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3 **Anakinra in hospitalized non-intubated patients with coronavirus disease 2019: a systematic**
4 **review and meta-analysis**
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Abstract

Background: Acute respiratory distress syndrome and cytokine release syndrome are the major complications of coronavirus disease 2019 (COVID-19) associated with increased mortality risk.

Objectives: We performed a meta-analysis to assess the efficacy and safety of anakinra in adult hospitalized non-intubated patients with COVID-19.

Search methods: Relevant trials were identified by searching literature until 24 April 2021 using the following terms: anakinra, interleukin 1, coronavirus, COVID-19, SARS-CoV-2.

Selection criteria: Trials evaluating the effect of anakinra on the need for invasive mechanical ventilation and mortality in hospitalized non-intubated patients with COVID-19.

Results: Nine studies (n=1,119) were eligible for inclusion in the present meta-analysis. Their bias risk with reference to the assessed parameters was high. In pooled analyses, anakinra reduced the need for invasive mechanical ventilation (odds ratio, OR: 0.38, 95% confidence interval, CI: 0.17-0.85, p=0.02, I²=67%; 6 studies, n=587) and mortality risk (OR: 0.32, 95% CI: 0.23-0.45, p<0.00001, I²=0%; 9 studies, n=1,119) compared with standard of care therapy. There were no differences regarding the risk of adverse events, including liver dysfunction (OR: 0.75, 95% CI: 0.48-1.16, p>0.05, I²=28%; 5 studies, n=591) and bacteremia (OR: 1.07, 95% CI: 0.42-2.73, p>0.05, I²=71%; 6 studies, n=727).

Conclusions: Available evidence shows that treatment with anakinra reduces both the need for invasive mechanical ventilation and mortality risk of hospitalized non-intubated patients with COVID-19 without increasing the risk of adverse events. Confirmation of efficacy and safety requires randomized placebo-controlled trials.

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3 **Keywords:** anakinra, interleukin 1, coronavirus, COVID-19, SARS-CoV-2
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6 **Key messages**
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- 9 • Our meta-analysis assessed the efficacy and safety of anakinra in hospitalized non-
10 intubated patients with COVID-19.
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 - 12 • Anakinra reduced the need for invasive mechanical ventilation and mortality risk in non-
13 intubated patients with COVID-19.
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 - 15 • Anakinra did not increase the liver enzymes or bacteremia risk in severely ill COVID-19
16 patients.
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Introduction

At the end of 2019, a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was identified as the cause of a cluster of pneumonia cases in Wuhan, in the Hubei Province of China and finally declared as pandemic in February 2020.[1] Until April 2021, about 147 million cases of coronavirus disease 2019 (COVID-19) and approximately 3 million deaths have been reported worldwide.[1] Although the majority of SARS-CoV-2 infections are mild to moderate, a considerable proportion of the infected patients develop severe disease and is hospitalized due to increased needs for ventilation.[1, 2] Among those, almost 30% are finally admitted to intensive care units (ICUs) to receive ventilation assistance because of acute respiratory distress syndrome (ARDS).[3-5] The reported mortality rates in such patients are high and range from 28 to 78%.[4, 6-8] Apart from dexamethasone in critically ill patients with COVID-19, there are no well-established effective therapies to treat SARS-CoV-2 infection.[9-11] Considering the noticed shortage of ICU beds and consequently the increased burden in medical wards,[12] identifying therapeutic modalities to improve adverse outcomes and prevent ICU admission and death in this population remains a public health emergency.

A subgroup of SARS-CoV-2 infected patients manifest hyperinflammatory symptoms that resemble the cytokine storm syndromes characterized by increased release of chemokines, growth factors and cytokines, including interleukins (ILs).[3, 13, 14] In this context, anakinra, an IL-1 receptor antagonist, used for the treatment of autoinflammatory disorders, has been considered in such patients.[15-17] Previous reports have demonstrated beneficial effects with anakinra in severe sepsis with multiorgan inflammatory dysfunction or secondary hemophagocytic lymphohistiocytosis,[18, 19] whereas case series and 2 recently published open label trials have

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3 shown that treatment with anakinra is associated with laboratory and clinical improvement in
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5 COVID-19 patients with hyperinflammation.[20-26]
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8 Considering the ongoing need for efficacious treatment modalities for patients severe
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10 COVID-19, we meta-analyzed available data reporting on the efficacy and safety of anakinra use
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12 in hospitalized non-intubated patients with COVID-19.
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19 **Materials and Methods**

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22 The present meta-analysis has been conducted according to the Preferred Reporting Items for
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24 Systematic Reviews and Meta-Analyses (PRISMA) (Supplementary).[27] Neither ethics approval
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26 nor patients' consent was required for this analysis.
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32 *Eligibility Criteria*

33 34 35 *Types of Studies*

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38 We aimed to include published randomized placebo-controlled trials (RCTs) in the present meta-
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40 analysis. In case of any lack of published RCTs, retrospective or prospective observational studies
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42 were included.
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49 *Study Participants*

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52 Studies including adult hospitalized non-intubated patients with COVID-19 were considered
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54 eligible. COVID-19 was diagnosed by quantitative RT-PCR and lung infiltrates depicted by either
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3 chest x-ray or computerized tomography (CT). The definition of COVID-19 severity was based
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5 on the presence of respiratory failure and need for non-invasive ventilation.[11] In case of studies
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7 enrolling patients who required invasive mechanical ventilation, we included only those reporting
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9 separate data on their non-intubated subjects.
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16 *Interventions*

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19 Studies comparing anakinra with standard of care therapy in COVID-19 were included in the
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21 present meta-analysis. Standard of care therapy included anticoagulant treatment, azithromycin,
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23 hydroxychloroquine, antibiotics, or corticosteroids. Trials comparing anakinra with other
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25 immunomodulating drugs were excluded from the present meta-analysis.
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31 *Outcomes*

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34 Mortality and need for admission to the ICU with invasive mechanical ventilation were our
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36 primary outcomes of interest. The following adverse events were the secondary outcomes of
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38 interest: liver enzyme increase and bacteremia.
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45 *Information Sources*

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48 Relevant trials were identified by searching MEDLINE, EMBASE, CENTRAL and
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50 clinicaltrials.gov.gr until 24 April 2021 using the following terms: anakinra, interleukin 1,
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52 coronavirus, COVID-19, SARS-CoV-2. The trials included in our analysis were also scrutinized
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54 for other trials fulfilling our eligibility criteria.
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Data Collection and Analysis

Selection of Studies

At the initial stage of review and each update, two authors (FB, SFN) independently selected the trials which were eligible for inclusion in the present meta-analysis.

Data Extraction and Management

Two review authors (FB and SFN) independently extracted data using an extraction form recording publication details, study population, randomization, allocation concealment, blinding, interventions and results of each trial. A standardized extraction tool was developed by consensus and refined after preliminary testing on a subset of the full-text articles. The extraction tool included a full description of study characteristics, the medications patients received (dose, frequency, route, duration) and the inferences made in each study. Any differences between them were resolved by consulting the other review authors (AL, EG, MK, EL, HM).

Assessment of Risk of Bias in Included Studies

In case of RCTs, we would assess the bias risk (low, unclear or high) of the following parameters: (i) sequence generation, (ii) allocation concealment, (iii) blinding (of participants, personnel and outcome assessors), (iv) incomplete outcome data addressed, (v) free of selective outcome reporting and vi) free of other bias.[28] Cohort studies were assessed using the Newcastle-Ottawa Scale.[29] The comparability domain of the Newcastle-Ottawa Scale was the primary differentiation point for a study's risk of bias in this context and was used to determine global risk

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3 of bias (0 = high risk, 1 = some concerns, and 2 = low risk).[30] Any differences between FB and
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5 SFN were resolved by consultation.
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11 *Measurements of Treatment Effect*

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14 The odds ratio (OR) and the corresponding 95% confidence intervals (CIs) have been estimated in
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16 order to assess the treatment effect of anakinra on the investigated outcomes of interest.
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22 *Synthesis of Results*

23 *Missing Data*

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28 Trials not reporting on our primary outcomes of interest in the investigated population have not
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30 been included in the present work.
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37 *Assessment of Heterogeneity*

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40 Heterogeneity between trial results was tested using a standard chi-square test ($p < 0.1$ was
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42 considered statistically significant) and I^2 statistic was used as a measure of heterogeneity.[9] The
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44 following ranges and descriptions were used: (i) 0–40%: might not be important, (ii) 30–60%: may
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46 represent moderate heterogeneity, (iii) 50–90%: may represent substantial heterogeneity and iv)
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48 75–100%: considerable heterogeneity.
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55 *Subgroup Analysis and Investigation of Heterogeneity*

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3 In case of observed statistically significant heterogeneity, a random-effect meta-analysis was
4 performed. Otherwise, a fixed-effect model was used.
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11 **Results**

12 *Study selection*

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17 Hitherto no placebo controlled RCT fulfilling our eligibility criteria has been completed yet
18 (Figure 1). Of the 449 references identified by electronic and manual search, 9 studies were
19 included in the present meta-analysis (n=1,119): 1 prospective and 6 retrospective cohorts, an
20 open-label, bayesian randomized clinical trial (CORIMUNO-ANA-1) nested with a cohort and an
21 open label trial (SAVE) with propensity-matched comparators.[25, 26, 31-37]
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32 *Study characteristics*

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35 The design of the studies along with the baseline characteristics of their subjects are demonstrated
36 in Table 1. Anakinra was administered subcutaneously in most studies, but its dose and treatment
37 duration varied across the included studies. Notably, 6 studies involved patients with severe
38 COVID-19, but only those presenting with increased inflammation markers (C-reactive protein,
39 CRP or ferritin). A high proportion of the study participants were diagnosed with comorbidities
40 associated with increased mortality risk in COVID-19. Standard of care therapy included broad-
41 spectrum antibiotics, azithromycin and hydroxychloroquine, whereas corticosteroid
42 administration rates were high in 3 studies.
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Bias Risk within Studies

As shown in Table 1, the noticed bias risk in most studies was high, mainly regarding their comparability and outcomes.

Effects of Interventions

The investigated outcomes of interest are presented in Table 2. The pooled analyses demonstrated that anakinra reduced the need for invasive mechanical ventilation (OR: 0.38, 95% CI: 0.17-0.85, $p=0.02$, $I^2=67\%$; Figure 2A) and mortality risk (OR: 0.32, 95% CI: 0.23-0.45, $p<0.00001$, $I^2=0\%$; Figure 2B) when compared with standard of care therapy.

No difference was noted regarding the risk of adverse events, including liver dysfunction (OR: 0.75, 95% CI: 0.48-1.16, $p>0.05$, $I^2=28\%$; Figure 3A) and bacteremia (OR: 1.07, 95% CI: 0.42-2.73, $p>0.05$, $I^2=71\%$; Figure 3B).

Apart from mortality risk, moderate to substantial heterogeneity was noticed in the rest pooled analyses (Table 2).

Discussion

The present meta-analysis shows that anakinra reduces the need for invasive mechanical ventilation and lowers mortality risk in hospitalized non-intubated patients with COVID-19, without increasing the risk of adverse events.

The pandemic COVID-19 remains a public health emergency.[1] Although the majority of SARS-CoV-2 infections are mild to moderate, 14% of patients develop severe disease presenting

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3 with dyspnea, hypoxia, or >50% lung involvement on imaging within 24 to 48 hours and 5%
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5 critical disease presenting with respiratory failure, shock and multi-organ dysfunction.[1, 2] One
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7 out of 3 hospitalized patients with COVID-19 develop ARDS and are finally admitted to ICUs to
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9 receive ventilation assistance with high mortality rates.[3-8] No well-established effective
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11 therapies confronting COVID-19 have been found yet.[9] Only dexamethasone has been shown to
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13 significantly reduce 28-day mortality in patients with critical COVID-19.[10, 11] Remdesivir, a
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15 novel nucleotide analogue, has been proposed in hospitalized patients with severe COVID-19
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17 requiring low-flow supplemental oxygen, given the potential reduction in time to clinical
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19 improvement,[10, 11, 38-40] but the World Health Organization recommends against its routine
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21 use.[11] In areas with high COVID-19 prevalence, the high number of severely ill patients with
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23 COVID-19 and ARDS exceeds the maximum capacity of ICUs.[12] Due to the shortage of ICU
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25 beds, many SARS-CoV-2 infected patients with ARDS have received maximum supportive
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27 treatment with non-invasive ventilation in medical wards, while they are awaiting for ICU access
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29 and further therapeutic approaches.[12] Although an effective vaccination remains the cornerstone
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31 to combat the emerging pandemic COVID-19,[41] finding therapies to reduce mortality and
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33 prevent ICU admission in this population remains an imperative need.
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41 A few SARS-CoV-2 infected patients develop symptoms indicating severe inflammation
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43 that is alike to other cytokine storm syndromes, such as secondary hemophagocytic
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45 lymphohistiocytosis, macrophage activation syndrome and chimeric antigen receptor [CAR] T-
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47 cell-mediated cytokine release syndrome.[3, 13, 14, 42] This hyper-inflammation is mirrored
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49 systemically by pronounced increases in CRP and ferritin levels and its orchestrating mediators
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51 include various cytokines and chemokines, such as IL-6, IL-1, IL-10, granulocyte-colony
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53 stimulating factor, monocyte chemoattractant protein 1, macrophage inflammatory protein 1 α , and
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3 tumor necrosis factor (TNF)- α . [3, 13, 14, 42] Hence, various monoclonal antibodies against
4 different cytokines or JAK–STAT inhibitors represent attractive therapeutic options in this
5 setting. [13, 17, 42] Indeed, anakinra, which blocks the activity of the proinflammatory cytokines
6 IL-1 α and IL-1 β and has been previously approved for the treatment of autoinflammatory
7 disorders, such as adult-onset Still’s disease, systemic-onset juvenile, idiopathic arthritis, and
8 familial Mediterranean fever, has been considered in such cases. [15, 32] Moreover, its remarkable
9 safety profile and short half-life makes anakinra more appealing to use in severely ill patients. [15]
10 Indeed, previous reports have confirmed its efficacy on cytokine release syndromes related with
11 multiorgan inflammatory dysfunction in severe sepsis or secondary hemophagocytic
12 lymphohistiocytosis. [18, 19]

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27 Although no placebo-controlled RCTs have been completed yet, accumulating evidence
28 favors the use of anakinra for the treatment of COVID-19. Case series and 2 recently published
29 open label trials have shown that anakinra is associated with laboratory and clinical improvement
30 in COVID-19 patients with hyperinflammation. [20-26] Previous meta-analyses ($n \leq 184$) including
31 up to 4 observational studies demonstrated that anakinra was associated with a lower mortality risk
32 and need for invasive mechanical ventilation compared with standard of care therapy. [43-45] In
33 contrast, the present meta-analysis integrates data from 9 studies ($n=1,119$) and focuses on the
34 efficacy and safety of anakinra in hospitalized non-intubated patients with COVID-19.
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46 Considering the reduction in both the need for invasive mechanical ventilation and
47 mortality risk, our meta-analysis is the most updated and largest to propose that anakinra represents
48 an effective treatment for non-intubated patients with COVID-19. Of note, most studies in our
49 meta-analysis enrolled patients with hyperinflammation. In line with our findings, RCTs
50 (RECOVERY and REMAP-CAP) handling tocilizumab, an IL-6 inhibitor, demonstrated the
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3 efficacy of active treatment in hospitalized COVID-19 patients with increased inflammatory
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5 markers.[46, 47]
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8 A recent report denoted that anakinra and tocilizumab may increase the risk for blood
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10 stream infections in ICU patients (n=235) with severe COVID-19 (HR: 3.20, 95% CI: 1.31-7.81,
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12 p=0.011).[48] Despite the difficulty in defining the side effects of a treatment modality in critically
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14 ill patients with systemic disease receiving additional therapies, our results derived from a larger
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16 sample indicate that anakinra remains a safe therapeutic option in SARS-CoV-2 infected patients,
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18 since it was not associated with a high risk of bacteremia or liver dysfunction.
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23 The acknowledged limitations of this meta-analysis relate with the design of the included
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25 studies, their sample size and follow-up disparities, along with the different dosage and route of
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27 anakinra administration.
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33 **Conclusions**

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36 Available evidence shows that treatment with anakinra reduces both the need for invasive
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38 mechanical ventilation and mortality risk in hospitalized non-intubated patients with COVID-19.
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40 In the context of the current pandemic and the great shortage of ICUs beds, treatment with anakinra
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42 should be promptly tested by randomized placebo-controlled trials.
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12
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25 and interpretation of data for the present work and drafted the present manuscript. Dr Kosmidou,
26 Prof Liberopoulos and Prof Milionis contributed to the conception and design of the present work
27 and they revised it critically for important intellectual content. All authors finally approved the
28 version to be published and agreed to be accountable for all aspects of the present work in ensuring
29 that questions related to the accuracy or integrity of any part of the work are appropriately
30 investigated and resolved.
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42 **Data Availability Statement:** The data underlying this article are available in the article.
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3 **Legends to Figures**
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6 **Figure 1.** PRISMA flowchart of study selection
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9 **Figure 2.** Forest plot for (A) the need for invasive mechanical ventilation and (B) mortality risk
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12 **Figure 3.** Forest plot for adverse effects: (A) liver enzyme increase and (B) bacteremia
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18 **Legends to Tables**
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21 **Table 1.** Characteristics of the included cohorts
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24 * Mortality and need for IMV was included in the secondary outcomes of interest
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27 Abbreviations: ARDS, acute respiratory distress syndrome; bid, 2 times a day; CRP, C-reactive
28 protein; CT, computerized tomography; IMV, invasive mechanical ventilation; IL-6, interleukin-
29 6; iv, intravenously; N/A, not applicable; PEEP, positive end-expiratory pressure; SARS-CoV-2,
30 serious acute respiratory syndrome coronavirus 2; tid, 3 times a day, qd, once a day; qid, 4 times
31 a day; sc, subcutaneously; WHO-CPS, WHO Clinical Progression Scale
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39 **Table 2.** Outcomes of interest
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Table 1

	Huet et al. [31]	Cavalli et al. 2020 [32]	Cauchois et al. [33]	Balkhair et al. [34]
Type of study	Retrospective cohort	Retrospective cohort	Retrospective cohort	Prospective open label trial
Bias risk	High	High	High	High
Anakinra (dose, route, duration)	100 mg (sc) bid for 3 days, followed by 100 mg qd for 7 days	100 mg (sc) bid or 10 mg/kg (iv) (divided in two doses) until sustained clinical benefit (>75% CRP reduction and pO ₂ /FiO ₂ >200 mmHg) or adverse events (death, bacteremia or side effects)	300 mg (iv) qd for 5 days, followed by 200 mg qd for 2 days and 100 mg qd for 1 day	100 mg (sc) bid for 3 days, followed by 100 mg (sc) qd for ≤7 days
Control group	Standard of care	Standard of care	Standard of care	Standard of care
Primary Outcome	IMV need or survival in 7 days	IMV need or survival in 21 days	IMV need or survival in 20 days	IMV need or survival in 14 days

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Inclusion criteria	-SARS-CoV-2 infection	-SARS-CoV-2 infection	-SARS-CoV-2 infection	-SARS-COV-2 infection
	-Bilateral infiltrates on a lung CT scan or chest x-ray	-Bilateral infiltrates on lung CT scan or chest x-ray	-Pneumonia rapidly deteriorating	-Bilateral infiltrates on chest x-ray
	-SpO ₂ ≤93% under ≥6 L/min of O ₂ or SpO ₂ ≤93% on 3 L/min with a saturation on ambient air decreasing by 3% in the previous 24 h	-pO ₂ /FiO ₂ <200 mmHg with PEEP ≥5 cm H ₂ O	-Increasing O ₂ requirement of >4 L/min within the previous 12 h	- respiratory rate >30/min and SpO ₂ <90% on ambient air or SpO ₂ <93% under O ₂ >6L/min or ARDS
N of participants	96	52	22	69
Sex (male), %	64	82	55	75
Mean age, years	71	67	60	51
Comorbidities				
Smoking, %	N/A	11	18	N/A

1					
2					
3	Body mass index,	27.3	N/A	26.3	N/A
4					
5	kg/m ²				
6					
7	Hypertension, %	63	50	32	41
8					
9	Diabetes, %	31	21	13	41
10					
11	Coronary artery	20	11	13	N/A
12					
13	disease, %				
14					
15	Pulmonary diseases, %	20	8	26	N/A
16					
17	Chronic kidney disease,	N/A	11	5	N/A
18					
19	%				
20					
21					
22					
23	Inflammatory				
24					
25	markers				
26					
27					
28	Lymphocyte count	990	N/A	N/A	1200
29					
30	cells/mm ³				
31					
32	CRP, mg/L	164	164	155	145
33					
34	D-dimers, ng/mL	3786	N/A	N/A	850
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Lactate dehydrogenase, U/L	471	471	N/A	519
Ferritin, ng/mL	2025	1497	1481	1274
Interleukin-6, pg/mL	93	N/A	N/A	77
Concomitant therapies, %				
Hydroxychloroquine	38	100	100	7
Azithromycin	43	100	100	87
Broad-spectrum antibiotics	92	10	100	99
Corticosteroids	2	0	0	59
Duration of symptoms before treatment, days	7 days	N/A	N/A	9

	Bozzi et al. [35]	Cavali 2021 et al. [36]	Franzetti et al. [37]	CORIMUNO-ANA-1 [25]	Kyriazopoulou et al. [26]
Type of study	Retrospective cohort	Retrospective cohort	Retrospective cohort	Open-label, Bayesian randomized clinical trial (CORIMUNO-ANA-1), nested within the CORIMUNO-19 cohort	Open label trial (SAVE) with propensity-matched standard-of care comparators
Bias risk	High	High	High	Some	Some
Anakinra (dose, route, duration)	200 mg (sc) tid for 3 days, followed by 100	10 mg/kg (iv) (divided in two doses) until sustained clinical	100 mg (sc) qid or 200 mg (iv) tid for 7 days	200 mg (iv) bid on days 1–3, 100 mg bid on day 4, 100 mg qd on day 5	100 mg (sc) qd for 10 days

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mg (sc) tid up to
day 14
benefit (sustained
improvement of
respiratory
parameters and
>75% CRP
reduction)

Control group	Standard of care	Standard of care	Standard of care	Standard of care	Standard of care
Primary Outcome	Survival in 28 days	Survival in 28 days	Survival in 28 days	IMV need or survival in 14 days	Severe respiratory failure incidence by day 14 *
Inclusion criteria	-SARS-CoV-2 infection -Pneumonia - Respiratory failure with need of supplemental	-SARS-CoV-2 infection - Bilateral lung infiltrates on a lung CT scan or chest x-ray	-SARS-CoV-2 infection - Bilateral lung infiltrates on a lung CT scan or chest x-ray	-SARS-CoV-2 infection -Need for ≥ 3 L/min of oxygen by mask or nasal cannula but	- SARS-CoV-2 infection - Lung infiltrates on a lung CT scan or chest x-ray compatible with

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	O ₂ (O ₂ therapy from 40% FiO ₂ venturi mask to MIV) -CRP >100 mg/L and/or ferritin ≥1000 ng/mL	-pO ₂ /FiO ₂ <300 mmHg -CRP >100 mg/L or/and ferritin >900 ng/ml	-PO ₂ /FiO ₂ <250 mmHg on ambient air requiring ventilatory support, either with CPAP or orotracheal intubation, to achieve a PEEP ≥8 cm H ₂ O - CRP ≥100 mg/L and/or ferritin ≥900 ng/ml	without ventilation assistance - WHO-CPS ≥5 -CRP ≥25 mg/L	lower-tract respiratory infection -suPAR ≥6 ng/ml
N of participants	120 (39 intubated subjects)	337	112 (12 intubated subjects)	116	260
Sex (male), %	80	75	78	66	63

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Mean age, years	62	67	67	66	64
Comorbidities					
Smoking, %	N/A	N/A	N/A	17	N/A
Body mass index, kg/m ²	N/A	N/A	N/A	26.6	N/A
Hypertension, %	N/A	N/A	53	N/A	48
Diabetes, %	N/A	20	17	29	28
Coronary artery disease, %	N/A	N/A	18	N/A	9
Pulmonary diseases, %	N/A	N/A	7	15	7
Chronic kidney disease, %	N/A	N/A	N/A	7	2
Inflammatory markers					

Lymphocyte count, cells/mm ³	750	900	689	800	964
CRP, mg/L	152	130	175	121	58
D-dimers, ng/mL	1246	N/A	3096	1111	N/A
Lactate dehydrogenase, U/L	N/A	380	423	447	N/A
Ferritin, ng/mL	1555	1279	1620	1298	572
Interleukin-6, pg/mL	N/A	N/A	N/A	N/A	N/A
Concomitant therapies, %					
Hydroxychloroquine	98	100	100	5	48
Azithromycin	N/A	100	100	13	77
Broad-spectrum antibiotics	N/A	100	100	67	N/A
Corticosteroids	54	18	0	51	38

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Duration of symptoms before treatment, days	7	N/A	7	10	8
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Table 2

Outcome	Included studies (n)	Anakinra patients	Control patients	Odds Ratio	95% Confidence Interval	P for effect	I²(%)
Overall Studies	9	485	634				
Need for invasive mechanical ventilation	6	63/317 (20%)	114/270 (42%)	0.38	0.17-0.85	0.02	67
Mortality	9	64/485 (13%)	194/634 (31%)	0.32	0.23-0.45	<0.00001	0
Liver enzyme increase	5	57/322 (18%)	62/269 (23%)	0.75	0.48-1.16	0.20	28
Bacteremia	6	46/391 (12%)	48/336 (14%)	1.07	0.42-2.73	0.90	71

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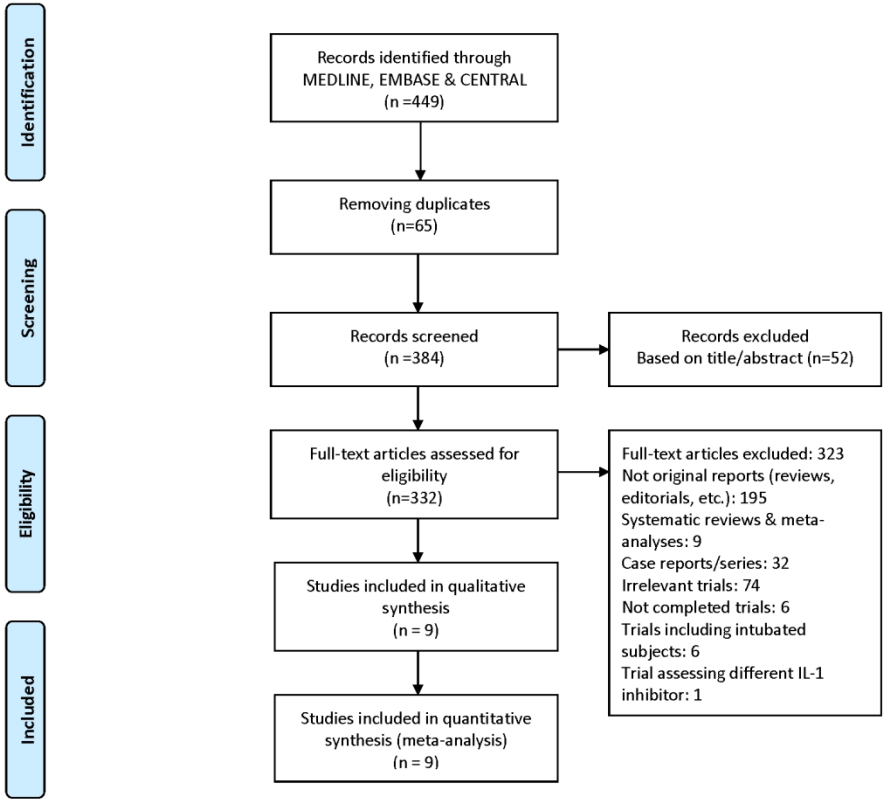


Figure 1

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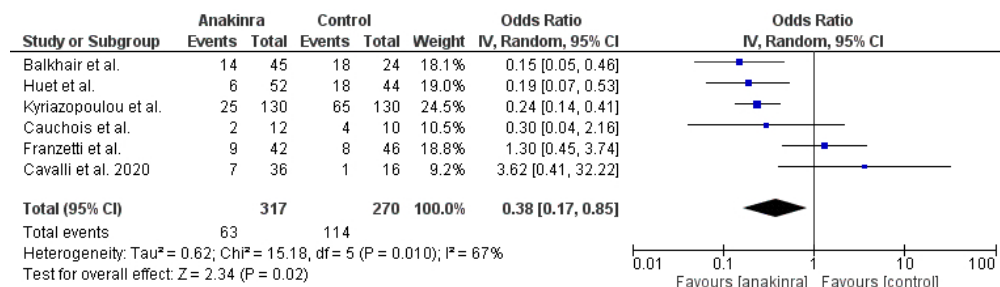


Figure 2a

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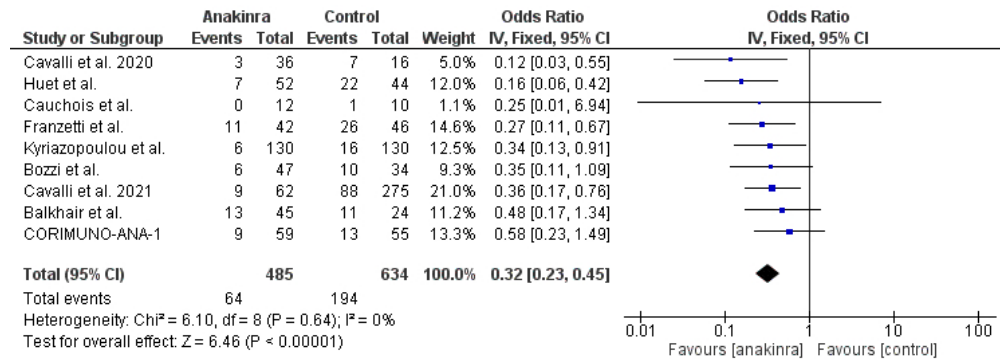


Figure 2b

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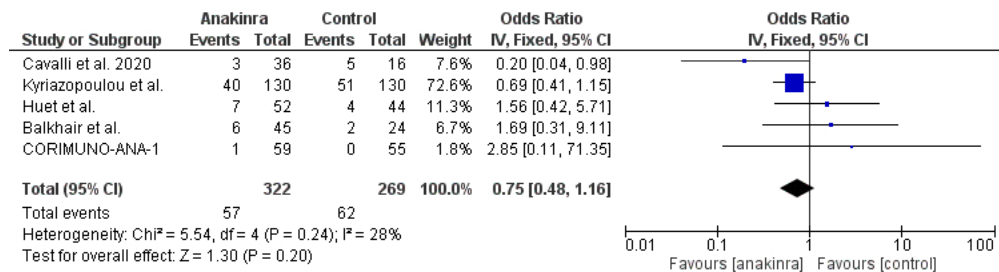


Figure 3a

31x8mm (600 x 600 DPI)

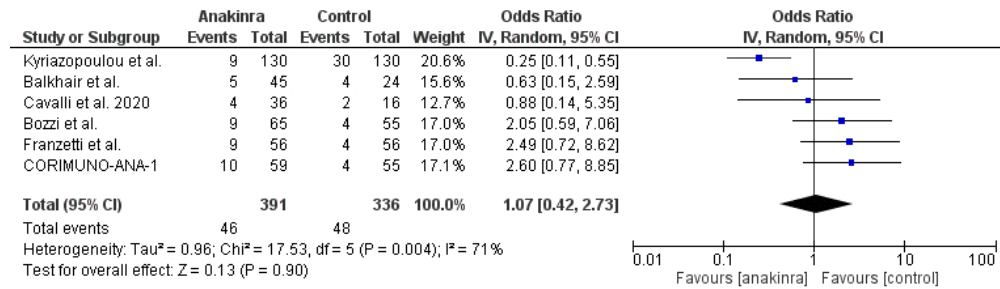


Figure 3b

32x9mm (600 x 600 DPI)