Original article

Interleukin-6 inhibitors reduce mortality in coronavirus disease-2019: An individual patient data meta-analysis from randomized controlled trials

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ABSTRACT

Objective: To assess the efficacy of IL-6 inhibitors compared to standard of care (SOC) in COVID-19 patients.
Data Sources: A systematic review of the MEDLINE and Scopus databases (last search: October 8th, 2021) was performed according to the PRISMA statement.
Study Selection: Randomized control trials (RCTs) comparing IL-6 inhibitors to SOC in hospitalized COVID-19 patients were deemed eligible.
Data Extraction and Synthesis: Individual patient data were extracted from the Kaplan-Meier curves or were obtained from authors of included studies. Additionally, the reviewers independently abstracted data and assessed study quality of each eligible report.
Results: Eleven studies were identified, incorporating 7467 patients (IL-6 inhibitors: 4103, SOC: 3364). IL-6 inhibitors were associated with decreased risk for death compared to SOC at the one-stage meta-analysis (Hazard Ratio [HR]: 0.75, 95% Confidence interval [CI]: 0.69–0.82, $p<0.0001$) and the two-stage meta-analysis (HR: 0.85, 95%CI: 0.77–0.93, $p<0.001$, $I^2 = 0.0\%$). Meta-regression analysis revealed that the difference in OS between the two groups was not influenced by the mean age of patients. At secondary meta-analyses, IL-6 inhibitors were associated with decreased odds for intubation OR:0.74, 95%CI:0.65–0.85, $p<0.001$, $I^2=0.0\%$). IL-6 inhibitors were associated with increased odds for discharge compared to SOC (OR:1.28, 95% CI:1.15–1.42, $p<0.001$, $I^2=0.0\%$).
Conclusions and Relevance: This meta-analysis of individual patient data from randomized trials shows that IL-6 inhibitors significantly reduce the risk of death compared to SOC. IL-6 inhibitors are also associated with better outcomes in terms of intubation and discharge rates compared to SOC.

1. Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in December 2019 and was declared a pandemic in March 2020 by the World Health Organization (WHO) [1]. Clinical manifestations of COVID-19 range widely [2]. Even though most patients experience mild to moderate symptoms, a fair number of them suffer from severe pneumonia, acute respiratory distress syndrome (ARDS) and multiorgan dysfunction, with increased mortality [2]. The global vaccination has

shown its effect, nevertheless, the incidence of COVID-19 hospitalizations and deaths is rapidly increasing over the last few months [1]. In this context, it is imperative to clarify the efficacy and safety of all available resources in order to optimize COVID-19 patient management.

It is currently well established that hyperinflammatory response triggered by SARS-CoV-2 can lead to the cytokine release syndrome [3], which is one of the main culprits of poor clinical outcomes [3]. Interleukin 6 (IL-6) is thought one of the most important mediators and plays a crucial role in this hyperinflammatory state, rendering IL-6 inhibition

a rational therapeutic strategy [4,5]. However, reports of randomized clinical trials (RCTs) are inconsistent regarding the effect of IL-6 inhibitors on COVID-19 [5–16]. Therefore, current guidelines recommend IL-6 inhibitor utilization in hospitalized patients who receive high-flow O_2 or invasive mechanical ventilation, but the level of recommendation is moderate (BIIa) [17].

Accounting the lack of clear consensus and the discrepancies between individual studies, we conducted a meta-analysis of RCTs comparing IL-6 inhibitors with standard of care (SOC) in patients with COVID-19. To impart a comprehensive synthesis of the survival estimates, we conducted a meta-analysis of individual patient data (IPD) solely based on randomized control trials (RCTs), which is suggested as the gold-standard method for high quality evidence synthesis [18,19].

2. Material and methods

2.1. Study selection

This systematic review and meta-analysis was performed according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guidelines [20] and the study's protocol was submitted in PROSPERO (ID: CRD42021284147). We applied the PICO (Population/Participants, Intervention Comparison and Outcome) criteria to define our research question:

1. Population/Participants: Adult patients with COVID-19.
2. Intervention: IL-6 inhibitors.
3. Comparison: standard of care.
4. Outcomes: The primary assessed outcome was the overall survival (OS). The secondary outcomes were the overall mortality, intensive care unit (ICU) admission rates, intubation rates, and discharge rates.

Original RCTs published in English, reporting on clinical characteristics and outcomes of COVID-19 patients met the inclusion criteria. Exclusion criteria were defined as follows: (i) studies published in a language other than English, (ii) studies reporting on patients receiving IL-6 inhibitors along with other immunomodulators compared to SOC, (iii) non-randomized studies, (iv) meta-analyses, systematic reviews, editorials, letters to the editor, (v) studies having only one arm (noncomparative).

2.2. Data sources and searches

We searched the MEDLINE (via PubMed) and Scopus databases (last search date: October 8th, 2021) using the following algorithm: ((interleukin-6 inhibitor OR tocilizumab OR sarilumab OR siltuximab OR IL-6 inhibitor) AND (coronavirus OR COVID-19 OR SARS-CoV-2) AND (trial OR randomized)). Title and abstract screening and full text eligibility were assessed by two independent investigators (ATA, CKA). Any disagreement was resolved after discussion with a third reviewer (PTT). The references of the relevant reviews or meta-analysis were hand-searched for potentially eligible studies using the snowball methodology [21].

2.3. Data extraction

Three investigators (ATA, CKA, IB) independently extracted the data into a standardized, pre-designed table for evidence synthesis. Any disagreements were resolved by reaching consensus. The following data were extracted: (i) study characteristics (first author, year of publication, study design, study center, study period, number of patients, (ii) patients' characteristics (age in years, gender, BMI, comorbidities such as hypertension, diabetes mellitus, COPD, chronic kidney disease and levels of CPK, CRP, D-dimers, IL-6), details for SOC (iv) OS, (v) secondary events (overall mortalities, ICU admissions, intubations, discharges).

2.4. Quality assessment

The revised Cochrane 'Risk of bias tool for randomized trials' was used to assess the risk of bias of the included RCTs [22]. Two independent investigators (CKA, IB) applied the tool to each study and examined the five domains that RoB 2.0 addresses; (1) bias arising from the randomization process; (2) bias due to deviations from intended interventions; (3) bias due to missing outcome data; (4) bias in measurement of the outcome; and (5) bias in selection of the reported result.

2.5. Data synthesis and analysis

2.5.1. Data pooling and meta-analysis

Continuous variables were summarized using means and standard deviations, while categorical variables using frequencies and percentages. The Hozo et al. and the Wan et al. methods were used to estimate the means and SDs of continuous variables whenever medians and ranges [23] and median and interquartile ranges were provided [24], respectively.

To compare the secondary outcomes of IL-6 inhibitors versus SOC, we used the odds ratio (OR) and 95% Confidence Interval (95% CI). An OR greater than 1 indicated that the outcome was more frequently present in the IL-6 inhibitors arm. Random-effects models (DerSimonian-Laird) were adopted to balance inherent clinical heterogeneity between the included studies. Forest plots were generated to display results. Between-study statistical heterogeneity was assessed with the Cochran Q statistic and by estimating I^2. High heterogeneity was confirmed with a significance level of $p < 0.10$ and $I^2 \geq 50\%$. Publication bias was assessed via funnel plots and Egger's test for each outcome of interest and $p < 0.10$ was considered statistically significant. All analyses were performed using STATA IC 16.0 (StataCorp LLC, College Station, Texas).

2.5.2. Reconstruction of individual patient survival data

We used the methods described by Wei et al. to reconstruct IPD from the Kaplan-Meier curves of all eligible studies for the long-term survival outcomes [25,26]. Raster and Vector images of the Kaplan–Meier survival curves were pre-processed and digitized, so that the values reflecting to specific time points with their corresponding survival/mortality information could be extracted. Where additional information (eg. number-at-risk tables or total number of events) were available, they were used to further calibrate the accuracy of the time-to-events. Departures from monotonicity were detected using isotonic regression and corrected with a pool-adjacent-violators algorithm [25,26]. To confirm the quality of the timing of failure events captured, we thoroughly checked the consistency with the reported survival or morality data provided in the original publications.

In cases where no Kaplan-Meier curves were provided, we thoroughly searched each study's manuscript and supplemental material to find IPD describing the time and the incidence of mortality and censoring. If that was not feasible, we reached out to the corresponding author of each study via email to request the aforementioned IPD.

2.6. Overall survival analysis

2.6.1. One-stage survival meta-analysis

The Kaplan–Meier method was used to calculate the OS. The Cox proportional hazards regression model was used to assess between-group difference. In this model every patient within each individual study is assumed to be similarly failure prone to other patients belonging to that study. For these Cox models, the proportional hazards assumption was verified holistically by plotting scaled Schoenfeld residuals, log–log survival plots, and predicted versus observed survival functions. We plotted survival curves using the Kaplan–Meier product limit method and calculated the Hazard Ratios (HRs) and 95% CIs of each group.

2.6.2. Two-stage survival meta-analysis

As a sensitivity analysis, we calculated summary HRs and 95% CIs for all individual studies based on the reconstructed IPD and pooled them under the conventional "two-step" meta-analysis. Random-effects models (DerSimonian-Laird) were utilized once again, and between-study statistical heterogeneity was assessed with the Cochran Q statistic.

2.6.3. Meta-regression

Pre-specified random effects meta-regression analysis was performed in order to examine the effect of the patients' mean age of each individual study to the difference in OS between the two compared groups.

2.6.4. Funding Source

None.

3. Results

3.1. Study selection and baseline characteristics

Through our systematic search, a total of 728 articles were retrieved. After removal of 95 duplicate records and 610 articles with irrelevant titles or abstracts, 23 potentially eligible studies remained for evaluation. These studies along with six additional articles identified through the snowball method, underwent full-text evaluation. Eventually, eleven studies incorporating 7467 patients, were deemed eligible (Fig. 1)5–15. A total of 4103 patients were randomized to the IL-6 inhibitor group and 3364 patients were randomized to the SOC group, respectively. Details describing study and patients' baseline characteristics are presented in Table 1 and Table 2, respectively. As it was expected, the schedules of SOC differed between individual studies as well as between individual patients within the included studies, because COVID-19 management and study recruitment fluctuated during the different phases of the pandemic. Information regarding the SOC used in each included study is summarized in Table 3.

3.2. Individual patient data and survival curve reconstruction

Overall, OS curves from 9 RCTs were processed, digitalized, and reconstructed [6–13,15]. A side-by-side comparison of our reconstructed Kaplan–Meier curves and those found in the original publications is provided in Appendix B. One study provided two separate Kaplan-Meier curves for patients considered to be in severe and critical condition, respectively [10]. IPD were also extracted from the manuscript and supplemental material of one included study [14].

3.3. Overall survival analysis

Among 7467 patients included in the overall individual patient data analysis, there were 983 deaths among 4103 IL-6 inhibitor assigned patients (24.0%) compared to 996 among 3364 patients assigned to SOC (29.6%).

The pooled OS curves of individual patients' data assigned to either an IL-6 inhibitor or SOC are presented in Fig. 2. Patients who received IL-6 inhibitors had significantly lower risk of death compared to those that received SOC (HR: 0.75, 95%CI:0.69–0.82, $p<0.0001$). Since we did not detect any major violation of the proportionality-of-hazards assumption by visualizing scaled Schoenfeld residuals, log–log survival plots, and predicted versus observed survival curves, we used the Cox proportional hazards model for our main analysis of OS (Appendix C).

The sensitivity cumulative two-stage meta-analysis based on the pooled HRs of the RCTs confirmed that IL-6 inhibition significantly reduced mortality compared to SOC (HR: 0.85, 95% CI: 0.77 - 0.93, p <0.001, $I^2 = 0.0\%$) (Appendix A Figure A.1).

Furthermore, a sensitivity analysis was performed to estimate the effect of the corticosteroid usage in our results regarding OS. We established a cut-off point at 50% and generated 2 subgroups of studies for each examined variable. Regarding studies that utilized corticosteroid to over 50% of the included patients, IL-6 provided statistically significant better OS compared to SOC (HR: 0.79, 95% CI: 0.72–0.86, $p<0.001$) (Appendix A Figure A.2).. Regarding studies that utilized corticosteroid to less than 50% of the included patients, IL-6 provided similar OS outcomes with SOC (HR:1.02, 95% CI: 0.74–1.44, $p= 0.87$)
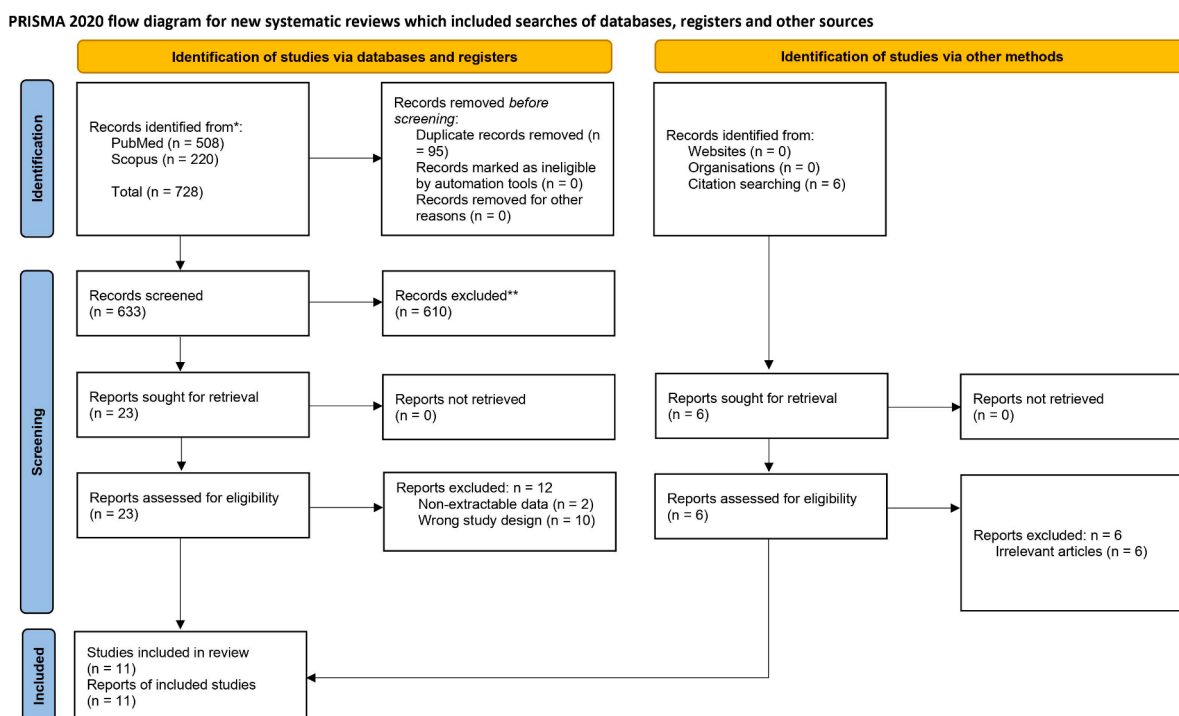

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers and other sources

Fig. 1. PRISMA 2020 flow diagram.

Table 1

Baseline characteristics of included studies.

Author		Gordon et al.	Hamed et al.	Hermine et al.	Lescure et al.	RECOVERY collaborative group	Rosas, Bräu et al.	Rosas, Diaz et al.	Salama et al.	Salvarani et al.	Stone et al.	Veiga et al.
Year		2021	2021	2021	2021	2021	2021	2021	2020	2020	2020	2021
Journal		The New England Journal of Medicine	Journal of Infection and Public Health	JAMA Internal Medicine	The Lancet	The Lancet	The New England Journal of Medicine	Intensive Care Medicine	The New England Journal of Medicine	JAMA Internal Medicine	The New England Journal of Medicine	British Medical Journal
Country		Multinational	United Arab Emirates	France	Multinational	United Kingdom	Multinational	Multinational	Multinational	Italy	USA	Brazil
Study period		19 April 2020-19 November 2020	June 2020	31 March 2020-18 April 2020	28 March 2020-3 July 2020	23 April 2020-24 January 2021	3 April 2020-28 May 2020	June 2020-March 2021	N/A	31 March 2020-11 June 2020	20 April 2020-15 June 2020	8 May 2020-17 July 2020
Patients(n)		803	49	130	416	4116	438	640	377	126	243	129
IL-6 i(n)		401	26	63	332	2022	294	430	249	60	161	65
SOC (n)		402	23	67	84	2094	144	210	128	66	82	64
ICU(n)	IL-6 i	401	N/A	0	120	N/A	113	65	36	0	0	N/A
	SOC	402	N/A	0	28	N/A	55	22	22	0	1	N/A
Intubated (n)	IL-6 i	112	N/A	0	39	268	111	59	0	0	0	11
	SOC	121	N/A	0	9	294	54	22	0	0	1	10
Follow-up (days)		90	45	28	60	28	60	60	60	30	28	29
Lost in follow-up	IL-6 i	N/A	0	8	0	58	7	9	0	0	0	0
	SOC	N/A	0	3	3	45	5	7	2	0	0	0

Abbreviations: ICU: intensive care unit; N/A: not available.

IL-6 i: patients who received anti-IL6 receptor therapy (tocilizumab, sarilumab); SOC: patients treated with the standard of care

Table 2

Patients' characteristics and antiviral or steroid use during trial.

Study		Gordon et al. 2021	Hamed et al. 2021	Hermine et al. 2021	Lescure et al. 2021	RECOVERY collaborative group 2021	Rosas, Bräu et al. 2021	Rosas, Diaz et al. 2021	Salama et al. 2020	Salvarani et al. 2020	Stone et al. 2020	Veiga et al. 2021
Patients (n)	IL-6i	401	26	63	332	2022	294	430	249	60	161	65
	SOC	402	23	67	84	2094	144	210	128	66	82	64
Age (years)	IL-6i	61.7 (±12.6)	51.5 (±10.8)	65.1 (±13)	58.2 (±13.2)	63.3 (±13.7)	60.9 (±14.6)	60.1 (±13.3)	56 (±14.3)	62.2 (±16.7)	59.2 (±17.4)	57.4 (±15.7)
	SOC	61.1 (±12.8)	45 (±11.1)	64.2 (±11.5)	60.8 (±12.4)	63.9 (±13.6)	60.6 (±13.7)	58.2 (±13.3)	55.6 (±14.9)	61 (±11.4)	56.3 (±17.4)	57.5 (±13.5)
Female gender (n)	IL-6i	101	4	19	125	685	89	164	99	20	65	21
	SOC	119	5	23	30	657	43	71	55	29	37	20
Diabetes mellitus (n)	IL-6i	136	13	20	92	569	105	172	105	10	45	22
	SOC	150	8	23	18	600	62	81	48	9	30	20
Hypertension (n)	IL-6i	N/A	7	N/A	138	N/A	178	267	119	27	80	30
	SOC	N/A	4	N/A	39	N/A	94	128	63	29	38	34
Chronic kidney disease (n)	IL-6i	34	N/A	5	13	118	N/A	N/A	N/A	N/A	29	5
	SOC	43	N/A	13	5	99	N/A	N/A	N/A	N/A	13	1
Chronic lung disease (n)	IL-6i	97	N/A	8	26	476	49	N/A	39	2	30	6
	SOC	98	N/A	6	9	489	22	N/A	21	2	14	3
Heart disease (n)	IL-6i	35	N/A	20	16	435	88	105	10	N/A	32	8
	SOC	47	N/A	20	6	497	35	45	9	N/A	13	6
IL6 serum levels (pg/ml)	IL-6i	N/A	N/A	N/A	14.2 (±14.8)	N/A	201.9 (±418.4)	N/A	N/A	57.3 (±49.5)	29.2 (±26.9)	192 (±313)
	SOC	N/A	N/A	N/A	13.4 (±15)	N/A	195.4 (±368.2)	N/A	N/A	37.5 (±30.7)	26.8 (±19.4)	208 (±586)
CRP serum levels (mg/L)	IL-6i	151.4 (±98)	1552.3 (±1001.3)	137.8 (±110.3)	103.3 (±91.4)	151 (±71.2)	168.4 (±101.4)	N/A	589.5 (±665.7)	100.3 (±72.9)	124.6 (±92.4)	160 (±104)
	SOC	136.3 (±102.2)	1489.1 (±998.1)	127.3 (±66)	111.8 (±97.2)	151.7 (±73.4)	172.6 (±114)	N/A	1024.8 (±1213.1)	71.7 (±65.2)	98.2 (±63.1)	193 (±283)
D-dimers levels (µg/L)	IL-6i	1002.4 (±961.1)	N/A	924.3 (±653.4)	570 (±600)	N/A	N/A	N/A	1114000 (±1440400)	668.7 (±677.9)	1029.3 (±867)	237.4 (±146.1)
	SOC	1208.3 (±1207.4)	N/A	1280.7 (±787.7)	613.3 (±731.7)	N/A	N/A	N/A	1308450 (±1695400)	430.3 (±367.5)	1073 (±935)	228.3 (±155.3)
Antiviral treatment during trial (n)	IL-6i	128	N/A	1	94	581	68	430	N/A	N/A	53	7
	SOC	133	N/A	4	17	656	35	210	N/A	N/A	24	3
Steroid treatment during trial (n)	IL-6i	298	N/A	19	136	1462	99	378	200	0	18	56
	SOC	293	N/A	37	39	1568	75	188	112	0	5	55

Abbreviations: CRP: c-reactive protein; N/A: not available Results are presented as mean ± SD, unless otherwise indicated. IL-6i: patients who received interleukin-6 inhibitor therapy; SOC: patients treated with the standard of care Chronic lung diseases: Chronic obstructive pulmonary disease, asthma, and tuberculosis. Heart diseases: chronic heart failure, coronary artery disease, atrial fibrillation Antiviral treatment: remdesivir, oseltamivir, lopinavir, ritonavir and/or favipiravir; steroid treatment: glucocorticoids, dexamethasone and/or prednisolone.

(Appendix A Figure A.3).

3.4. Secondary outcomes

Intubation rate was reported in eight studies [5–9,11–13]. IL-6 inhibitors significantly reduced the odds of intubation and mechanical ventilation compared to SOC (OR: 0.74, 95% CI: 0.65–0.85, $p<0.001$, $I^2=0.0\%$) (Appendix A Figure A.4).

Discharge rate was reported in seven studies [5,6,9–12,14]. IL-6 inhibitors were associated with increased odds for discharge compared to SOC (OR: 1.28, 95% CI: 1.15–1.42, $p<0.001$, $I^2=0.0\%$) (Appendix A Figure A.5).

3.5. Meta-regression

Random-effects meta-regression analysis was performed to examine potential relationships between patients' mean age and differences in OS between IL-6 inhibitors and SOC. This analysis revealed that the differences between the two arms in terms of OS tended be more apparent in favor of IL-6 inhibitors as the patient mean age increased, however this finding was not statistically significant ($p = 0.17$) (Appendix A Fig. A.6).

3.6. Quality of evidence and publication bias assessment

We utilized the RoB 2.0 tool to assess the quality of the included RCTs. Detailed RoB 2.0 results are shown in Appendix D. In addition, heterogeneity was insignificant in all performed analyses.

Egger's test revealed no publication bias in the funnel plots of all the assessed outcomes with the exception of the two-stage cumulative survival analysis. (Appendix D).

Table 3
Standard of care.

Study	Standard of care
Gordon et al.	Remdesivir, Corticosteroids
Hamed et al.	Chloroquine, hydroxychloroquine, lopinavir/ritonavir and/or favipavir, anticoagulants
Hermine et al.	Anticoagulants, azithromycin, hydroxychloroquine, lopinavir-ritonavir, lopinavir, remdesivir, oseltamivir, immuno-modulators*, corticosteroids, dexamethasone
Lescure et al.	Hydroxychloroquine/chloroquine, antivirals, systemic corticosteroids, dexamethasone, antibacterial agents, azithromycin
RECOVERY Collaborative Group	Convalescent plasma, REGN-COV2†, lopinavir-ritonavir, remdesivir
Rosas, Bräu et al.	Low dose glucocorticoids, convalescent plasma, ritonavir, remdesivir, lopinavir, ritonavir, chloroquine, hydroxychloroquine, and hydroxychloroquine sulfate.
Rosas, Diaz et al.	Azithromycin, broad spectrum antibiotics, low-dose corticosteroids, antivirals
Salama et al.	Antiviral, glucocorticoids
Salvarani et al.	Antiretrovirals, hydroxychloroquine, heparin and LMWH, azithromycin
Stone et al.	Remdesivir, corticosteroids, hydroxychloroquine
Veiga et al.	Antibiotics, antiviral, corticosteroids, heparin

All patients also received supportive care such as non-steroidal anti-inflammatory drugs, antipyretic drugs, acetaminophen, and oxygen.
Abbreviations: LMWH = Low-Molecular-Weight Heparin.
* Anakinra, anakinra-eculizumab
† REGN-COV2 =Combination of two monoclonal antibodies against the spike protein of SARS-CoV2

4. Discussion

To our knowledge, this is the only IPD meta-analysis of randomized trials of IL-6 inhibitors in patients with COVID19. It shows that IL-6 inhibitors offer a survival advantage compared to SOC. Furthermore, meta-regression analysis revealed that as the patients' age increases the survival advantage of IL-6 inhibitors becomes more apparent. However, this finding was not statistically significant. Finally, IL-6 inhibitors were associated with decreased odds for intubation and increased odds for discharge compared to SOC alone.

Current guidelines of Infectious Diseases Society of America on COVID-19 recommend the implementation of IL-6 inhibitors in addition to corticosteroids, only in severely or critically ill adult patients (low certainty of evidence) [27]. Moreover, NIH guidelines recommend IL-6 inhibitors solely in patients who receive high-flow O_2 or invasive mechanical ventilation, but again with low level of certainty (BIIa) [17]. We incorporated a total of 7467 individual patients with various baseline clinical characteristics in our final synthesis. Our cumulative OS findings are fairly robust and indicate that IL-6 inhibitors offer a clear survival advantage compared to SOC. These results reinforce the available evidence regarding IL-6 inhibitors' role in COVID-19.

Our results are in congruence with the RECOVERY trial, where the beneficial effects of IL-6 inhibitors in terms of survival were consistent regardless of the level of respiratory support and baseline characteristics of the patients being examined [6]. Therefore, we believe that the small sample size of some included RCTs could potentially conceal a statistically significant effect, which however, became apparent in our cumulative synthesis of effect estimates. This could also serve as a possible explanation for the discrepancies noted between the included studies [5–16].

Not only the included studies, but also other non-RCTs studies came to different results regarding the benefit of IL-6 inhibitors in COVID-19 patients. In a prospective open-label observational study from our department, the use of IL-1 and IL-6 inhibitors showed a reduction in both intubation and mortality rates [28]. On the other hand, there are many observational studies, whose results did not reveal any clinical improvement by using IL-6 inhibitors in COVID-19 patients [29,30].

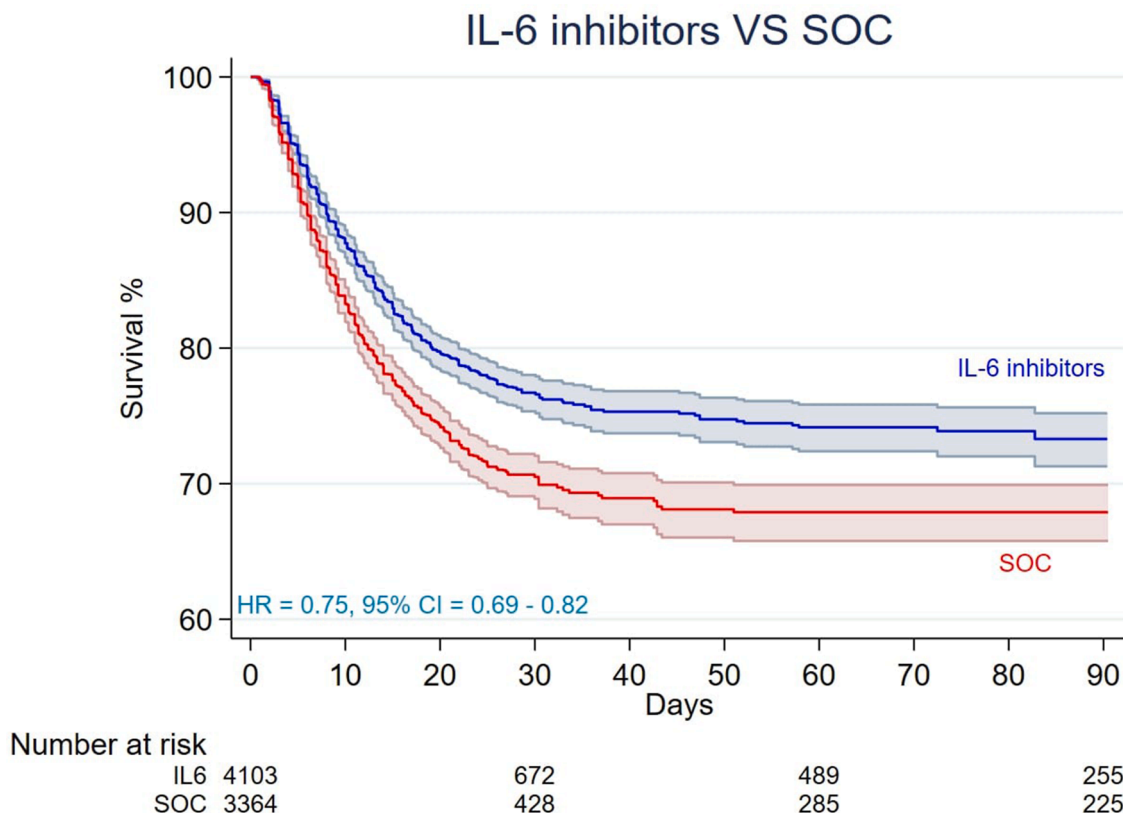IL-6 inhibitors are monoclonal antibodies, which bind to membrane-

Fig. 2. Pooled overall survival curves of individual patients' data.

bound or soluble forms of the IL-6 receptor (Tocilizumab, Sarilumab) or directly on IL-6 to neutralize it (Siltuximab) [31]. Accounting that IL-6 triggers and facilitates the progression of many inflammatory reactions [32], and that severe COVID-19 is by definition a hyperinflammatory reaction syndrome with high levels of IL-6 [33], the beneficial effect of IL-6 inhibitors in COVID-19 is the anticipated finding in all comparative studies. Nevertheless, a lot of immune mediators additional to IL-6 are produced after Severe Acute Respiratory Syndrome Corona Virus 2 infection and therefore by blocking only IL-6, many patients remain in a strongly hyperinflammatory state [33]. This could be a potential explanation of the not beneficial results in favor of the IL-6 inhibitors of some studies.

To evaluate the benefit of IL-6 inhibitors for COVID-19 patients, the adverse effects (AEs) of this treatment should be taken into account as well. The main AEs of the IL-6 inhibitors group seem to be: secondary infections (mainly bacterial), abnormal liver-function values, hypersensitivity reactions, bleeding events, hypertension, mmyocardial infraction, stroke, cardiac arrhythmias, neutropenia, lymphopenia, anaemia, thrombosis and renal impairment [5–16]. The most common AE of IL-6 inhibitors, however, is reported to be the secondary infections, which are potentially attributed to the immunosuppression that sequels IL-6 blockage [32].

Our cumulative results on intubation and discharge rates were mainly driven by the RECOVERY trial [5–15]. Previous non-IPD meta-analyses reported the beneficial effect of IL-6 inhibitors on COVID-19 patients' clinical status and rate of recovery [34,35], which is mediated by the blockage of the hyperinflammatory response and the consequent syndrome through the inhibition of IL-6 action [4,5].

5. Limitations

There are certain limitations in this study that we acknowledge. Firstly, whereas our methodology allowed us to reconstruct IPD in terms of survival time and censoring status, it does not provide us with patient-level prognostic covariates. Thus, we were unable to examine thoroughly the effect of the differences in SOC between the included studies in our findings. In addition, we were unable to examine the notion that differences in each country-level COVID-19 peak incidence during the trial window might have confounded our finding. Finally, we decided to focus solely on RCTs that provide Kaplan-Meier curves or IPD in the manuscript. This way we excluded a few observational studies, however, we believe that our results are more robust and impart decreased risk for selection and confounding biases.

In conclusion, this IPD meta-analysis of randomized trials of IL-6 inhibitors in patients with COVID-19 reveals a benefit in patients allocated to the IL-6 inhibitor group compared to the SOC group in terms of overall survival, intubation and discharge rates.

Role in the study

Dr Tasoudis: acquisition of data, analysis and interpretation, preparation aof the article.

Dr Arvaniti: acquisition of data, analysis and interpretation, and critical revision of the article for important intellectual content.

Dr Adamou: acquisition of data, analysis and interpretation, and critical revision of the article for important intellectual content.

Dr Belios: acquisition of data, analysis and interpretation, and critical revision of the article for important intellectual content.

BACC Bay Tocilizumab Trial investigators.: acquisition of data, critical revision of the article for important intellectual content.

Dr Stone: acquisition of data, critical revision of the article for important intellectual content.

Dr Horick: acquisition of data, critical revision of the article for important intellectual content.

Dr Sagris: study design, preparation of the manuscript and critical revision of the article for important intellectual content.

Dr Dalekos: critical revision of the article for important intellectual content.

Dr Ntaios: study concept and design, preparation of the article, and study supervision.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejim.2022.04.004.

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