) p0.942 CALCULATED MEAN = 0.88 ± 0.1533 vs 0.89 ± 00.1533	0.26 (0.20–0.31) vs 0.26 (0.20–0.31) p0.851 CALCULATED MEAN = 0.26 ± 0.0733 vs 0.26 ± 0.0733	Severe COVID (Non Severe vs Severe)
NA	3.8(3.6–4.3) vs 4.2(4.0 –4.4) p0.001	4.2(3.8–4.9) vs 4.5(4.1–4.8) p0.089 CALCULATED MEAN = 4.2 ± 0.733 vs 4.5 ± 0.4667	2.16(2.07 –2.22) vs 2.22(2.11 –2.33) p0.126	5.78(5.10–7.19) vs 9.93(8.58–11.92) p0.001 CALCULATED MEAN = 5.78 ± 1.393 vs 9.93 ± 2.23	N/A	4.93(4.25–5.55) vs 6.54(5.96–7.44) p0.001 CALCULATED MEAN = 4.93 ± 0.8667 vs 6.54 ± 0.98667	0.84(0.72–0.95) vs 0.91(0.82–1.01) p0.91 CALCULATED MEAN = 0.84 ± 0.1533 vs 0.91 ± 0.12667	0.16(0.13–0.23) vs 0.24(0.19–0.35) p0.006 CALCULATED MEAN = 0.16 ± 0.0667 vs 0.24 ± 0.10667	Severe COVID (Non Severe vs Severe)
NA	(IL2R) 441.7 ± 169.9 vs 1202.4 ± 380.2 p0.001	NA	NA	18.8 ± 13.9 vs 73.8 ± 67.9 p0.066	24.7 ± 25.4 vs 61.8 ± 67.1 p0.21	6.6 ± 2.1 vs 10.9 ± 1.8 p0.001	NA	NA	Severe COVID
NA	IL2R 566.5 (448.0–858.3) vs 1189.0 (901.0–1781.0) (MEDIAN IQR) CALCULATED MEAN = 566.5 ± 273.533 vs 1189.0 ± 586.667	NA	NA	13.0 (4.0–26.2) vs 72.0 (35.6–146.8) (MEDIAN IQR) CALCULATED MEAN = 13.0 ± 14.8 vs 72 ± 74.133	11.4 (7.8–20.2) vs 28.3 (18.7–72.1) (MEDIAN IQR) CALCULATED MEAN = 11.4 ± 8.267 vs 28.3 ± 35.6	5.0 (5.0–8.4) vs 12.8 (8.8–19.6) (MEDIAN IQR) CALCULATED MEAN = 5 ± 2.667 vs 12.8 ± 7.2	0.9 (0.8–1.0) vs 0.8 (0.6 –0.9) (MEDIAN IQR) CALCULATED MEAN = 0.9 ± 0.133 vs 0.8 ± 0.2	0.3 (0.2–0.3) vs 0.2 (0.2 –0.3) (MEDIAN IQR) 0.3 ± 0.0667 vs 0.2 ± 0.0667	Mortality
4.9(4.0–4.9) Vs 4.5(4.0–4.9) P0.388 CALCULATED MEAN = 4.9 ± 0.6 vs 4.5 ± 0.6	(IL2R) 571.5(353.0–821.8) Vs 1166.5(898.8–1788.5) P0.001 CALCULATED MEAN = 571.5 ± 312.533 vs 1166.5 ± 593.1333	NA	NA	4.2(1.9–16.4) Vs 48.4(12.6–154.1) P0.001 CALCULATED MEAN = 4.2 ± 9.667 vs 48.4 ± 94.33	9.3(6.4–18.6) Vs 22.0(14.0–28.4) P0.006 CALCULATED MEAN = 9.3 ± 8.133 vs 22.0 ± 9.6	4.9(4.0–4.9) Vs 4.9(4.0–10.0) P0.6 CALCULATED MEAN = 4.9 ± 0.6 vs 4.9 ± 4	NA	NA	Mortality
NA	NA	NA	NA	12.0(6.4–19.7) vs 38.8(22.7–57.2) p < 0.001 MEDIAN IQR CALCULATED MEAN = 12.0 ± 8.8667 vs 38.8 ± 34.5	NA	NA	NA	NA	SEVERE COVID
NA	NA	(1.69 ± 0.070) vs (1.83 ± 0.185) 0.4317	NA	(13.41 ± 1.84) vs (37.77 ± 7.801) <0.0001	NA	(2.464 ± 0.085) vs (4.59 ± 0.378) <0.0001 IL 17: (1.095 ± 0.0226) vs (1.16 ± 0.0571) p0.246	NA	NA	SEVERE COVID
NA	NA	NA	NA	0(0–7.3) vs 4.6(0–28.2) p0.116 CALCULATED MEAN 0 ± 4.8667 vs 4.6 ± 18.8	NA	NA	NA	NA	Severe COVID
NA	NA	NA	NA	2.8(1.7–7.8) vs 13.9(7.2 –22.7) p0.001 CALCULATED MEAN = 2.8 ± 4.0667 vs 13.9 ± 10.33	NA	NA	1.3(1.2–1.4) vs 1.4(1.3 –1.5) p0.097 CALCULATED MEAN = 1.3 ± 0.133 vs 1.4 ± 0.133	0.31(0.26–0.39) vs 0.32(0.30–0.43) p0.268 CALCULATED MEAN = 0.31 ± 0.08667vs 0.32 ± 0.08664	Severe COVID
NA	NA	NA	NA	6.29 (5.36–7.83) vs 7.39 (5.63–10.89) p0.03 CALCULATED MEAN = 6.29 ± 1.65 vs 7.39 ± 3.506	NA	NA	NA	NA	ARDS IN COVID

NA	NA	NA	NA	6.05 (5.12−6.99)vs 10.07 (7.36−14.80) p < 0.001 CALCULATED MEAN = 6.05 ± 1.245 vs 10.07 ± 4.96	NA	NA	NA	NA	Mortality in ARDS
NA	NA	NA	NA	5.9 (2.8−10.9) vs 14.8 (7.5−45.3) 0.009 CALCULATED MEAN = 5.9 ± 5.4 vs 14.8 ± 25.2	NA	NA	NA	NA	Severe COVID
NA	NA	NA	NA	6.3 (5.0−7.9) vs 11.0 (7.5−14.4) p0.001 CALCULATED MEAN = 6.3 ± 1.933 vs 11.0 ± 4.6	NA	NA	NA	NA	Mortality
NA	NA	NA	NA	NA	NA	NA	1.15 (1.04−1.29) vs 0.99 (0.87−1.28) p0.059 CALCULATED MEAN = 1.15 ± 0.1667 vs 0.99 ± 0.27333	0.32 (0.27−0.38) vs 0.3 (0.25−0.33) p0.114 0.32 ± 0.06 vs 0.3 ± 0.0533	ICU Care
NA	NA	NA	NA	NA	NA	NA	0.8 ± 0.2 vs 0.8 ± 0.1 p0.389	0.3 ± 0.1 vs 0.3 ± 0.1 p 0.426	Severe COVID
NA	NA	NA	NA	10.4(3.8−31.0) vs 5.8(3.1−16.9)p0.001 CALCULATED MEAN = 10.4 ± 18.133 vs 5.8 ± 11.2	NA	NA	NA	NA	Severe COVID
NA	NA	NA	NA	10.4(3.8−31.0) vs 64.0(25.6−111.9) p0.001 CALCULATED MEAN = 10.4 ± 18.133 vs 64.0 ± 57.533	NA	NA	NA	NA	ICU Care (Critical)
NA	(IL2R) 677 (496−1016) vs 1538 (1214−1937) CALCULATED MEAN 647 ± 346.667 vs 1538 ± 482	NA	NA	13.0 (2.4, 39.8) 124.5 (65.1, 199.9) IL6 13 ± 24.9333 vs 124.5 ± 89.8667	IL8 11.0 (6.8, 21.8) 49.1 (25.2, 92.4) 11 ± 10 vs 49.1 ± 44.8	IL10 5.2 (5, 7.5) 14.9 (5.9, 18.6) 5.2 ± 1.667 vs 14.9 ± 8.4667	NA	NA	ICU Care

Table 2
Comorbidities of study Subjects included in Meta-Analysis.

Authors	Study Design	Samples	Non Outcome vs Outcome	Male (%)	Overall age	Hypertension (%)	CAD/ CVD (%)	DM (%)	CKD (%)	COPD (%)	Medications administered
Qin et al.	retrospective	452	166 vs 286	52	58 (47–67)	29.5 (36.7 vs 18.1)	5.9 (8.4 vs 1.8) (CVD)	16.4 (18.5 vs 13.3)	2.2 (2.4 vs 2.1)	2.6 (3.1 vs 1.8)	NA
Nie S et al., 2020	retrospective	97	28vs 25	34	39 (30–60)	15.5 (40 vs 6.9)	2.1 (8 vs 0)	5.2 (8 vs 4,2)	3.1 (8 vs 1.4)	2.1 (4 vs 1.4) (CLD)	88.7% patients received antiviral therapy (oseltamivir or arbidol), 48.5% received antibiotic therapy,36.1% received immunomodulatory therapy (hydroxychloroquine or chloroquine phosphate), 27.8% patients were given short-term (3–5 days) and low-dose systematic corticosteroids.
Chen G et al., 2020	retrospective	21	10vs11	17	56.3 ± 14.3	23.8 (36.4 vs 10)	N/A	14.3 (18.2 vs 10)	N/A	N/A	(90.5%) patients received antiviral therapy (oseltamivir and ganciclovir). All patients were given empirical antimicrobial treatment (moxifloxacin or cefoperazone-sulbactam). (85.7%) were administered corticosteroids (methylprednisolone).
Chen T et al.	retrospective	274	161 vs 113	62	Median age of deceased 68 y.o Recovered 51 y.o	34 (48 vs 24)	8 (14 vs 4) (CVD)	17 (21 vs 14)	1.5 (3.5 vs 0.6)	7 (10 vs 4) (CLD)	236 patients received antiviral therapy(oseltamivir, arbidol, or lopinavir/ritonavir), 217 received glucocorticoid, 249 received antibiotics(moxifloxacin, cefoperazone, or azithromycin), 54 received IVIG, 89 received inhalated IFN
Li K et al.	Retrospective	102	87 vs 15 (death)	58%	57 (45–70)	30 (47 vs 28)	4 (13 vs 2)	15 (13 vs 15)	N/A	2 (7 vs 1)	NA
Cai Q et al., 2020	prospective	298	240 vs 58 (Severe covid)	50%	47 (33–61)	12.8	3.7 (CVD)	6.4	N/A	N/A	76.8% received Lopinavir/ritonavir, 10.1% Favipiravir. Severe cases, 3–5 days duration of intravenous methylprednisolone (1–2 mg/kg/d) combined with human gamma-globulin (10–20 g per day) were prescribed. 37 patients received antibacterial therapy.
Wan S et al.	Prospective Cohort	123	102/21	53.6	43.05 ± 13.12 in mild group vs 61.29 ± 15.55 in severe group	9.6 (10 vs 9.4)	5.2 (15 vs 1) (CVD)	8.9 (22.5 vs 3.1)	3 (10 vs 0)	N/A	NA
Lei L et al., 2020	Retrospective	51	44 vs 7 (Severe)	62.7	45 (34–51)	7.8 (14.3 vs 6.8)	N/A	7.8 (57.1 vs 0)	N/A	N/A	all Px received aerosol inhalation of recombinant human interferon a-1b for injection and oral antiviral therapy (Lopinavir and Ritonavir). 17.3% received oseltamivir, 3.9% received arbidol. 86.3% given Bacillus licheniformis capsules regulated intestinal flora treatment 10 patients (19.6%) received short-term (3–5 days) glucocorticoid treatment.
Ma LK 2020	Observational Retrospective	84	(20/64)	57.1%	48 (42.3 –62.5)	14.3 (20.0 vs 12.5)	6 (10 vs 4.7)	11.9 (35 vs 4.7)	N/A	6.0 (10.0 vs 4.7) (CLD)	NA
Wu C et al., 2020	Retrospective Cohort	201	117 vs 84	63.7%	51 (43–60)	19.4 (27.4 vs 13.7)	4 (6 vs 2.6)	10.9 (19 vs 5.1)	1	2.5 (CLD)	30.8% received methylprednisolone, 97.5% received antibiotics, 84.6% received antiviral [oseltamivir (n = 134 [66.7%]), ganciclovir (n = 81 [40.3%]), lopinavir/ritonavir (n = 30 [14.9%]), and interferon alfa (n = 22 [10.9%])], 34.8% received immunomodulator (immunoglobulin, thymosin, and recombinant human granulocyte colony stimulating factor.), 52.7% received antioxidant (glutathione and N-acetyl-L-cysteine)
Wu C et al. 2020	Retrospective Cohort	84	40/44	63.7%	51 (43–60)	27.4 (36.4 vs17.5)	9.5 (9.1 vs 10) (CVD)	19 (25 vs 12.5)	N/A	N/A	(see above)
Xu Y et al., 2020		69	44/25	50.7%	57 (43–69)	N/A	N/A	N/A	N/A	N/A	55.1% received antiviral (oseltamivir), 44.9% received antibiotic, 1.5% received antifungal, 8.7% received corticosteroid
Zhou F et al., 2020	Retrospective cohort	191	137/54	62%	56.0 (46.0 –67.0)	30.4 (48 vs 23)	8 (24 vs 1)	19 (31 vs 14)	1 (4 vs 0)	3 (7 vs 1)	95% patients received antibiotics and 21% received antivirals (lopinavir/ritonavir). 30% received corticosteroid, 24% received IVIG
Cao M et al., 2020	Observational retrospective	198	179/19	51	50.1 ± 16.3	21.2 (31.6 vs 20.1)	6.0 (26.3 vs 3.9) (CVD)	7.6 (10.5 vs 7.3)	N/A	N/A	NA

(*continued on next page*)

Table 2 (*continued*)

Authors	Study Design	Samples	Non Outcome vs Outcome	Male (%)	Overall age	Hypertension (%)	CAD/ CVD (%)	DM (%)	CKD (%)	COPD (%)	Medications administered
Liu J et al.	Prospective cohort	40	27/13	37.5	48.7 ± 13.9	15 (38.5 vs 3.7)	N/A	15 (30.8 vs7.4)	N/A	N/A	NA
Chen X et al., 2020	Prospective Cohort	48	21/10	77.1	64.6 ± 18.1	25 (10 vs 19)	N/A	49.7 (50 vs 28.6)	N/A	N/A	NA
Chen X et al., 2020	Prospective Cohort	48	21/17	77.1	64.6 ± 18.1	25 (41.2 vs 19)	N/A	49.7 (70.6 vs 28.6)	N/A	N/A	NA
Wang F et al., 2020	Retrospective	28	14/14	75	68.6 ± 9	53.6 (71.4 vs 35.7)	14.3 (28.6 vs 0)	N/A	0 (0 vs 0)	14.3 (7.1 vs 7.1) (CLD)	100% patients received antiviral (oseltamivir, arbidol, or both) and 96.45% received antibacterial

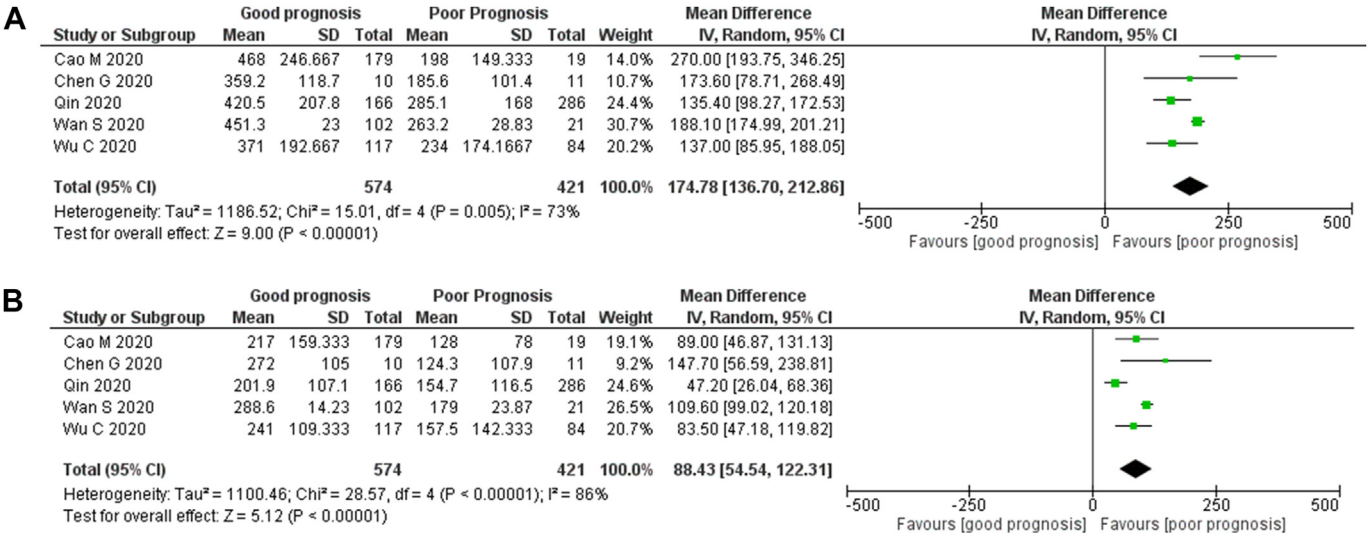

Fig. 2. A. CD4 Count on treatment B. CD8 Count on Treatment.

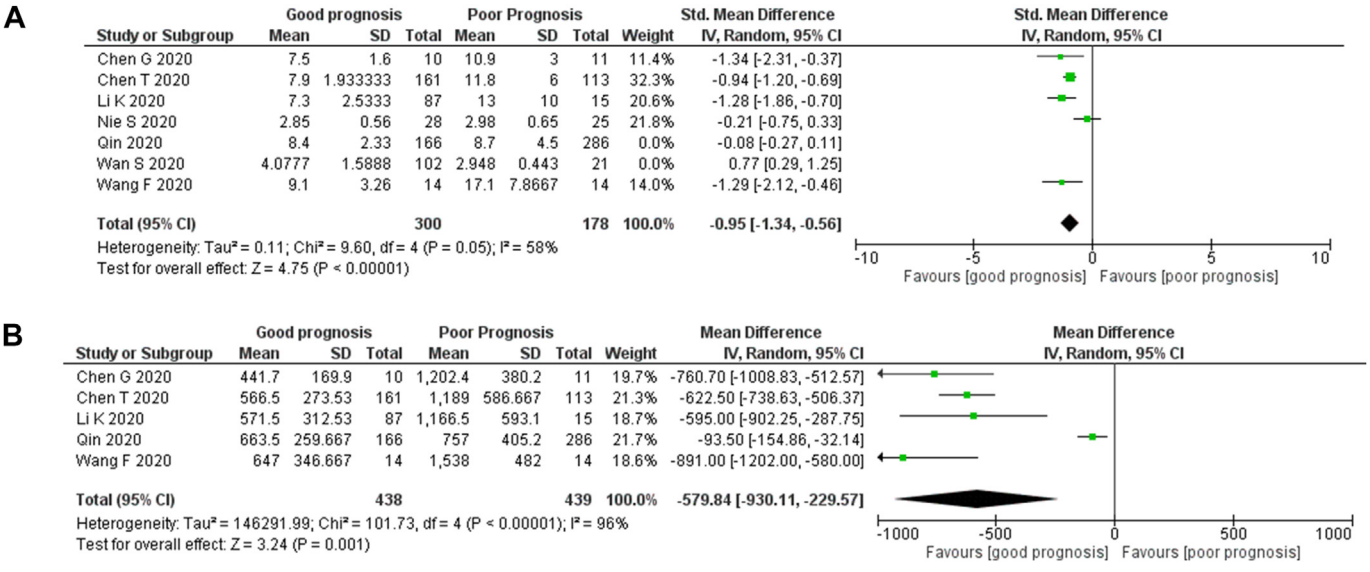

Fig. 3. A. TNF-A levels B. IL2R levels.

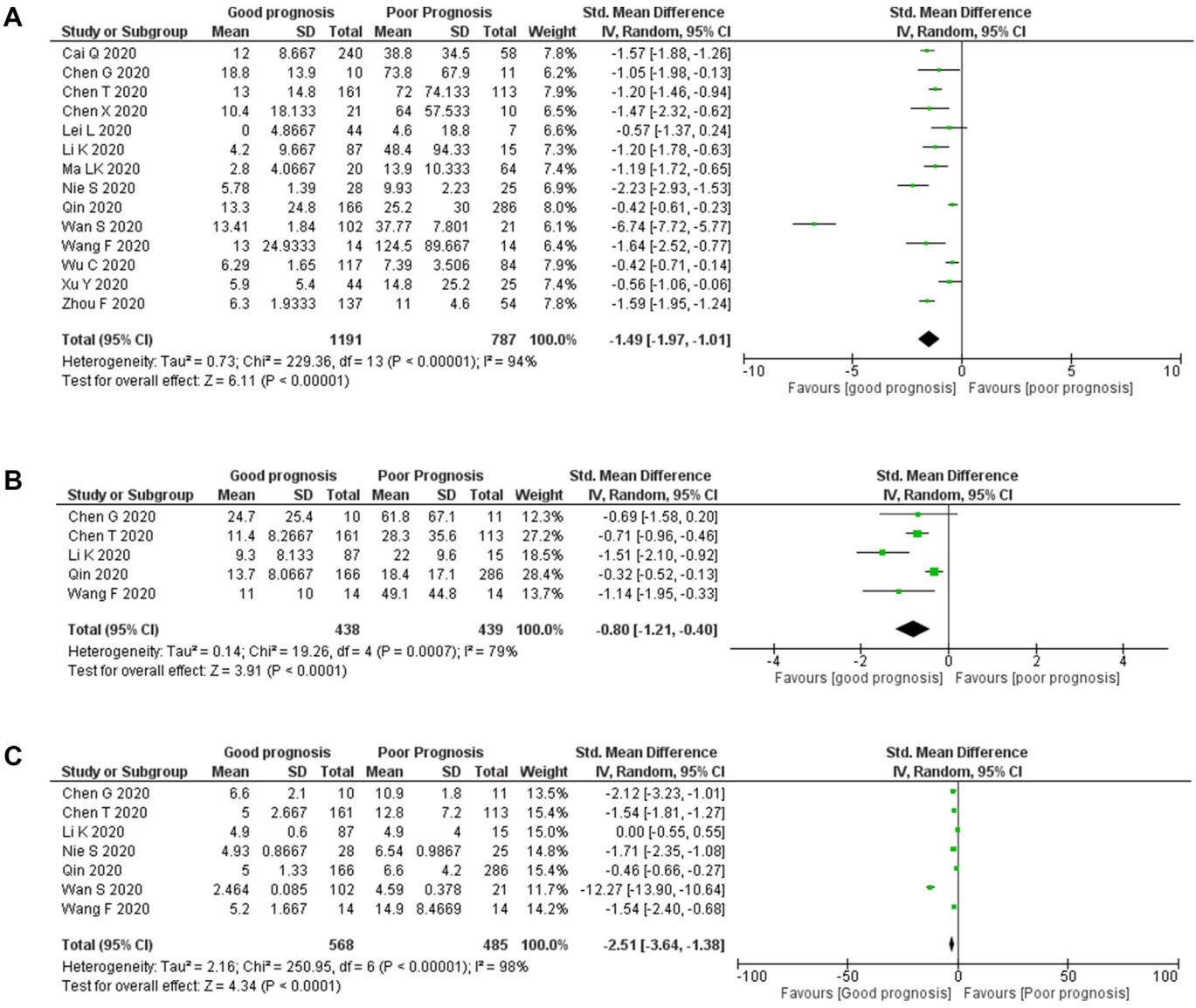

Fig. 4. A. IL6 levels B. IL8 levels C. IL10 levels.

$p < 0.001$)(Fig. 4A).

3.8. IL8 levels

Five studies reported a statistically significant difference in IL8 levels between COVID 19 patients with good and poor prognosis. The pooled standardized mean difference comparing IL8 levels between the patients was −0.80 (pg/mL) (−1.21, −0.40, $p < 0.001$), with high heterogeneity (I2 79%), patients with good prognosis had lower levels of IL8 compared to those with poor prognosis. Sensitivity analyses were performed and removal of the study by Qin et al. resulted in a pooled standardized mean difference of −0.99 (pg/mL) (−1.42, −0.55, $p < 0.001$), with moderate heterogeneity (I^2 55%, $p = 0.08$). Removal of the study by Li K et al. resulted in a pooled standardized mean difference of −0.60 (pg/mL) (−0.93, −0.28, $p < 0.001$), with moderate-high heterogeneity (I^2 65%, $p = 0.04$). Removal of both studies by Qin et al. and Li K et al. resulted in a pooled standardized mean difference of −0.74 (pg/mL) (−0.97, −0.51, $p < 0.001$), with low heterogeneity (I^2 0%, $p = 0.6$) (Fig. 4B).

3.9. IL10 levels

Seven studies reported a statistically significant difference in IL10 levels between COVID 19 patients with good and poor prognosis. The pooled standardized mean difference comparing IL10 levels between the patients was −2.51 (pg/mL) (−3.64, −1.38, $p < 0.001$), with high heterogeneity (I^2 98%, $p < 0.001$), patients with good prognosis had lower levels of IL10 than those with poor prognosis. Sensitivity analyses were performed and removal of the study by Wan et al. resulted in a pooled standardized mean difference of −1.16 (pg/mL) (−1.80, −0.53, $p < 0.001$), with high heterogeneity (I [2] 92%, $p < 0.001$). Removal of the studies by Li et al., Qin et al., and Wan et al. resulted in a pooled standardized mean difference of −1.59 (pg/mL) (−1.83, −1.35, $p < 0.001$), with low heterogeneity (I^2 0%, $p = 0.76$) (Fig. 4C).

3.10. C3 levels

The meta-analysis performed on C3 Levels in patients with COVID 19 yielded a statistically insignificant result. Pooled

standardized mean difference comparing C3 levels between patients with good and poor prognosis was 0.05 (g/L) (−0.40, 0.50, p = 0.81), with high heterogeneity (I^2 89%, p < 0.001).

3.11. C4 levels

Results of meta-analysis performed on C4 Levels in patients with COVID 19 yielded a statistically insignificant result. Pooled standardized mean difference comparing C3 Levels between patients with good and poor prognosis yielded a result of 0.15 (g/L) (−0.54, 0.85, p = 0.66), high heterogeneity (I^2 95%, p < 0.001).

3.12. Meta-regression

Meta-regression analysis showed that age (coefficient: 1.99, p = 0.006) and hypertension (coefficient: 1.57, p = 0.005) significantly influenced the association between IL-6 and poor outcome. On the other hand, male sex (coefficient: 0.48, p = 0.348) and diabetes (coefficient: 0.97, p = 0.075) did not significantly influence the effect estimate.

4. Discussion

Several studies have discussed the association between immune dysregulation and poor prognosis in COVID 19 patients [11,26,27].

Giamarellos-Bourboulis et al. and Arabi et al., described the phenomenon of sudden respiratory failure (SRF) in patients with COVID 19; SRF occurs in 7–8 days after initial symptoms, a timing also corroborated by Huang et al. who reported the onset of dyspnea at 8 days. Giamarellos-Bourboulis et al. and Huang et al. also reported lymphopenia in COVID 19 patients [11,27,28]. In their study, Giamarellos-Bourboulis et al. reported that compared to patients with bacterial community-acquired pneumonia (CAP), patients with SARS-CoV-2 Pneumonia have less severe scoring results on Sequential Organ Failure Assessment (SOFA) and Acute Physiology and Chronic Health Evaluation II (APACHE II) scores. This difference in SOFA and APACHE II Scores between patients with bacterial CAP and SARS-CoV-2 pneumonia who experiences SRF indicates that COVID 19 patients who progressed to SRF developed acute immune dysregulation before their disease becomes as severe as traditional bacterial CAP or sepsis [11]. Giamarellos-Bourboulis et al. observed that all patients with SRF showed decreased HLA-DR expression and a decrease in CD4, CD19, and NK cell counts. This result is consistent with our results where a decrease in CD4 count was seen in patients with poor prognosis. We also observed an interesting phenomenon where the decrease in CD4 was accompanied by a concurrent decrease in CD8 cells, signifying impairment of both cellular and humoral immune response in patients with COVID 19 [11]. The impairment of humoral immune response is further emphasized by the decrease in IFN levels seen across studies in patients with poor prognosis in this meta-analysis.

Interestingly, in the study by Cao M et al., the CD4/8 ratio between patients with good and poor prognosis was >1 (1.68 [1.23–2.32] vs. 1.78 [1.29–2.15], for patients with good and poor prognosis respectively); this indicates that unlike patients with HIV infection, the decrease in CD4 counts in COVID 19 was not accompanied by a reversal in the CD4/8 ratio, and that the role of the helper T cells in COVID 19 is intact but suppressed. However, there is also a possibility that a more extensive suppression of CD8 than CD4 occurs in SARS-CoV-2 infection, which keeps the CD4/8 ratio >1 [29–32].

We also observed a higher level of TNF-a in patients with poor prognosis in this meta-analysis, a result that is consistent with the findings of other studies. It is also interesting to note that an increase in TNF production was also seen in patients with H1N1 infection in 2009. This finding is in contrast with patients suffering from bacterial CAP induced sepsis, in these patients, immunoparalysis of sepsis occurs which is characterized by deficiency in monocytes and cytokine functions upon ex vivo stimulation. In their study, Giamarellos-Bourboulis et al., found that peripheral blood mononuclear cells of SARS-CoV-2 pneumonia patients showed sustained TNF production after stimulation, a finding which might explain the elevated TNF levels in COVID 19 pneumonia [11].

Several concerns have arisen regarding the occurrence of the cytokine storm and even secondary hemophagocytic lymphohistiocytosis (sHLH) in COVID 19, which manifests as concurrent hypercytokinemia with multiorgan failure [10,33]. In accordance with this hypothesis, we observed an increase in TNF, IFN, IL2R, IL-4, IL6, IL8, and even IL 10 levels. However, it is important to note that IL2R itself is a poor diagnostic marker for HLH [34,35].

An increase in IL2R observed across studies included in this meta-analysis further solidifies the possible occurrence of HLH secondary to viral pneumonia induced sepsis [34–36]. In this meta-analysis, we observe a higher IL2R levels in patients with poor prognosis. This finding indicates a widespread activation of T-Cell, as IL2R, which are upregulated on activated T cells, are shed into serum from activated T cell surfaces. However, IL2R levels might also be elevated in conditions that could provoke HLH, such as sepsis, which we must seek to differentiate from primary HLH [37].

In this meta-analysis, we observed differences in IL8 levels in COVID 19 patients: patients with good prognosis had lower levels of IL8 than those with poor prognosis. However, we have not found any other studies on IL8 levels in COVID 19 patients. The role of IL8 in sepsis has been extensively studied, and it is interesting to note that low IL8 levels were seen in septic patients [38,39].

The increase in IL 10 reflects the occurrence of exaggerated immune response secondary to COVID 19, which triggers negative feedback via the IL-10 pathway on T cells. The elevation of IL2 in patients with poorer prognosis explains the trigger for such negative feedback on T cell through IL10 synthesis, IL 10 will directly inhibit activation and proliferation of T cells resulting in reduced IL2 [40]. However, an increase in IL-10 might also indicate an enhancement of B cell function alongside IL6 [41].

We observed high IL 6 levels in patients with poor prognosis in this study (standardized mean difference of 1.49 (−1.97, −1.01, p < 0.001)), with high heterogeneity (I^2 94%, p < 0.001). High IL6 levels in patients with poor prognosis might reflect dysregulated excessive and persistent synthesis of IL 6. This finding serves as a possible ground for future therapy using IL6 inhibitors in severe cases of COVID 19. However, with the recent concerns of COVID 19 inducing a cytokine storm, we did not observe IL6 levels >1000 pg/mL, usually observed in cytokine storm syndrome [42].

Prior Observations in elderly patients showed a delayed immune and inflammatory response after injury but an augmented response at later time points [43]. A previous meta-analysis showed that the difference in lymphocyte count on admission became narrower as the age increased; this indicates a dampened early immune response like the aforementioned observation [44]. The present meta-analysis included studies that measured IL-6 level during the course of hospitalization, where the mean differences became wider with increasing age. This finding is consistent with the augmented immune response in elderly patients later during the course of hospitalization. This finding might be explained by a phenomenon called “immunosenescence”, aging of the immune system, especially in individuals age >60, which involves low levels of chronic inflammation, known as inflammaging [45,46]. Inflammaging is characterized by a persistent low level activation of immune cells which primarily originates from the

innate immune system and an elevated levels of cytokines and chemokines, locally and systemically [47]. Amongst these pro-inflammatory cytokines, Interleukin-6, which are seen to be elevated as age progress in this meta-regression, are chronically increased in elderly patients, and is commonly used as an indicator of inflammaging [48]. This phenomenon is caused by the accumulation of senescent immune cells, which as a consequence of their aging, chronically releases pro-inflammatory cytokines [49].

In this meta-analysis, we observed an insignificant mean difference in the levels of C3 and C4 between patients with good and poor prognosis, indicating the limited role of complements in immune dysregulation in COVID 19.

Higher levels of IL6 in patients with poor prognosis might indicate underlying immune dysfunction. Ideally, this will have to be studied using pro-inflammatory/anti-inflammatory ratios, such as IL6/IL10 ratio, however, we are limited by the absence of raw data, and this will have to be done in a patient-level meta-analysis. Pro-inflammatory/anti-inflammatory ratios, as higher ratio is associated with poorer prognosis in several conditions [50–53]. We hope that future studies will include this ratio.

The results on IL6 in this meta-analysis further reveal the plausibility of the use of IL6 antagonists (tocilizumab) in COVID 19 cases. The results of this study are in accordance with a study by Alattar et al. who used tocilizumab to suppress IL6 levels, improve the radiological imaging findings, and reduce the requirements for ventilators [54]. The possible benefit of using tocilizumab was derived from finding that IL6 with other cytokines mediated the occurrence of the cytokine storm in COVID 19 patients [55,56].

The results on cytokines, such as TNF and IL2R, could be regarded as a basis for further studies to explore the role of specific treatments with cytokine antagonists, especially the role of tocilizumab in COVID 19 treatment.

Several factors pose limitations to this meta-analysis, such as the large number of preprint studies included in this meta-analysis. Several studies were conducted in the same city, posing the risk of subject overlap. Finally, the severe nature of subjects included in this meta-analysis means that the result of this meta-analysis results are applicable to patients admitted with severe clinical conditions and might not apply to patients in mobile hospitals, which commonly have patients with a milder clinical condition. We encourage further studies to develop prognostic model/scoring based on these immunological parameters along with other patients' characteristics and biomarkers [57,58].

5. Conclusion

Elevated immune response to the virus occurs in COVID 19 patients. This immune response is mediated by various cytokines. This phenomenon does not seem to be mediated by complements. Lower levels of TNF-a, IL6, IL8, and IL10 were observed in patients with good prognosis compared to patients with poor prognosis. Higher levels of IL2R were observed in patients with good prognosis compared to patients with poor prognosis, albeit lower respective counts of CD4 and CD8. Patients with COVID19 also retained the CD4/8 balance. In our meta-regression, we also observed wider gap in IL-6 levels between older age patients with good and poor outcomes. Our results suggest that IL6 antagonists may play a plausible role in the treatment of COVID 19 and curbing this elevated immune response. Further studies are needed to explore the role of inhibitor against other cytokines in the treatment of COVID 19.

Consent for publication

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Declaration of competing interest

All authors declare no conflict of interest.

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