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RESEARCH ARTICLE

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Anakinra treatment efficacy in reduction of inflammatory biomarkers in COVID-19 patients: A meta-analysis

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Abstract

Introduction: Anakinra is being empirically considered for the treatment of COVID-19 patients. The aim is to assess the efficacy of anakinra treatment on inflammatory marker reduction, including c-reactive protein (CRP) concentrations, serum ferritin, and serum d-dimer levels.

Methods: Adhering to PRISMA 2020 statement guidelines, a systematic search was conducted across the following databases from December 2019 until January 10, 2022: PubMed/MEDLINE, Cochrane Central, Web of Science, Scopus, and EMBASE. The following keywords were employed: Anakinra, COVID*, SARS-CoV-2, inflammatory, CRP, D-dimer, Ferritin, hematological, laboratory, clinical, trials. The findings were collated and presented in a tabulated manner, and statistically analyzed using Review Manger 5.4 (Cochrane).

Results: In total, 2032 patients were included (881 in the anakinra and 1151 in the control/standard care group); 69.1% of them were males. Overall, the mean difference from admission until last follow-up in CRP values was −9.66, where notable reductions were seen in the anakinra group (SMD = −0.46, $p < 0.00001$, $N = 655$). Serum ferritin mean values were reduced by 1467.16 in the anakinra group (SMD = −0.31, $p = 0.004$, N = 537). D-dimer mean values were largely reduced by 4.04 in the anakinra group (SMD = −0.38, $p = 0.0004$, N = 375).

Conclusion: This study finds that anakinra is potentially a strong candidate as an anti-inflammatory agent to reduce mortality in COVID-19 patients, specifically in patients with elevated inflammatory biomarkers.

KEYWORDS
acute-phase reactant, anakinra, c-reactive protein, d-dimer, interleukin-1, serum ferritin

1 | INTRODUCTION

Inflammation is a key driver of the severity of COVID-19 infection among patients.[1] Preliminary reports since the initial stages of the pandemic have demonstrated that elevated concentrations of pro-inflammatory markers are more pronounced in severe or critically ill COVID-19 patients than milder cases.[2] Anakinra is a recombinant interleukin-1 receptor antagonist (IL-1Ra), a regulatory molecule with activity against both IL-1α and IL-1β, that emerged as a candidate to reduce hyper-inflammation and concomitant mortality in COVID-19 patients.[3] The pro-inflammatory cascade is similar to the macrophage activation syndrome (MAS), and COVID-19 hyper-inflammation may benefit from cytokine-blocking agents such as Anakinra.[4,5] The severe hyper-inflammation in a subset of COVID-19 patients resembles MAS and is associated with hyper-ferritinemia, fever, and diffuse intravascular coagulation (DIC).[4,6] Anakinra has been used empirically across several clinical settings in COVID-19 and has had positive effects, including mortality reduction.[7-9] As the potential effect of Anakinra is due to inhibition of the pro-inflammatory cascades, it is likely to lead to suppression of systematic inflammation, control of fever, and inhibition of host inflammatory responses to viral replication in COVID-19.[7,10] Although systematic inflammation may not be significant in all patients, there is evidence of localized hyper-inflammation in the lungs, making Anakinra an attractive candidate for moderate-to-severe COVID-19 infections as concomitant therapy.[7,11-13]

So far, Anakinra has been administered as an off-label medication for patients with clinical or laboratory signs of hyper-inflammation in COVID-19 patients to mitigate IL-1-mediated pro-inflammatory cascades.[14] The severe hyper-inflammation in these patients is characterized by laboratory markers including c-reactive protein (CRP), serum ferritin, and d-dimer levels.[15] It remains unclear whether Anakinra confers an additional advantage to COVID-19 patients to mitigate hyper-inflammation beyond the current standard of care. Reports of COVID-19 increasingly recognize two types of distinct, yet overlapping phenotypic and pathological subsets of pneumonia—these include viral pneumonitis and virus-triggered overreacting immune response.[16,17] The later phenotype is a more severe form of disease and is typified by rapid progression to acute respiratory failure, often necessitating invasive ventilatory support. With severe COVID-19 pneumonia on invasive ventilatory support, excessive mortality is documented.[16,17] The excessively high rates of death are attributed to severe hyper-inflammation.[4,8,16] The aim of this meta-analysis is to document whether anakinra in patients with COVID-19 pneumonia is beneficial for improvement of inflammatory biomarkers (i.e., CRP, serum ferritin, and d-dimer).

2 | MATERIALS AND METHODS

In accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement 2020, randomized controlled trials and observational studies employing an intervention group (anakinra) compared to the control/standard of care (SoC) group were included. The studies reported inflammatory biomarkers at baseline (on admission or enrollment) and on endline (completion of study or last follow-up). These laboratory-based outcomes were reported in anakinra and control/SoC groups. The data were systematically reviewed and meta-analyzed to quantify the standardized changes of inflammatory laboratory markers (CRP, serum ferritin, and d-dimer).

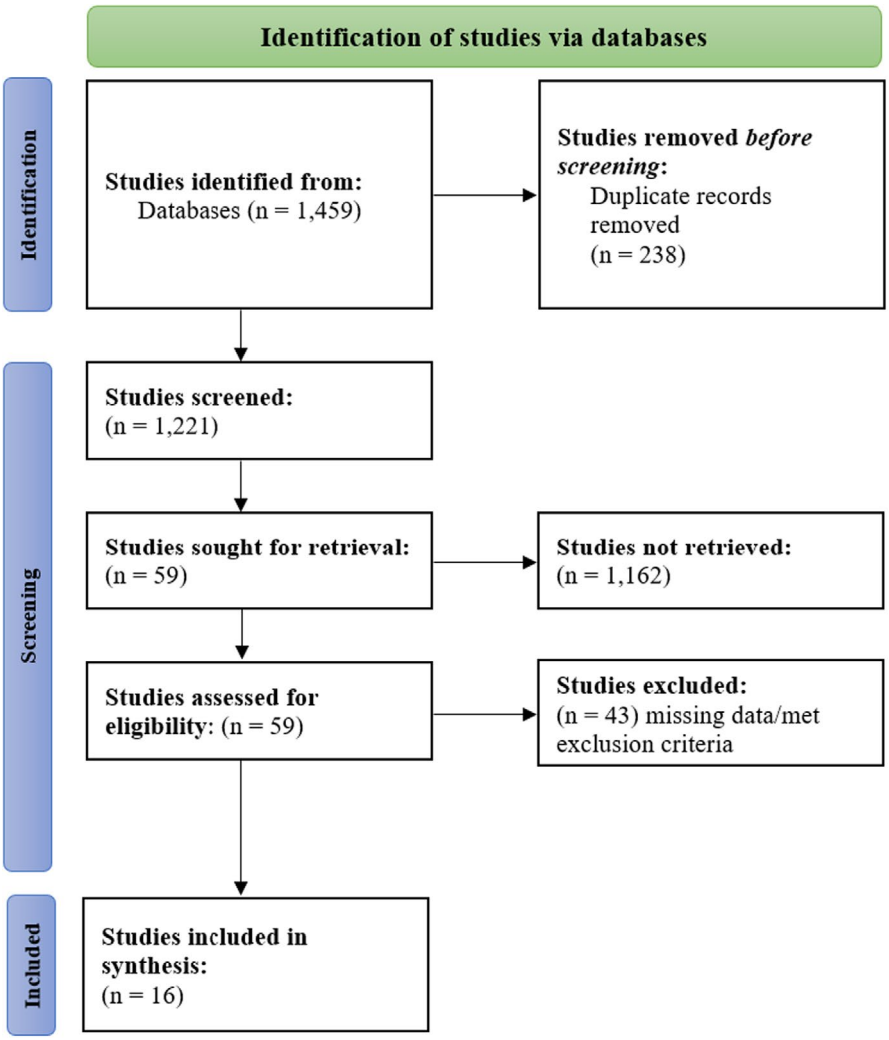
Randomized clinical trials, retrospective or prospective cohorts, were considered. Case series, case reports, systematic reviews, meta-analyses, and letters were omitted due to the high risk of biases associated with the study types and lack of control groups for comparison purposes. The studies were required to include adult participants, aged 18 or above, with no restrictions to genders of enrolled individuals. The follow-up period was not predetermined due to the limitations of existent data. Instead, the maximum follow-up of the reported outcomes was enlisted as the endline laboratory value. The target condition was COVID-19, and all the studies were in-hospital based with patients of any severity of disease (mild, moderate, or severe) as per the NIH classification.[18]

Databases including PubMed/MEDLINE, Cochrane Central, Web of Science, Scopus, and EMBASE were systematically searched from December 2019 until January 10, 2022. Other sources were manually searched including Science Direct, SAGE, Elsevier, and Google Scholar to ensure that no studies were omitted. The search terms across the databases and additional sources were a combination of the following: Anakinra, COVID*, SARS-CoV-2, inflammatory, CRP, D-dimer, Ferritin, hematological, laboratory, clinical, trials. No language restrictions were applied, and in case a non-English study was identified, google translate was to be used.

The titles and abstracts of all screened studies from the databases and additional sources were screened together by two authors (AS, ZS). On shortlisting studies, all authors conducted a full-text review of the studies. All disagreements were actively resolved through consensus and with the final reviewer (ZS). The Cohen's Coefficient of Agreement was calculated to compute the inter-reviewer agreement. The search process with PRISMA flowchart is depicted in Figure 1.

All the identified studies were de-duplicated by entering bibliographic details into EndNote X9 (Clarivate Analytics). The methodology was both quantitative and analytical where the mean difference (MD) on admission/enrollment and on last follow-up was analyzed. The mean difference is a common meta-analytical measure to note the difference in means from the baseline to endline, which may be both negative and positive. These laboratory values were continuous in nature and were aligned to a single scale across CRP, serum ferritin, and d-dimer. The standardized mean difference (SMD), which is an effect measure, was computed applying 95% confidence intervals (CI). A fixed-effects model was applied for the laboratory outcomes since they were converted to a single unit of measure, as recommended by Cochrane's handbook. The additional outcome for mortality was conducted using a random-effects model, with outcomes reported as Risk Ratio (RR) using 95% CI. Forest plots

FIGURE 1 PRISMA flowchart



were generated for all the outcomes that represented the effect size (SMD and RR), heterogeneity, and overall test results. Funnel plots accompanied the forest plots for all outcomes. At least 2 or more studies were required to report the same outcome measure to be meta-analyzed. Heterogeneity was testing using the χ^2-based Q test and the I^2 index. All statistical tests were conducted using Review Manger 5.4 (Cochrane). The protocol is attached in the supplementary materials.

3 | RESULTS

The overall Kappa score computed for the inter-reviewer agreement was 0.91, suggesting good agreement. The characteristics of included studies are enlisted in Table 1. In total, 2032 patients were included, of which 881 were intervened with anakinra, whereas 1151 were treated with standard care of were controls. A total of 12 observational studies (N = 1444) and 4 randomized controlled trials (N = 588) were meta-analyzed. The countries represented in this analysis include Belgium (1), France (3), Greece (2), Iran (1), Italy (4), the Netherlands (1), Oman (1), and Spain (3). Anakinra dosage and route of administration parameters are described in Table 1.

The laboratory values for d-dimer (mg/L), CRP (mg/L), and ferritin (ng/ml) are reported in Table S1. The values were reported at baseline, that is, on admission and on the last day of follow-up or peak where applicable, were presented as mean (SD) unless stated otherwise (Table S1).

Of 2032 patients included in this study, a total of 613 (69.6%) were males in the anakinra group (N = 881), and 792 (68.8%) were males in the control/SoC group (N = 1151). The MD for CRP was computed for all included studies based on the differences in admission (baseline) and endline. The overall MD was −9.66, 95% −15.47, −3.84 (p = 0.001), suggesting that the anakinra group had notable reductions in CRP laboratory values compared to control/SoC. CRP values were reported among 286 patients in the anakinra group and 369 patients in the control/SOC group. The SMD was yielded as follows: −0.46, 95% CI = −0.63, −0.28 (p < 0.001) (Figure 2).

Ferritin values were reported for 222 and 315 patients in the anakinra and control/SoC groups. The overall MD was calculated as −1467.16, 95% CI = −1583.81, −1350.5 in favor of anakinra (p < 0.001). The SMD was yielded as follows: −0.31, 95% CI = −0.52, −0.1 (p = 0.004) (Figure 3).

D-dimer laboratory values were reported at endline and baseline, both in a total of 375 patients (141 in the anakinra group and

TABLE 1 Characteristics of included studies

ID	Author, year	Study type	Country	Sample size (Anakinra vs. Control/SoC)	Gender (Male) (Anakinra vs. Control/SoC)	Anakinra dosage and route of administration
1	Cauchois et al., 2020[46]	Observational	France	22 (12 vs. 10)	6 (50%) vs. 6 (60%)	Infused IV over 2 h as a single daily dose of 300 mg for 5 days, then tapered to 200 mg for two days, and then 100 mg for 1 day
2	Huet et al., 2020[32]	Observational	France	96 (52 vs. 44)	36 (69%) 25 (57%)	Subcutaneously at a dose of 100 mg twice daily for 72 h, followed by 100 mg daily for 7 days
3	Cavalli et al., 2020[33]	Observational	Italy	52 (36 vs. 16)	29 (80.5%) vs. 14 (88%)	Low-dose anakinra was administered subcutaneously at a dose of 100 mg twice daily; high-dose anakinra was administered IV at 10 mg/kg per day (5 mg/kg twice daily, infused over 1 hour)
4	Bozzi et al., 2021[47]	Observational	Italy	120 (65 vs. 55)	52 (80%) vs. 44 (80%)	Anakinra was administered subcutaneously at 200 mg every 8 h for 3 days, then 100 mg every 8 hours up to day 14; IV approach was used if the patient was on invasive mechanical ventilation
5	Kooistra et al., 2020[14]	Observational	The Netherlands	60 (21 vs. 39)	14 (67%) vs. 33 (85%)	300 mg anakinra IV followed by 100 mg IV every six hours
6	Balkhair et al., 2021[48]	Observational	Oman	69 (45 vs. 24)	35 (78%) vs 17 (71%)	100 mg twice daily for 3 days, followed by 100 mg daily for a maximum of 7 days, subcutaneous
7	CORIMUNO−19, 2021[49]	Randomized controlled trial	France	114 (59 vs. 55)	43 (73%) vs. 37 (67%)	200 mg IV twice a day (total 400 mg) on days 1–3, then at 100 mg IV twice a day (total 200 mg) on day 4, and 100 mg IV once on day 5; 3 supplementary treatment at 400 mg IV per day on days 4–6, followed by 200 mg IV per day on day 7 and 100 mg IV per day on day 8
8	Kyriazopoulou et al., 2021[50]	Observational	Greece	260 (130 vs. 130)	81 (62.3%) vs. 84 (64.6%)	Subcutaneous anakinra 100 mg once daily for 10 days
9	Pontali et al., 2021[51]	Observational	Italy	128 (63 vs. 65)	42 (66.7%) vs. 45 (69.2%)	Anakinra 100 mg IV every 8 h for 3 days, followed by tapering (100 mg every 12 h for 1–3 days, followed by 100 mg every 24 h for 1–3 days)

TABLE 1 (Continued)

ID	Author, year	Study type	Country	Sample size (Anakinra vs. Control/SoC)	Gender (Male) (Anakinra vs. Control/SoC)	Anakinra dosage and route of administration
10	Aomar-Millán et al., 2021[52]	Observational	Spain	143 (10 vs. 133)	10 (100%) vs. 79 (59.4%)	Patients weighing 50–60 kg received 100 mg/12 h, patients weighing 60–75 kg received 100 mg/8 h, and patients weighing >75 kg received 100 mg/6 h. On the second day, all patients received 100 mg/12 h from day 2 to day 6; subcutaneous
11	Kharazmi et al., 2021[53]	Randomized controlled trial	Iran	30 (15 vs. 15)	8 (53.3%) vs. 11 (73.3%)	Anakinra 100 mg IV once daily
12	Garcia et al., 2021[54]	Observational	Spain	342 (125 vs. 217)	70 (56%) vs. 127 (58%)	Anakinra administrated subcutaneously at a standard dose of 200 mg twice on day 1, followed by 100 mg twice daily until a course of 10 days was completed
13	Franzetti et al., 2021[55]	Observational	Italy	112 (56 vs. 56)	41 (73.2%) vs. 46 (82.1%)	Subcutaneously for 7 days at 100 mg, four times a day in a regular ward or 200 mg three times daily IV if in intensive care
14	Calle et al., 2021[56]	Observational	Spain	40 (20 vs. 20)	14 (70%) vs 12 (60%)	Subcutaneously at 100 mg/12 h on day 0, then at 100 mg/24 h from day 1 to day 5; re-evaluated on day 6 based on clinical progress
15	Karakike et al., 2021[57]	Randomized controlled trial	Greece	102 (60 vs. 42)	45 (75%) vs. 34 (81%)	Anakinra was administered at 200 mg IV every 8 hours for 7 days
16	Declercq et al., 2021[58]	Randomized controlled trial	Belgium	342 (112 vs. 230)	87 (78%) vs. 178 (77%)	100 mg once daily subcutaneously for 28 days or until hospital discharge on top of standard of care

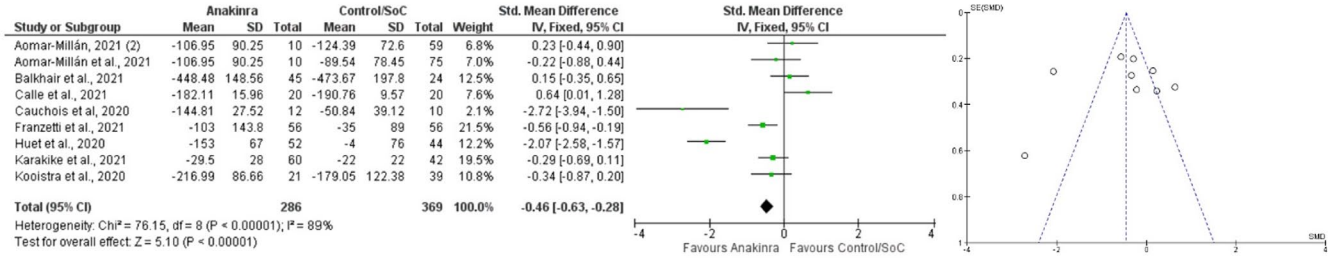


FIGURE 2 Forest plot and funnel plot of CRP (mg/L) (mean difference) in anakinra versus control/SoC groups. Heterogeneity: $Chi^2 = 76.15$, df = 8 ($p < 0.00001$); $I^2 = 89\%$. Test for overall effect: $Z = 5.10$ ($p < 0.00001$)

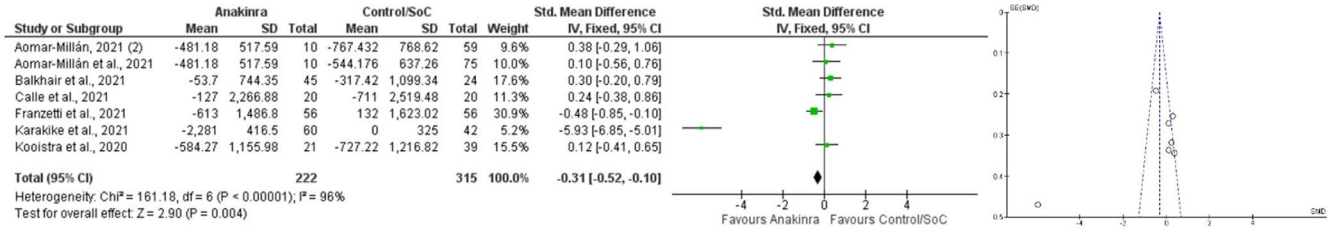


FIGURE 3 Forest plot and funnel plot of ferritin (ng/ml) (mean difference) in anakinra versus control/SoC groups. Heterogeneity: $Chi^2 = 161.18$, df = 6 ($p < 0.00001$); $I^2 = 96\%$. Test for overall effect: $Z = 2.90$ ($p = 0.004$)

234 in the anakinra/SoC group). The MD was computed as −4.04, 95% CI = −4.43, −3.64, favoring the anakinra group ($p < 0.001$). The SMD was yielded as follows: −0.38, 95% CI = −0.63, −0.12 ($p = 0.004$) (Figure 4).

The death (mortality) trends were reported as a common endpoint across all studies with a patient population of 917 participants in the anakinra group and 1390 in the control/SoC group. The results were yielded as follows: RR = 0.64, 95% CI = 0.49–0.83 ($p < 0.001$). The results indicate that the risk of mortality was reduced in the anakinra group by 36% ($I^2 = 48\%$) (Figure 5).

To note any sources of bias, a funnel plot was generated and studied. While we expected for there to be large sources of heterogeneity due to the differing nature of study types included, the funnel plot shows an otherwise inverted funnel shape with only 3 studies deviating from the total of 16. It may be stated that minimal-moderate sources of bias were present in this meta-analysis (Figure 6).

4 | DISCUSSION

Our results indicate that, in patients admitted with COVID-19, anakinra reduces hyper-inflammatory markers compared to the standard of care. This effect is significant for CRP concentrations, serum ferritin, and d-dimer levels. Of these biomarkers, CRP is the most commonly tested to document the extent of inflammation in COVID-19 patients. Our results demonstrate a profound reduction in the hyper-inflammatory phenotype of COVID-19, known as cytokine storm syndrome (CSS), which is associated with a high mortality rate. The underlying etiologies that are currently undergoing investigation include systemic inflammation, hyper-ferritinemia, hemodynamic instability, and multiorgan failure, for which we have evaluated the most important biomarkers.

CRP is clinically used as a plasma inflammatory signature, and it serves as an important biomarker to document pathological inflammatory responses.[19] CRP is the prototype of acute-phase reactants (APPs) produced primarily by hepatocytes in response to various inflammatory cytokines, including IL-1β and IL-6.[20] Up to 86% of severe COVID-19 patients have elevated CRP, which is considered a relevant downstream biomarker.[21] The clinical utility of CRP as a prognostic test for COVID-19 severity has previously been established, and it remains broadly relevant to correlate with severity and treatment responses.[22] The IL-1 signaling pathway is a major target for immune modulation and serves as the apical pro-inflammatory mediator, especially in innate immunity.[23] Anakinra is a short-acting IL-1Ra leading to dual IL-1α and IL-1β inhibition, which is associated with lower CRP concentration.[24] IL-β is the primary form of circulating IL-1, whereas IL-1α remains largely membrane-bound.[25] IL-1α and IL-1β bind to the universally expressed cell surface receptor, IL-1R, to activate the cascade of IL-1-mediated inflammatory responses downstream.[23] Anakinra antagonizes the IL-1R to control the activity of the NLRP3 inflammasome through caspase-1-mediated activation of IL-1β and production of a variety of innate inflammatory responses downstream, including IL-6, which is closely linked to the severity of COVID-19 infection.[26,27] Overall, anakinra is mechanistically and clinically emerging as a strong candidate to target the pro-inflammatory syndrome observed in COVID-19 patients with a significant reduction in CRP levels reported in our findings as well as other studies.[28]

Anakinra has previously shown efficacy in patients with sepsis and features of MAS.[29] MAS is associated with an excessive inflammatory response, specifically high ferritin concentrations.[30] The

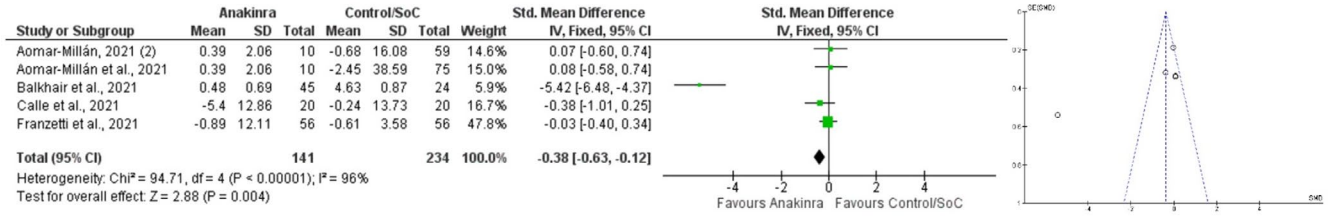


FIGURE 4 Forest plot and funnel plot of D-dimer (mg/L) (mean difference) in anakinra versus control/SoC groups. Heterogeneity: $Chi^2 = 94.71$, df = 4 ($p < 0.00001$); $I^2 = 96\%$. Test for overall effect: $Z = 2.88$ ($p = 0.004$)

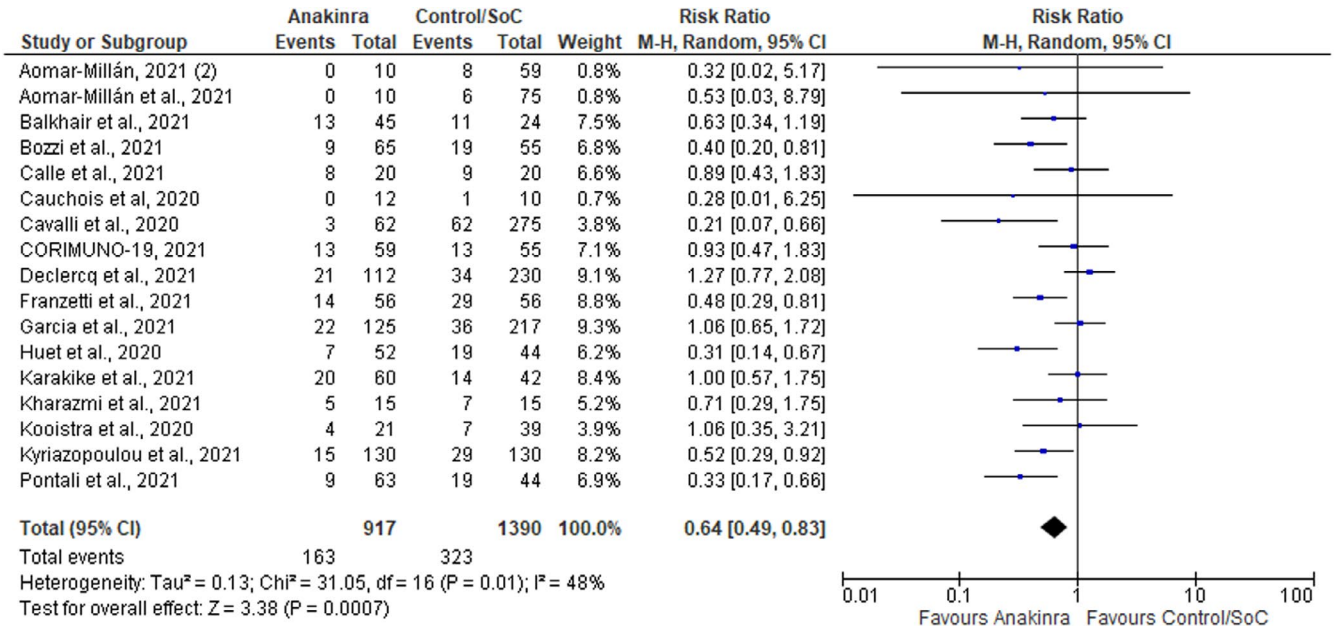
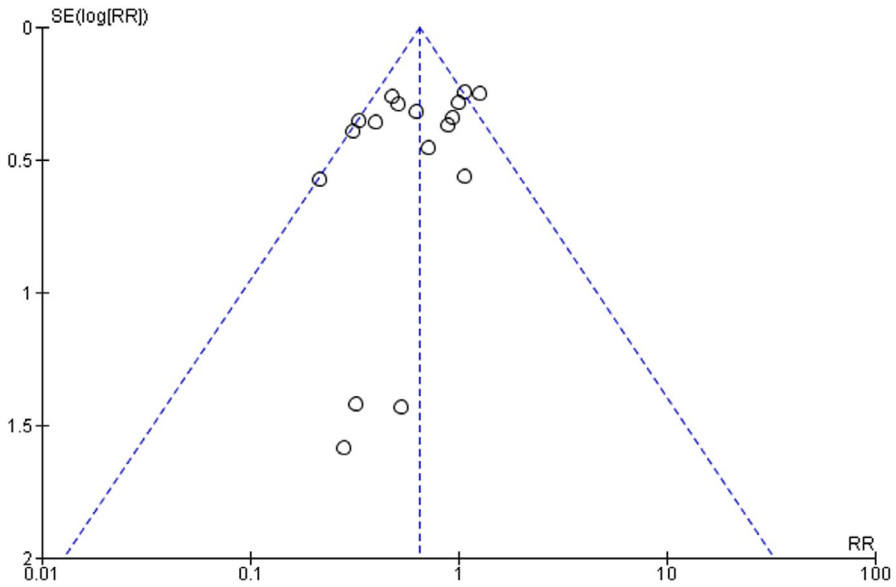


FIGURE 5 Forest plot for mortality (endpoint) in anakinra versus control/SoC groups. Heterogeneity: $Tau^2 = 0.13$; $Chi^2 = 31.05$, df = 16 ($p = 0.01$); $I^2 = 48\%$. Test for overall effect: $Z = 3.38$ ($p = 0.0007$)

FIGURE 6 Funnel plot to assess for publication bias



cutoff established for ferritin levels in MAS is higher than 2000 ng/ml.[31] While the hyper-inflammation in COVID-19 and MAS cannot be equated, ferritin levels are being assessed as a biomarker to detect clinical improvement in COVID-19 patients following high-dose anakinra treatment across clinical trials.[10,32,33] Ferritin is an APP that seems to augment immediately in COVID-19 patients.[34] The H-chain

of ferritin-activating macrophages and increased iron metabolism required for controlling viral infections is a potential mechanism for increased pro-inflammatory cytokines in COVID-19.[35] Also, ferritin may be related to inflammatory parameters and suggestive of cellular damage when its value is over 600 ng/ml.[36] The high ferritin levels observed in COVID-19 patients also result in ferroptosis, one of the underlying mechanisms in acute respiratory distress syndrome (ARDS), similar to COVID-19 pneumonia.[37] Iron parameters including ferritin have also been correlated with improvement in the sequential organ failure assessment (SOFA) score, which provides further rationale for the utility of Anakinra in COVID-19 patients.[38] While the role of ferritin as an inflammatory biomarker in COVID-19 remains unclear, Anakinra has a potential role in the hyper-ferritinemia associated with COVID-19 progression and severity.[39] We demonstrate the reduction in serum ferritin levels with anakinra use which is encouraging.

D-dimer is a fibrin degradation product and a well-recognized biomarker for thrombotic disorders.[40] Its utility as a prognostic marker has already been established in community-acquired pneumonia and more recently in COVID-19 patients.[41,42] While there is variation in the cutoff for morbidity and mortality prediction, a value less than 0.5 ug/ml is widely considered normal.[43] Anakinra treatment has been shown to reduce d-dimer levels in COVID-19 patients in clinical trials, suggesting a positive effect on underlying cardiovascular and thrombotic pathologies.[44,45] Our results similarly demonstrate beneficial outcomes with anakinra treatment and d-dimer reduction in COVID-19 patients.

On noting the mortality trends and outcomes across all studies, we find favorable results among patients that have elevated inflammatory markers with markedly low risk ratio (RR = 0.64). The analysis highlights the requirement for antithrombotic therapy in patients with COVID-19 that are hospitalized. In hospitalized patients with COVID-19, coagulation and hematologic parameters are typically measured. Patients who are receiving anticoagulant therapy for underlying chronic conditions ought to continue medications once diagnosed with COVID-19. However, current guidelines for non-hospitalized patients with COVID-19 state that anticoagulant therapy ought not to be initiated for the prevention of VTE or arterial thrombosis unless the patient has other indications for therapy. On the whole, our laboratory analysis and mortality outcomes suggest that there is a requirement for better antithrombotic management and guidelines for hospitalized patients because thrombosis may be more driven with inflammation at this stage.

To the best of our knowledge, this is the first patient-level meta-analysis that evaluates the effect of anakinra treatment in COVID-19 patients and relevant hyper-inflammatory biomarkers to advance the current understanding of this treatment. Our findings suggest a positive impact on the hyper-inflammatory biomarkers noted in COVID-19 patients. However, anakinra is an immunosuppressive drug that may theoretically cause more harm than benefit when targeting "beneficial" inflammation.[28] Anakinra is noted to have positive effects on hyper-inflammation, which needs to be evaluated further. The current criteria for anakinra administration in clinical trials consider CRP, serum ferritin, and d-dimer levels; there is no consensus on the standard cutoff in COVID-19 patients. Another important consideration is the dose and route of administration of anakinra due to its short half-life. This study's main limitation is the observational design of many studies included in the meta-analysis. These studies may be biased and have possible confounders such as concomitant use or lack of dexamethasone as the standard of care. Anakinra, regardless, remains a strong potential candidate, as demonstrated by our findings, and it is recommended to conduct randomized clinical trials with caution. These trials may focus on homogenous eligibility criteria and dosing regimens to provide meaningful insight into the efficacy of anakinra in COVID-19 patients with hyper-inflammation.

5 | CONCLUSION

This meta-analysis reports the favorable effects of anakinra treatment in patients with COVID-19 in reducing hyper-inflammatory markers characteristic of the severity of the disease, specifically CRP concentrations, serum ferritin, and d-dimer levels. Large randomized control trials are required to confirm the benefits of anakinra treatment in COVID-19 patients. As the COVID-19 pandemic is challenged with new variants, it is of utmost importance to consider the evaluation of anakinra in the anti-COVID-19 armamentarium.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

All data obtained for the purpose of this meta-analysis are freely available online.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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