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Immunomodulators for immunocompromised patients hospitalized for COVID-19: a meta-analysis of randomized controlled trials

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Summary

Background Although immunomodulators have established benefit against the new coronavirus disease (COVID-19) in general, it is uncertain whether such agents improve outcomes without increasing the risk of secondary infections in the specific subgroup of previously immunocompromised patients. We assessed the effect of immunomodulators on outcomes of immunocompromised patients hospitalized for COVID-19.

Methods The protocol was prospectively registered with PROSPERO (CRD42022335397). MEDLINE, Cochrane Central Register of Controlled Trials and references of relevant articles were searched up to 01-06-2022. Authors of potentially eligible randomized controlled trials were contacted to provide data on immunocompromised patients randomized to immunomodulators vs control (i.e., placebo or standard-of-care).

Findings Eleven randomized controlled trials involving 397 immunocompromised patients hospitalized for COVID-19 were included. Ten trials had low risk of bias. There was no difference between immunocompromised patients randomized to immunomodulators vs control regarding mortality [30/182 (16.5%) vs 41/215 (19.1%); RR 0.93, 95% CI 0.61–1.41; p = 0.74], secondary infections (RR 1.00, 95% CI 0.64–1.58; p = 0.99) and change in World Health Organization ordinal scale from baseline to day 15 (weighed mean difference 0.27, 95% CI -0.09–0.63; p = 0.15). In subgroup analyses including only patients with hematologic malignancy, only trials with low risk of bias, only trials administering IL-6 inhibitors, or only trials administering immunosuppressants, there was no difference between comparators regarding mortality.

Interpretation Immunomodulators, compared to control, were not associated with harmful or beneficial outcomes, including mortality, secondary infections, and change in ordinal scale, when administered to immunocompromised patients hospitalized for COVID-19.

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The members of CORIMUNO-19 Collaborative Group, DisCoVeRy Study Group, ACTT-2 Study Group, and ACTT-3 Study Group are listed in the Supplementary Material.

Research in context

Evidence before this study

Relevant guidelines acknowledge the uncertainty regarding the effect of immunomodulators against the new coronavirus disease (COVID-19) in the specific subgroup of previously immunocompromised patients.

Three investigators systematically searched MEDLINE and the Cochrane Central Register of Controlled Trials to identify randomized controlled trials, which tested immunomodulators vs control (i.e., placebo or standard-of-care) in patients hospitalized for COVID-19, enrolled immunocompromised patients and reported data on all-cause mortality. Databases and reference lists of the initially retrieved articles were searched up to June 1st, 2022, without language restrictions.

Out of the 55 initially identified randomized controlled trials, none specifically reported data on the effect of immunomodulators on outcomes of immunocompromised patients with COVID-19.

Added value of this study

After contacting authors of the initially identified randomized controlled trials, we clarified that 11 trials (reported in 10 articles), involving 397 immunocompromised patients

hospitalized for COVID-19 (182 immunomodulators, 215 control), provided data on clinical outcomes.

We found no statistically significant difference between immunocompromised patients randomized to immunomodulators vs control regarding mortality, secondary infections and change in World Health Organization ordinal scale from baseline to day 15. The main findings persisted in several subgroup analyses.

Implications of all the available evidence

The findings of this meta-analysis (albeit based on imprecise estimates due to limited number of events) are compatible with a benefit of the same magnitude as observed for the general population of COVID-19 patients. Therefore, these findings may support the guidelines, which recommend immunomodulators for immunocompromised patients similar to the general population.

That being said, given that immunocompromised patients remain potentially at risk for developing severe COVID-19 even at this stage of the pandemic since they respond worst to vaccination, randomized controlled trials specifically testing the effect of immunomodulators on outcomes of previously immunocompromised patients hospitalized for COVID-19 are needed.

Introduction

Although several immunomodulators have established benefit against the new coronavirus disease (COVID-19) in general,[1–3] it is uncertain whether such agents improve outcomes of the specific subgroup of previously immunocompromised patients. The latter subgroup of patients remains important because they may experience blunted immunological responses to vaccines.[4]

While acknowledging that additional immunomodulation in immunocompromised patients might increase the risk of secondary infections, relevant guidelines from the United States Centers for Disease Control and Prevention (CDC) state that "for most hospitalized patients with COVID-19 who are immunocompromised, the Panel recommends using immunomodulatory therapies at the doses and durations that are recommended for the general population".[5] However, this recommendation was based on limited evidence, because immunocompromised patients were either excluded from or poorly represented in major clinical trials.[5] Given that even major individual clinical

trials may lack power to identify a true effect of immunomodulators in immunocompromised patients, a meta-analytic approach may provide a distinct opportunity to better define this effect.

Accordingly, a meta-analysis was conducted to assess the effect of immunomodulators on clinical outcomes (i.e., mortality, secondary infections, and clinical response) of immunocompromised patients hospitalized for COVID-19.

Methods

The meta-analysis was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

Identification of trials

The protocol of the meta-analysis was prospectively registered with PROSPERO (CRD42022335397). Three investigators (NAX, KG and EP) systematically searched MEDLINE and the Cochrane Central Register of Controlled Trials using the following search phrase:

(COVID-19 OR "Coronavirus disease 19″ OR SARS-CoV-2 OR "severe acute respiratory syndrome coronavirus 2″) AND (dexamethasone OR corticosteroid* OR steroid* OR tocilizumab OR anakinra OR baricitinib OR interferon OR immunosuppressant). Databases and reference lists of the initially retrieved articles were searched up to June 1st, 2022, without language restrictions.

Randomized controlled trials, which tested immunomodulators vs control (i.e., placebo or standard-of-care) in patients hospitalized for COVID-19, enrolled immunocompromised patients and reported data on all-cause mortality, were considered eligible. Observational studies, case reports, editorials and reviews; trials involving outpatients; trials excluding immunocompromised patients and trials testing inhaled agents were excluded.

As immunomodulators for COVID-19 were considered the following: systemic steroids, interleukin (IL)-1 inhibitors, IL-6 inhibitors, Janus kinase inhibitors, granulocyte-macrophage colony-stimulating factor inhibitors, LIGHT inhibitors, interferon beta-1a and tumour necrosis factor inhibitors.

Immunocompromised patients were defined by the presence of any of the following medical conditions prior to the diagnosis of COVID-19: hematologic malignancy (lymphoid or myeloid hemopathy, or haematopoietic stem cell transplantation); active solid malignancy; solid organ transplantation; auto-immune disorder under immunomodulators; pre-hospital immunomodulatory treatment; human immunodeficiency virus/acquired immunodeficiency syndrome not on highly active antiretroviral therapy and primary immune deficiency.

Development of meta-analysis

Corresponding authors and/or funding agencies (such as the United States National Institute of Allergy and Infectious Diseases) of potentially eligible randomized controlled trials were contacted. After confirming that their trials indeed enrolled more than one immunocompromised patient, authors were invited to participate in the meta-analysis and to provide relevant data.

The following data from each trial were retrieved: acronym (or first author); year of publication; intervention; total number of enrolled patients; number of immunocompromised patients among enrolled; number of patients with hematologic cancer among enrolled; median age; sex and outcomes.

The primary outcome of the meta-analysis was all-cause 28-day mortality. Secondary outcomes were secondary infections and change in World Health Organization (WHO) ordinal scale from baseline to day 15 (Supplementary eTable S1).

Two authors (EP and KG) independently assessed the risk of bias for all-cause 28-day mortality (i.e., the primary outcome) for the retrieved randomized controlled trials, using "Cochrane Risk of Bias tool for randomized trials (RoB 2)".[6] The RoB 2 tool consisted of the following five domains: 1) the randomization process, 2) the deviations from the intended interventions, 3) the missing outcome data, 4) the measurement of the outcome, and 5) the selection of the reported results. Accordingly, the trials were categorized as having "low risk of bias" or "some concerns" or "high risk of bias".

Two authors (EP and KG) independently utilized the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) to assess the certainty of the evidence regarding the effect of administration of immunomodulators on mortality of immunocompromised patients hospitalized for COVID-19. Any disagreements regarding the risk of bias or certainty of the evidence were discussed with the corresponding author (IIS).

Statistical analysis

Data synthesis was conducted using Review Manager 5.4 (Cochrane Collaboration). Pooled dichotomous effect measures were expressed as risk ratio (RR) with 95% confidence intervals (CI) and pooled continuous effect measures as weighed mean difference with 95% CI. Change in ordinal scale from baseline to day 15 was calculated by subtracting the ordinal scale of day 15 from the baseline ordinal scale. Continuous values presented as medians were transformed to means, as instructed by the Cochrane Handbook version 6.3, 2022. Statistical heterogeneity was assessed with I^2, corresponding to the percentage of the variability in effect measures due to heterogeneity between studies. An inverse variance random-effects model was utilized. A p value < 0.05 denoted statistical significance.

Role of the funding source

The funding source had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Results

Fig. 1 shows the flow diagram for study selection. Out of the 55 initially identified randomized controlled trials, none specifically reported data on the effect of immunomodulators on outcomes of immunocompromised patients with COVID-19. After contacting authors of the trials, it was clarified that eight trials included zero or one immunocompromised patients. Finally, 11 randomized controlled trials (reported in 10 articles), involving 397 immunocompromised patients hospitalized for COVID-19 (182 immunomodulators, 215 control), were incorporated in our meta-analysis.[7–16] Table 1 and Table 2 summarize baseline characteristics and outcomes of included patients, respectively. Fig. 2
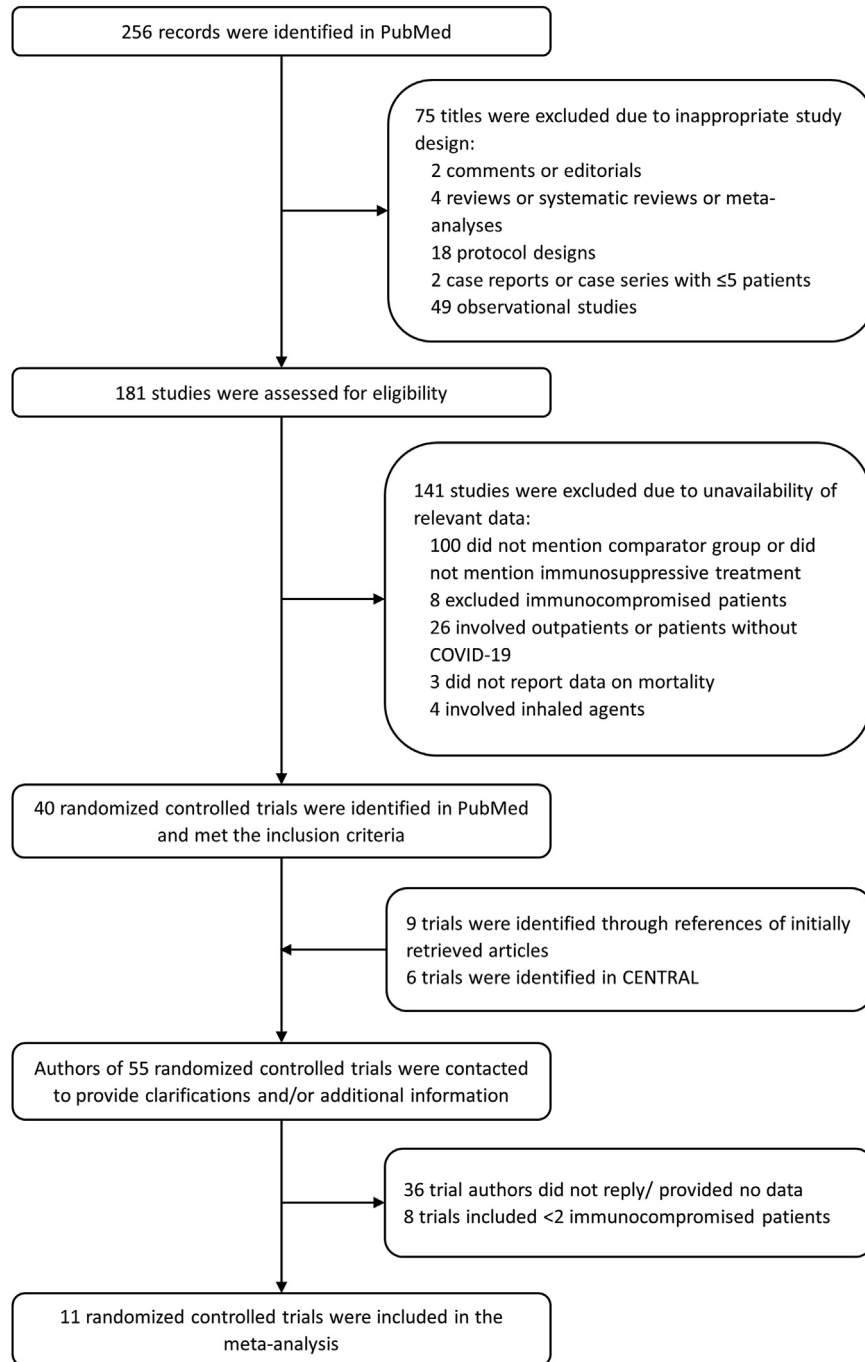
Fig. 1: Study flow diagram.

summarizes risk of bias assessment of the included trials. Ten trials had low risk of bias,[7,8,10–16] while the remaining trial had some concerns regarding the selection of the reported results.[9]

All 11 trials provided data on mortality.[7–16] No statistical heterogeneity was detected (I^2 = 0%). There was no difference between immunocompromised patients randomized to immunomodulators vs control regarding mortality [71 deaths; 30/182 (16.5%) vs 41/215 (19.1%); RR 0.93, 95% CI 0.61–1.41, p = 0.74; Fig. 3A]. The certainty of evidence was low (Supplementary eTable S2).

Acronym or First Author	Year	Intervention	Total number of patients	Number of immunocompromised patients	Number of patients with hematologic cancer	Age (years)	Female sex	Baseline ordinal scale
ACTT-2 [6]	2021	Baricitinib	445 vs 446	33 (7.6) vs 27 (6.3)	NA	62.0 (53.0-67.5) vs 65.5 (56.5-77.5)	11 (33.3) vs 8 (29.6)	5.0 (5.0-6.0) vs 5.0 (5.0-5.0)
ACTT-3 [7]	2021	Interferon beta-1a	403 vs 414	60 (15.1) vs 66 (15.9)	NA	67.5 (54.3-74.0) vs 68.0 (56.0-77.5)	33 (55.0) vs 39 (59.1)	5.0 (5.0-5.0) vs 5.0 (5.0-5.0)
Branch-Elliman [8]	2022	Sarilumab	20 vs 30	3 (15.0) vs 1 (3.3)	1 (33.3) vs 0 (0.0)	76.9 (75.8-89.9) vs 75.5	0 (0.0) vs 0 (0.0)	5.0 (5.0-5.0) vs 5.0
CORIMUNO ANA-1 [9]	2021	Anakinra	59 vs 55	9 (15.3) vs 9 (16.3)	6 (67.0) vs 2 (22.2)	67.0 (66.1-72.7) vs 69.3 (63.4-82.8)	4 (44.4) vs 4 (44.4)	5.0 (5.0-5.0) vs 5.0 (5.0-5.0)
CORIMUNO SARI-1 [10]	2021	Sarilumab	68 vs 76	12 (17.6) vs 9 (11.8)	3 (25.0) vs 5 (55.5)	63.2 (50.2-75.0) vs 68.0 (65.1-72.3)	4 (33.3) vs 3 (33.3)	5.0 (5.0-5.0) vs 5.0 (5.0-5.0)
CORIMUNO SARI-2 [11]	2022	Sarilumab	50 vs 41	4 (8.0) vs 4 (9.7)	1 (25.0) vs 1 (25.0)	57.2 (52.1-61.5) vs 56.1 (50.7-64.2)	2 (50.0) vs 1 (25.0)	6.5 (6.0-7.0) vs 6.5 (6.0-7.0)
CORIMUNO TOCI-1 [12]	2021	Tocilizumab	63 vs 67	11 (17.5) vs 15 (22.4)	5 (45.5) vs 3 (20.0)	67.2 (63.0-71.9) vs 63.4 (60.4-69.0)	4 (36.4) vs 6 (40.0)	5.0 (5.0-5.0) vs 5.0 (5.0-5.0)
CORIMUNO TOCI-2 [11]	2022	Tocilizumab	51 vs 46	7 (13.7) vs 5 (10.9)	3 (42.9) vs 2 (40.0)	61.8 (60.2-65.9) vs 66.8 (65.8-67.4)	3 (42.9) vs 0 (0.0)	7.0 (7.0-7.0) vs 7.0 (6.0-7.0)
CORIMUNO TOCIDEX [13]	2022	Tocilizumab	224 vs 226	18 (8.0) vs 21 (9.3)	5 (27.8) vs 6 (28.6)	67.0 (54.4-73.1) vs 73.2 (57.5-78.0)	5 (27.8) vs 5 (23.8)	5.0 (5.0-5.0) vs 5.0 (5.0-5.0)
DISCOVERY [14]	2021	Interferon beta-1a	147 vs 446	14 (9.6) vs 47 (10.5)	1 (7.2) vs 6 (12.8)	64.0 (53.0-71.0) vs 63.0 (54.0-71.0)	44 (29.9) vs 128 (28.7)	4.0 (4.0-6.0) vs 4.0 (4.0-6.0)
TOCIBRAS [15]	2021	Tocilizumab	65 vs 64	11 (17.2) vs 11 (17.2)	1 (10.0) vs 0 (0.0)	64.8 (55.2-77.2) vs 52.9 (43.4-69.3)	2 (18.2) vs 5 (45.5)	6.0 (5.0-6.0) vs 5.0 (5.0-7.0)

NA, not available/applicable. Data are expressed as numbers (%) or median (interquartile range). In ACTT-2 and ACTT-3 trials, data on baseline immunocompromised status were missing for 27 (8 in the immunomodulators vs 19 in the control group) and 8 (5 in the immunomodulators vs 3 in the control group) patients, respectively. In those trials, patients with cancer were considered to be immunocompromised.

Table 1: Characteristics of included randomized controlled trials and immunocompromised patients with COVID-19 randomized to immunomodulators vs control.

Nine trials provided data on secondary infections.[9–16] No statistical heterogeneity was detected (I^2 = 0%). There was no difference between comparators regarding secondary infections (53 events; 21.3% vs 27.9%; RR 1.00, 95% CI 0.64–1.58, p = 0.99; Fig. 3B).

Ten trials provided data on change in ordinal scale from baseline to day 15.[7,8,10–16] No statistical heterogeneity was detected (I^2 = 0%). There was no difference between comparators regarding change in ordinal scale from baseline to day 15 (393 patients; weighed mean difference 0.27, 95% CI -0.09–0.63, p = 0.15; Fig. 3C).

There were no differences in terms of mortality between comparators in the subgroup analyses including only immunocompromised patients with hematologic malignancy (7 trials[10–15]; 15 deaths; 25.0% vs 36.0%; RR 0.69, 95% CI 0.36–1.34, p = 0.27; Fig. 4A), including only trials with low risk of bias (10 trials[7,8,10–16]; 71 deaths; 16.8% vs 19.2%; RR 0.93, 95% CI 0.61–1.41, p = 0.74; Fig. 4B), only trials administering IL-6 inhibitors (6 trials[11–14,16]; 32 deaths; 23.8% vs 26.2%; RR 0.95, 95% CI 0.51–1.77, p = 0.86; Fig. 4C), or only trials administering immunosuppressants (i.e., after exclusion of trials administering interferon beta-1a which aimed to boost the antiviral response) (9 trials[7,9–14,16]; 50 deaths; 21.3% vs 26.5%; RR 0.82, 95% CI 0.50–1.34, p = 0.42; Fig. 4D).

Consistently, there were no differences in terms of mortality between comparators in the subgroup analyses including only immunocompromised patients receiving supplemental oxygen (9 trials[7–11,13–16]; 47 deaths; 11.5% vs 17.1%; RR 0.73, 95% CI 0.44–1.22, p = 0.23) or including only immunocompromised patients with severe/critical COVID-19 receiving advanced respiratory support (namely, high-flow nasal oxygen, mechanical ventilation or extracorporeal membrane oxygenation) (6 trials[7,8,12,15,16]; 23 deaths; 39.4% vs 28.6%; RR 1.39, 95% CI 0.71–2.72, p = 0.33).

Discussion

By incorporating data from 11 randomized controlled trials (10 of them with low risk of bias) involving 397 immunocompromised patients hospitalized for COVID-19, this meta-analysis found no statistically significant difference between patients randomized to immunomodulators vs control in terms of mortality, secondary infections, and change in ordinal scale.

We found that none of the initially retrieved randomized controlled trials specifically reported data on the effect of immunomodulators on outcomes of immunocompromised patients with COVID-19. This finding may justify statements from experts, who emphasized that immunocompromised patients have been neglected in COVID-19 randomized controlled trials and called for action.[17,18] Examples of such action may be a preferential inclusion of immunocompromised patients in ongoing platform trials, a focus on safety (such as secondary infections) and the

Acronym or First author	Mortality of immunocompromised patients	Mortality of patients with hematologic cancer	Secondary infections	Change in ordinal scale from baseline to day 15
ACTT-2	5 (15.2) vs 3 (11.1)	NA	NA	3.0 (1.0–4.0) vs 3.0 (0.0–3.0)
ACTT-3	2 (3.3) vs 4 (6.1)	NA	NA	3.0 (3.0–3.0) vs 3.0 (3.0–3.0)
Branch-Elliman	0 (0.0) vs 0 (0.0)	NA	1 (33.3) vs 1 (100.0)	NA
CORIMUNO ANA-1	3 (33.3) vs 7 (77.8)	2 (33.3) vs 2 (100.0)	1 (11.1) vs 1 (11.1)	0.0 (−2.0 to 3.0) vs −3.0 (−3.0 to −3.0)
CORIMUNO SARI-1	2 (16.7) vs 1 (11.1)	1 (33.3) vs 0 (0)	1 (8.3) vs 1 (11.1)	0.0 (0.0–1.0) vs 0.0 (−1.0 to 0.0)
CORIMUNO SARI-2	1 (25.0) vs 1 (25.0)	1 (100.0) vs 1 (100.0)	0 (0) vs 0 (0)	2.5 (−0.2 to 5.0) vs 1.0 (−0.2 to 2.8)
CORIMUNO TOCI-1	2 (18.2) vs 5 (33.3)	1 (20.0) vs 1 (33.3)	0 (0) vs 3 (20.0)	1.0 (0.0–4.0) vs −2.0 (−2.0 to 4.0)
CORIMUNO TOCI-2	1 (14.3) vs 1 (20.0)	0 (0) vs 1 (50.0)	2 (28.6) vs 2 (40.0)	0.0 (0.0–1.5) vs 0.0 (−1.0 to 1.0)
CORIMUNO TOCIDEX	5 (27.8) vs 7 (33.3)	1 (20.0) vs 1 (16.7)	2 (11.1) vs 5 (23.8)	4.0 (0.0–4.0) vs 0.5 (−2.2 to 4.0)
DISCOVERY	5 (35.8) vs 10 (29.8)	0 (0) vs 3 (50.0)	7 (5%) vs 18 (4%)	1.0 (0.0–2.0) vs 2.0 (0.0–2.0)
TOCIBRAS	4 (36.4) vs 2 (18.2)	NA	5 (45.5) vs 3 (27.3)	−1.0 (−2.0 to 4.0) vs 2.0 (0.0–4.0)

NA, not available/applicable. Data are expressed as numbers (%) or median (interquartile range). Change in ordinal scale from baseline to day 15 was calculated by subtracting the ordinal scale of day 15 (or, if not available, day 14) from the baseline ordinal scale. In TOCIBRAS trial, patients discharged home were considered to have score 1 on the ordinal scale (i.e., "not hospitalized-no limitations on activities"), and those hospitalized without oxygen were considered to have score 3 (i.e., "hospitalized, not requiring supplemental oxygen—no longer requires ongoing medical care").

Table 2: Outcomes of immunocompromised patients with COVID-19 randomized to immunomodulators vs control.

implementation of innovative trial design (such as basket trials), which takes into consideration the variability of immunocompromised conditions.[17] To generate relevant evidence in a timely manner, the above action should leverage the collective research expertise of health centers who care for such patients.[19] As an example of such collaborative research effort may serve the present meta-analysis.

Given that immunocompromised patients represented an extreme minority of participants or were completely excluded from trials testing immunomodulators against COVID-19, evidence to inform decisions in such patients is currently derived from observational studies[20–22] or, most commonly, is extrapolated from studies involving populations with physiologic immunological baselines.[18] In this context, the present meta-analysis might represent a comprehensive attempt to
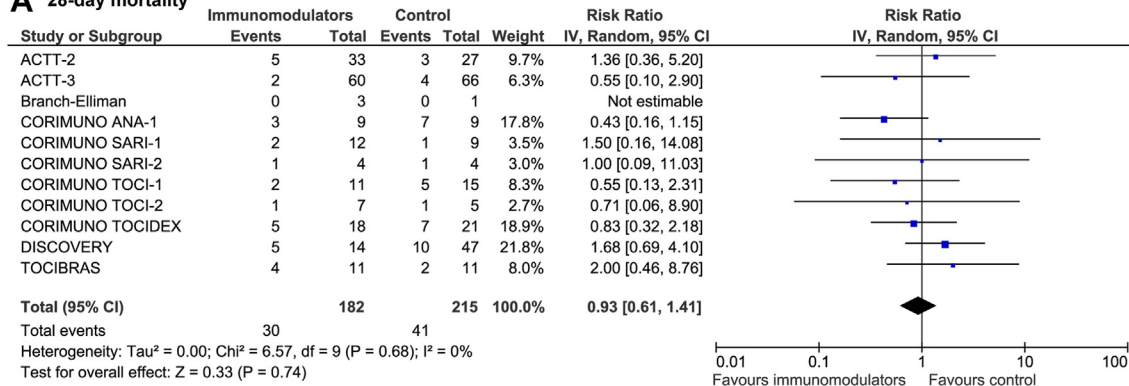
inform decisions regarding the management of immunocompromised patients based on data from randomized controlled trials.

Although the present meta-analysis revealed no significant effect in the group of immunocompromised patients, the estimates were imprecise due to limited number of events and, therefore, solid recommendations cannot be made. That being said, the estimates of the meta-analysis are compatible with a benefit of the same magnitude as observed for the general population of COVID-19 patients. This might mean that enhancing immunosuppression in already immunocompromised patients may not alter the development of specific responses aimed to clear the virus; a reassuring conjecture given that such patients often experience high viral loads and prolonged virologic clearance.[23] Taken together, the results of the meta-analysis may have a
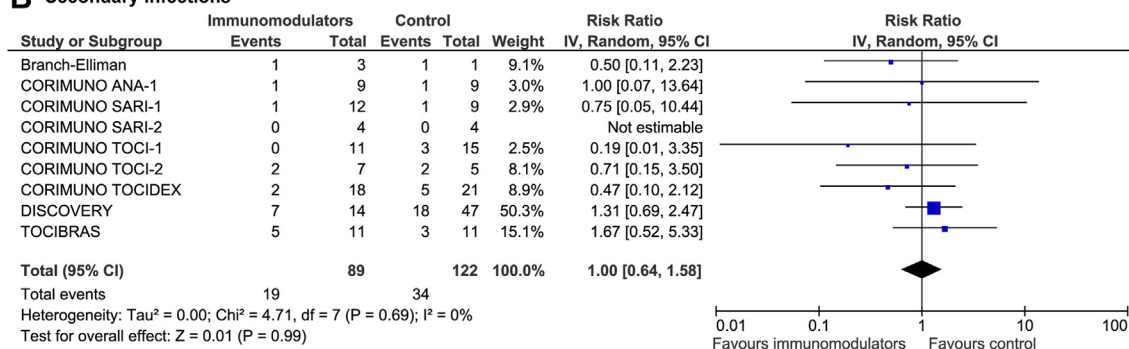

Fig. 2: Risk of bias assessment of included randomized controlled trials. Risk of bias for the primary outcome of the meta-analysis (namely, all-cause 28-day mortality) was assessed using the "Cochrane Risk of Bias tool for randomized trials (RoB 2)". The tool consisted of five domains: 1) the randomization process, 2) the deviations from the intended interventions, 3) the missing outcome data, 4) the measurement of the outcome, and 5) the selection of the reported results. Each domain had up to seven questions. The green circles represent "low risk of bias", the yellow circles represent "some concerns", and the red "high risk of bias".

A 28-day mortality

Study or Subgroup	Immunomodulators Events	Total	Control Events	Total	Weight	Risk Ratio IV, Random, 95% CI
ACTT-2	5	33	3	27	9.7%	1.36 [0.36, 5.20]
ACTT-3	2	60	4	66	6.3%	0.55 [0.10, 2.90]
Branch-Elliman	0	3	0	1		Not estimable
CORIMUNO ANA-1	3	9	7	9	17.8%	0.43 [0.16, 1.15]
CORIMUNO SARI-1	2	12	1	9	3.5%	1.50 [0.16, 14.08]
CORIMUNO SARI-2	1	4	1	4	3.0%	1.00 [0.09, 11.03]
CORIMUNO TOCI-1	2	11	5	15	8.3%	0.55 [0.13, 2.31]
CORIMUNO TOCI-2	1	7	1	5	2.7%	0.71 [0.06, 8.90]
CORIMUNO TOCIDEX	5	18	7	21	18.9%	0.83 [0.32, 2.18]
DISCOVERY	5	14	10	47	21.8%	1.68 [0.69, 4.10]
TOCIBRAS	4	11	2	11	8.0%	2.00 [0.46, 8.76]
Total (95% CI)		182		215	100.0%	0.93 [0.61, 1.41]
Total events	30		41			

Heterogeneity: Tau² = 0.00; Chi² = 6.57, df = 9 (P = 0.68); I² = 0%
Test for overall effect: Z = 0.33 (P = 0.74)

Favours immunomodulators — Favours control

B Secondary infections

Study or Subgroup	Immunomodulators Events	Total	Control Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Branch-Elliman	1	3	1	1	9.1%	0.50 [0.11, 2.23]
CORIMUNO ANA-1	1	9	1	9	3.0%	1.00 [0.07, 13.64]
CORIMUNO SARI-1	1	12	1	9	2.9%	0.75 [0.05, 10.44]
CORIMUNO SARI-2	0	4	0	4		Not estimable
CORIMUNO TOCI-1	0	11	3	15	2.5%	0.19 [0.01, 3.35]
CORIMUNO TOCI-2	2	7	2	5	8.1%	0.71 [0.15, 3.50]
CORIMUNO TOCIDEX	2	18	5	21	8.9%	0.47 [0.10, 2.12]
DISCOVERY	7	14	18	47	50.3%	1.31 [0.69, 2.47]
TOCIBRAS	5	11	3	11	15.1%	1.67 [0.52, 5.33]
Total (95% CI)		89		122	100.0%	1.00 [0.64, 1.58]
Total events	19		34			

Heterogeneity: Tau² = 0.00; Chi² = 4.71, df = 7 (P = 0.69); I² = 0%
Test for overall effect: Z = 0.01 (P = 0.99)

Favours immunomodulators — Favours control

C Change in ordinal scale from baseline to day 15

Study or Subgroup	Immunomodulators Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
ACTT-2	2.27	1.84	33	1.93	2.04	27	13.1%	0.34 [-0.65, 1.33]
ACTT-3	2.73	1.55	60	2.58	1.71	66	40.0%	0.15 [-0.42, 0.72]
CORIMUNO ANA-1	0.33	4.37	9	-3	0	9		Not estimable
CORIMUNO SARI-1	0.33	0.84	12	-0.33	0.87	9	23.6%	0.66 [-0.08, 1.40]
CORIMUNO SARI-2	2.43	5.68	4	1.2	3.28	4	0.3%	1.23 [-5.20, 7.66]
CORIMUNO TOCI-1	1.67	3.39	11	0	4.91	15	1.3%	1.67 [-1.52, 4.86]
CORIMUNO TOCI-2	0.5	1.38	7	0	2.01	5	3.1%	0.50 [-1.54, 2.54]
CORIMUNO TOCIDEX	2.67	3.22	18	0.77	4.93	21	1.9%	1.90 [-0.68, 4.48]
DISCOVERY	1	1.65	14	1.33	1.53	47	13.8%	-0.33 [-1.30, 0.64]
TOCIBRAS	0.91	2.81	11	1.82	2.23	11	2.9%	-0.91 [-3.03, 1.21]
Total (95% CI)			179			214	100.0%	0.27 [-0.09, 0.63]

Heterogeneity: Tau² = 0.00; Chi² = 6.32, df = 8 (P = 0.61); I² = 0%
Test for overall effect: Z = 1.45 (P = 0.15)

Favours control — Favours immunomodulators

Fig. 3: Comparison of immunocompromised patients with COVID-19 randomized to immunomodulators vs control in terms of (A) all-cause 28-day mortality, (B) secondary infections, and (C) change in ordinal scale from baseline to day 15. Pooled risk ratio (RR) and 95% confidence intervals (CI) were calculated using a random-effects model.

direct implication for clinical practice by supporting the guidelines, which recommend immunomodulators for immunocompromised patients similar to the general population.[5] While keeping this general guidance into mind, clinicians caring for immunocompromised patients should appreciate that the evidence basis informing the use of immunomodulators in this population is limited and, thus, clinical decision making for how best to manage these patients is complicated and individual risk/benefit analysis may be needed to inform bedside practice.[18]

This meta-analysis has limitations. Firstly, not all authors of individual trials responded to our invitation to participate in the meta-analysis. However, the most likely explanation for non-responsiveness may be that those authors had not included any immunocompromised patients. Secondly, no trials evaluating steroid monotherapy were included in the meta-analysis. Finally, we lacked detailed data on the extent or type of immunosuppression and, therefore, as previously in the literature,[5,18,19] we considered patients with a variety of different immunocompromised conditions as a
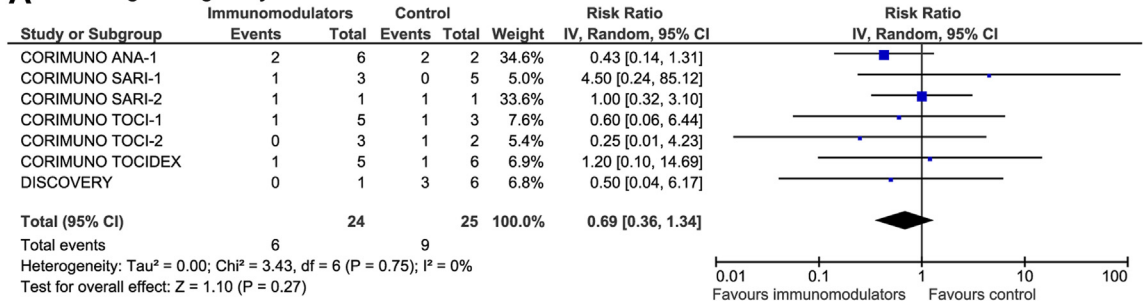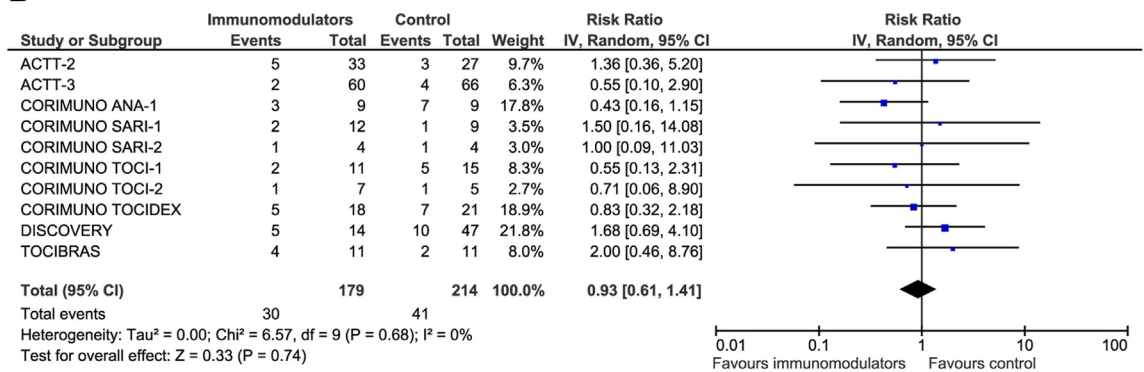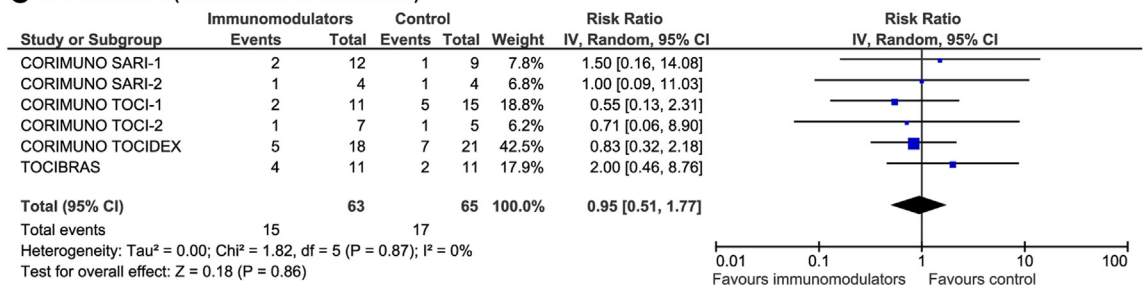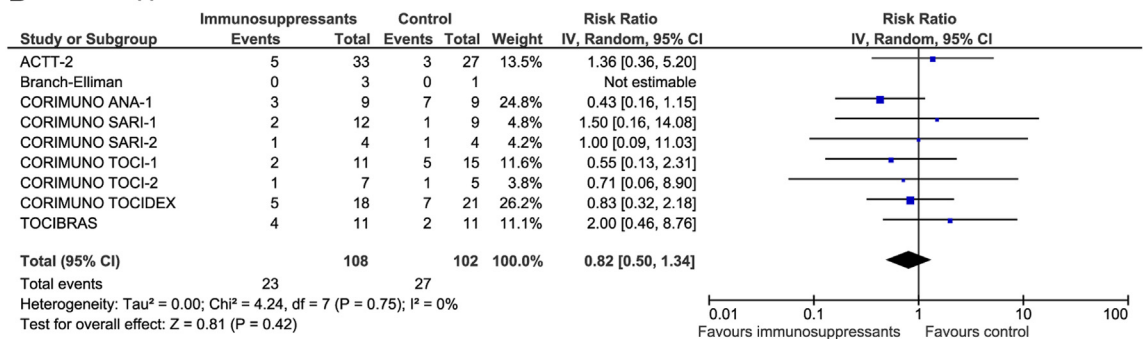
Fig. 4: All-cause 28-day mortality of immunocompromised patients with COVID-19 randomized to immunomodulators vs control in the subgroup analyses (A) including only immunocompromised patients with hematologic malignancy, (B) including only trials with low risk of bias, (C) including only trials administering IL-6 inhibitors, and (D) including only trials administering immunosuppressants. Pooled risk ratio (RR) and 95% confidence intervals (CI) were calculated using a random-effects model.

single risk group. We alert the reader that the study population of immunocompromised patients was heterogenous with potentially differential outcomes. Indeed, in sepsis not related to COVID-19, patients with bone marrow transplantation may have higher mortality,[24] but patients with solid organ transplantation may have lower mortality,[25] when compared to non-transplant patients. In COVID-19, evidence suggests that patients with some types of immunosuppression (e.g., associated with ongoing receipt of cytotoxic chemotherapy or receipt of multiple immunosuppressive medications) remain at higher risk of severe disease when compared to patients with other risk profiles.[26,27] It is possible that patients with different types of immunosuppression may exhibit differential treatment responses to immunomodulators that were not able to measure in this study. Patients with different types of immunosuppression also have variable antibody response to mRNA vaccination against COVID-19.[28] However, this heterogeneity of our study population reflects clinical practice and the main findings were consistent among subgroup analyses.

Immunomodulators, compared to control, were not associated with harmful or beneficial outcomes, including mortality, secondary infections, and change in ordinal scale, when administered to immunocompromised patients hospitalized for COVID-19. However, uncertainty due to imprecision indicates that randomized controlled trials more inclusive of immunocompromised patients are needed.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2024.102472.

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