The impact of therapeutics on mortality in hospitalised patients with COVID-19: systematic review and meta-analyses informing the European Respiratory Society living guideline

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Abstract

Hospitalised patients with coronavirus disease 2019 (COVID-19) have a high mortality rate. There are an increasing number of published randomised controlled trials for anti-inflammatory, anti-viral and other treatments. The European Respiratory Society Living Guidelines for the Management of Hospitalised Adults with COVID-19 were published recently, providing recommendations on appropriate pharmacotherapy.

Patient, Intervention, Comparator and Outcomes questions for key interventions were identified by an international panel and systematic reviews were conducted to identify randomised controlled trials meeting the inclusion criteria. The importance of end-points were rated, and mortality was identified as the key "critical" outcome for all interventions. Random-effects meta-analysis was used to pool studies and provide effect estimates for the impact of treatments on mortality.

Corticosteroids, hydroxychloroquine, azithromycin, remdesivir, anti-interleukin (IL)-6 monoclonal antibodies, colchicine, lopinavir/ritonavir and interferon-β have been reviewed.

Our results found further evidence in support of the use of corticosteroids, particularly dexamethasone, and anti-IL-6 receptor monoclonal antibody therapy. These data support the need to identify additional therapies with beneficial effects on mortality.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the virus that causes coronavirus disease 2019 (COVID-19). The outbreak of this coronavirus was first identified in Wuhan (Hubei, China) in December 2019, and it was declared as pandemic by the World Health Organization in March 2020. By 27 June 2021, reported cases exceeded 180 million and its significant mortality rate (2.3% altogether, but ~10% in the elderly and ~50% in the intensive care unit) [1] has led to almost 4 million deaths globally [2], making mortality a key outcome for treatment decision making.

Awaiting results from clinical trials, clinicians quickly began prescribing repurposed treatments based on their pharmacological properties, pre-clinical data (mostly from *in vitro* experiments) and clinical studies in other viral diseases [3]. Today, several vaccines against SARS-CoV-2 have been approved, and there are currently >2000 ongoing clinical trials focusing on the use and effectiveness of various therapies registered

on clinicaltrials.gov. Some examples include antiviral agents and drugs with antiviral properties, antibiotics, anti-inflammatory drugs and antimalarial agents.

Recommendations on clinical practice for severe COVID-19 management were eagerly awaited by clinicians; however, early in the pandemic such recommendations could be based only on expert opinion, which led some scientific societies such as the European Respiratory Society (ERS) and American Thoracic Society (ATS) to use the term "guidance" rather than "guidelines" [4–6]. This was to avoid any confusion with evidence-based clinical practice guidelines developed using a robust and strict methodology such as the one proposed by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group [7]. While the aforementioned guidance was produced by ERS/ATS taskforces [4–6], the ERS decided to initiate the preparation of evidence-based living guidelines on the management of COVID-19. The term "living guideline" refers to the objective of the taskforce to revise the recommendations whenever required following the release of new evidence with potential practical implications. The first topic addressed has been the management of hospitalised patients, which produced guidelines answering 11 Patients, Intervention, Comparison and Outcomes (PICO) questions addressing the following therapeutic options: corticosteroids, anti-interleukin (IL)-6, remdesivir, anticoagulants, hydroxychloroquine, azithromycin, hydroxychloroquine/azithromycin combination, colchicine, lopinavir/ritonavir, interferon-β and ventilatory support. These guidelines relied on comprehensive systematic reviews and explicit evidence-to-decision processes described in detail in the original publication [8]. For each outcome, the effect of treatment on mortality was identified as the key clinical outcome for decision making. The rapidly evolving evidence base for COVID-19 means that a large number of additional studies have been published since the first version of the ERS living guideline. In this article we present updated results of the systematic review and meta-analyses informing the ERS COVID-19 living guideline showing the impact of different COVID-19 therapeutics on mortality in hospitalised patients. It does not aim to provide additional/updated recommendations, as this will be done in future updates of the living guideline

Methods

The guideline methodology has been described in detail [8]. The objective of this systematic review and meta-analysis was to investigate the effect of nine treatment modalities on mortality in hospitalised patients with COVID-19. In the original guideline development process, no randomised trials were identified for the PICO questions addressing anticoagulation and ventilation; therefore, no randomised trials could be included for meta-analysis in this update. These topics will be addressed, along with new topics, in the next update of the living guideline. This update focused on the nine interventions for which randomised controlled studies were identified: corticosteroids, anti-IL-6 monoclonal antibodies, remdesivir, hydroxychloroquine, azithromycin, hydroxychloroquine/azithromycin combination, colchicine, lopinavir/ritonavir and systemic interferon-β.

Systematic literature review

This update followed the same method with systematic literature searches carried out in PubMed and Embase for published peer-reviewed studies, supplemented by searches of MedRxiv for preprints until 31 May 2021 (supplementary figure S1). The systematic review and data extraction were performed by two independent reviewers (MLC and PCG) with extracted data verified and discrepancies resolved by a third independent reviewer (JDC). The original search strategies were reviewed, and Medical Subject Headings (MeSH) terms and keywords were updated where necessary by experienced librarians (KT and TV). Searches for interferon-β and colchicine were conducted using the individual search terms plus a set of search terms for COVID-19 using PubMed and MedRxiv only. As it was expected that searches for hydroxychloroquine and azithromycin individually would capture trials in which both drugs were used in combination, no repeat searches were performed and trials were selected from the hydroxychloroquine and azithromycin search results for inclusion in the analysis. The search terms used for each PICO question are reported in the original guideline [8]. In addition, the authors identified and searched relevant published systematic reviews and meta-analyses for trials not identified by the relevant searches. The authors also searched reference lists of relevant trials and included any new trials published following the original search dates which became known to authors during writing of the article, to ensure data were as up to date as possible.

Inclusion criteria

Studies were eligible for inclusion if they were randomised clinical trials according to the International Committee of Medical Journal Editors definition (a research study that prospectively assigns a group of people to an intervention, with or without concurrent comparison or control groups, to study the relationship between a health-related intervention and a health outcome); published in English; included

hospitalised patients with COVID-19 infection; and tested one of the interventions included in the PICO questions. For the purposes of analysis, we sought trials that tested the intervention against standard care. Where studies had been identified previously by literature searches conducted prior to the publication of the first guideline, updated data were sought; for example, preprints were replaced by peer-reviewed data and preliminary reports were replaced by more definitive reports.

Data extraction and statistical analysis

Data were extracted from source publications, tabulated and entered into RevMan 5 software version 5.3 (Cochrane Collaboration). We extracted the number of enrolled patients, baseline patient demographics, details of the patient population and mortality in the intervention and control groups in each study. Data extracted were from the intention-to-treat population wherever possible. Where mortality data were reported for multiple time points, the longest duration of follow-up was used for comparison unless the primary outcome was specified as mortality in which case the time point for the primary outcome was displayed. Random-effects meta-analysis was used based on expected heterogeneity in trial designs and patient characteristics. Heterogeneity was assessed using the I^2 statistic. Based on interpretations in the Cochrane Handbook, 0–30% was considered no heterogeneity, 30–50% was considered moderate heterogeneity, 51–75% was considered substantial heterogeneity and 76–100% considerable heterogeneity. Where heterogeneity was detected, additional analyses were performed to explore the source of the heterogeneity. Sub-analyses were performed where a significant effect on mortality was observed in the primary analysis. In the case of a primary analysis with $p>0.05$, no sub-analyses were performed. $p<0.05$ was considered statistically significant for all comparisons. The GRADE approach was used to assess the quality of evidence for each outcome. GRADE has four levels of evidence: very low, low, moderate and high. GRADE was implemented using GRADEpro software and was performed by three investigators (MLC, NR and JDC), supervised by an experienced methodologist (TT).

Results

The original ERS guideline for management of hospitalised patients with COVID-19 published in March 2021 was based on a literature search up until the end of February 2021. This search identified 44 eligible references from 14 851 articles and provided recommendations for 11 PICO topics: corticosteroids, IL-6 receptor antagonist monoclonal antibody, hydroxychloroquine, azithromycin, hydroxychloroquine in combination with azithromycin, lopinavir/ritonavir, remdesivir, colchicine, interferon-β, anticoagulation and noninvasive ventilatory support.

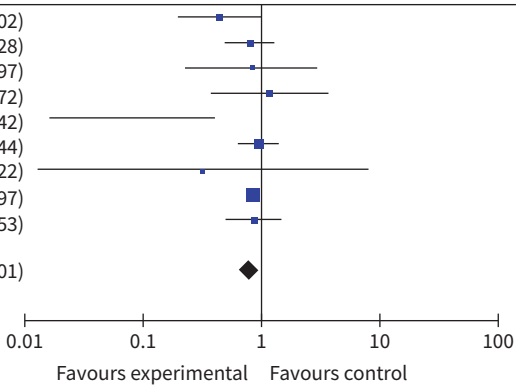
The literature search for this update retrieved an additional 12 960 articles between PubMed and Embase across nine searches (anticoagulation and noninvasive ventilatory support are not included). After removal of duplicates and exclusion of citations that did not meet the established inclusion criteria while screening titles and abstracts, a total of 15 new trials meeting the eligibility criteria were identified. A search of the MedRxiv database identified a further five preprints. Together, these searches have identified 20 new references which were included in this update and were pooled with data extracted from the 44 studies identified in the searches up to February 2021.

Corticosteroids

We identified nine studies [9–17] with 7766 subjects, including three additional studies [13, 15, 17] following publication of the guidelines. Overall, mortality in the treatment groups was 714 (25.6%) out of 2793, and in the control groups was 1365 (27.4%) out of 4973. The pooled effect estimate showed OR 0.80 (95% CI 0.64–1.01, p=0.06), indicating a mortality benefit that narrowly failed to meet the pre-specified level of statistical significance. 2104 (75.3%) out of 2793 patients receiving corticosteroids and 4321 (86.9%) out of 4973 patients receiving standard care were from a single trial, the RECOVERY trial of 6 mg daily dexamethasone. The forest plot is shown in figure 1. There was moderate heterogeneity (I^2=30%). The heterogeneity was entirely resolved (I^2=0%) after excluding the study by Edalatifard *et al.* [9] (IRCT20200404046947N1), which showed an extreme beneficial effect (OR 0.08, 95% CI 0.02–0.42). A sub-analysis was performed to investigate whether the beneficial effects of corticosteroids were limited to dexamethasone or extend to other corticosteroids (supplementary figure S2). Four studies investigated methylprednisolone, giving an OR 0.48 (95% CI 0.16–1.46, p=0.02) [9, 14, 15, 17]; three trials investigated dexamethasone, showing OR 0.86 (95% CI 0.76–0.97, p=0.01) [12, 13, 16]; and the final two studies investigated the use of hydrocortisone: OR 0.67 (95% CI 0.35–1.29, p=0.23) [10, 11]. The test for subgroup analysis did not show any significant differences between groups (p=0.46). In the RECOVERY trial, the treatment benefit was seen most clearly in patients requiring mechanical ventilation at randomisation (rate ratio 0.64, 95% CI 0.51–0.81) and patients receiving supplementary oxygen (rate ratio 0.82, 95% CI 0.72–0.94). No benefit was observed in those not requiring oxygen (rate ratio 1.19, 95% CI 0.92–1.55). Three studies (CoDEX, CAPE COVID and REMAP-CAP) were primarily or exclusively

Study or subgroup	Corticosteroid Events	Total	Control Events	Total	Weight	Odds ratio M-H, Random, 95% CI
CAPE COVID	11	76	20	73	6.4%	0.45 (0.20–1.02)
CoDEX	85	151	91	148	15.4%	0.81 (0.51–1.28)
GLUCOCOVID	5	29	7	35	2.9%	0.83 (0.23–2.97)
IRCT20151227025726N17	16	25	15	25	3.5%	1.19 (0.38–3.72)
IRCT20200404046947N1	2	34	12	28	1.8%	0.08 (0.02–0.42)
METCOVID	72	194	76	199	18.0%	0.96 (0.64–1.44)
NCT04273321	0	43	1	43	0.5%	0.33 (0.01–8.22)
RECOVERY	482	2104	1110	4321	39.5%	0.86 (0.76–0.97)
REMAP-CAP	41	137	33	101	12.0%	0.88 (0.51–1.53)
Total (95% CI)		2793		4973	100.0%	0.80 (0.64–1.01)
Total events	714		1365			

Heterogeneity: Tau²=0.03; Chi-squared=11.38, df=8 (p=0.18); I²=30%
Test for overall effect: Z=1.91 (p=0.06)



Study or subgroup	IL-6 receptor antagonists Events	Total	Control Events	Total	Weight	Odds ratio M-H, Random, 95% CI
BACC Bay	9	161	3	81	0.6%	1.54 (0.41–5.85)
COALITION	14	65	6	64	0.9%	2.65 (0.95–7.42)
CORIMUNO-TOC	7	63	8	67	0.8%	0.92 (0.31–2.71)
COVACTA	58	294	28	144	3.9%	1.02 (0.62–1.68)
COVINTOC	11	91	15	88	1.4%	0.67 (0.29–1.55)
EMPACTA	26	249	11	128	1.8%	1.24 (0.59–2.60)
NCT04315298	287	1136	83	309	12.1%	0.92 (0.69–1.22)
NCT04327388	35	332	9	84	1.6%	0.98 (0.45–2.13)
RCT-TCZ-COVID-19	2	60	1	63	0.2%	2.14 (0.19–24.21)
RECOVERY	621	2022	729	2094	57.9%	0.83 (0.73–0.95)
REMAP-CAP	475	1426	150	406	18.7%	0.85 (0.68–1.07)
Total (95% CI)		5899		3528	100.0%	0.87 (0.79–0.96)
Total events	1545		1043			

Heterogeneity: Tau²=0.00; Chi-squared=8.17, df=10 (p=0.61); I²=0%
Test for overall effect: Z=2.71 (p=0.007)

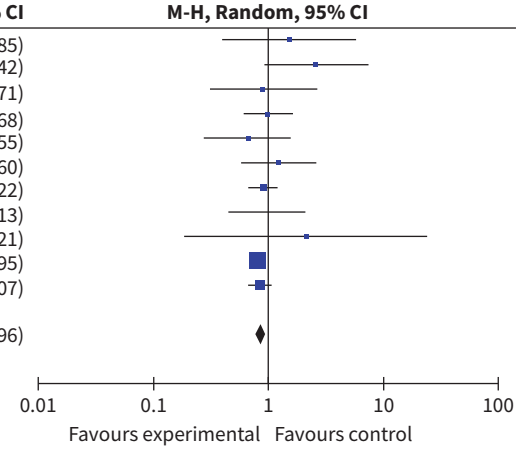


FIGURE 1 Forest plots showing the effects of corticosteroids and interleukin (IL)-6 receptor antagonists on mortality of hospitalised adult patients with coronavirus disease 2019. Study name has been used unless no name was available, in which case the trial registration identifier has been used. The weight represents the percentage contribution of each study to the summary effect estimate.

conducted in intensive care units and showed an effect estimate of 0.76 (0.55–1.05). The certainty of evidence was graded as moderate (supplementary table S1).

IL-6 receptor antagonist monoclonal antibodies

We identified 11 studies [18–28] with 9427 subjects, including two additional studies [18, 23] and two preprints [19, 24] following publication of the guidelines. Two reports of the REMAP-CAP trial were identified, reporting results for tocilizumab and sarilumab [19, 29]. It was established these were overlapping datasets containing data from the same subjects, and so the larger report from Derde *et al.* [19] was included in the analysis. The original guidelines included one preprint and two preliminary reports, which have all been updated using finalised published data to complete this review [19, 21, 22]. Sivapalasingam *et al.* [24] (NCT04315298) reported results of a phase 2 and phase 3 programme for sarilumab in a single article. In addition, this article reported results for a dose of 200 mg intravenous sarilumab and 400 mg *i.v.* sarilumab. For the purposes of analysis, these were treated as a single trial and data for both doses pooled. Lescure *et al.* [23] (NCT04327388) also randomised patients to both 200 mg and 400 mg sarilumab doses, which were both pooled for analysis. This study presented data with mortality at both day 29 and day 60. Mortality at day 60 was used.

Overall, mortality in the treatment group was 1545 (26.2%) out of 5899 and in the control group was 1043 (29.6%) out of 3528. The pooled effect estimate was OR 0.87 (95% CI 0.79–0.96, p=0.007), showing significant reduction in mortality with anti-IL-6 treatment. There was no heterogeneity (I^2=0%). The forest plot is shown in figure 1. It was noted that despite the overall significant effect, only one of the 11 trials showed statistically significant differences in favour of the intervention, the RECOVERY trial [21]. In

terms of timing of treatment, the majority of studies were conducted on populations of patients outside the intensive care unit or a moderate–severe population including those receiving oxygen or ventilatory support. The largest study, the RECOVERY trial, showed a similar benefit in patients not receiving ventilator support (rate ratio 0.81, 95% CI 0.67–0.99) and receiving noninvasive ventilation (rate ratio 0.86, 95% CI 0.74–1.00), with the suggestion of a lesser effect in those invasively ventilated at randomisation (rate ratio 0.93, 95% CI 0.74–1.18) [21].

As the review included data for both sarilumab and tocilizumab, a sub-analysis was conducted separately analysing the three sarilumab trials [19, 23, 24] and the nine tocilizumab trials [18–22, 25–28] (supplementary figure S3). One trial, REMAP-CAP, included both sarilumab and tocilizumab arms, and so is included in both analyses [19]. We found no meaningful difference in effect estimates between the two: sarilumab OR 0.88 (95% CI 0.73–1.07, p=0.19) and tocilizumab OR 0.87 (95% CI 0.78–0.96, p=0.009), resulting in a nonsignificant subgroup difference of p=0.89. The certainty of evidence was graded as moderate (supplementary table S2).

Hydroxychloroquine

We identified 13 eligible studies [30–42] with 8721 subjects, including five additional published studies [31, 34–36, 42] and one preprint [39] following publication of the guidelines. Preprints used in the original analysis have been updated in this analysis [30, 41]. Mortality in the treatment group was 628 (17.5%) out of 3589, and in the control group was 984 (19.2%) out of 5132. The pooled effect estimate was OR 1.09 (95% CI 0.97–1.22, p=0.14) with no heterogeneity (I^2=0%). The forest plot is shown in figure 2. Four randomised controlled trials of hydroxychloroquine were excluded from our analysis due to the patient population being community based rather than hospital based [43–46]. The results from these studies showed no benefits from treatment in clinical status, with Réa-Neto *et al.* [44] identifying a significant worsening of clinical status, including an increased need for invasive mechanical ventilation relative risk (2.15, 95% CI 1.05–4.40; p=0.030). Reis *et al.* [43] stopped the hydroxychloroquine arm of their trial at first interim analysis due to futility based on data from another study. The certainty of evidence was graded as moderate (supplementary table S3).

Azithromycin

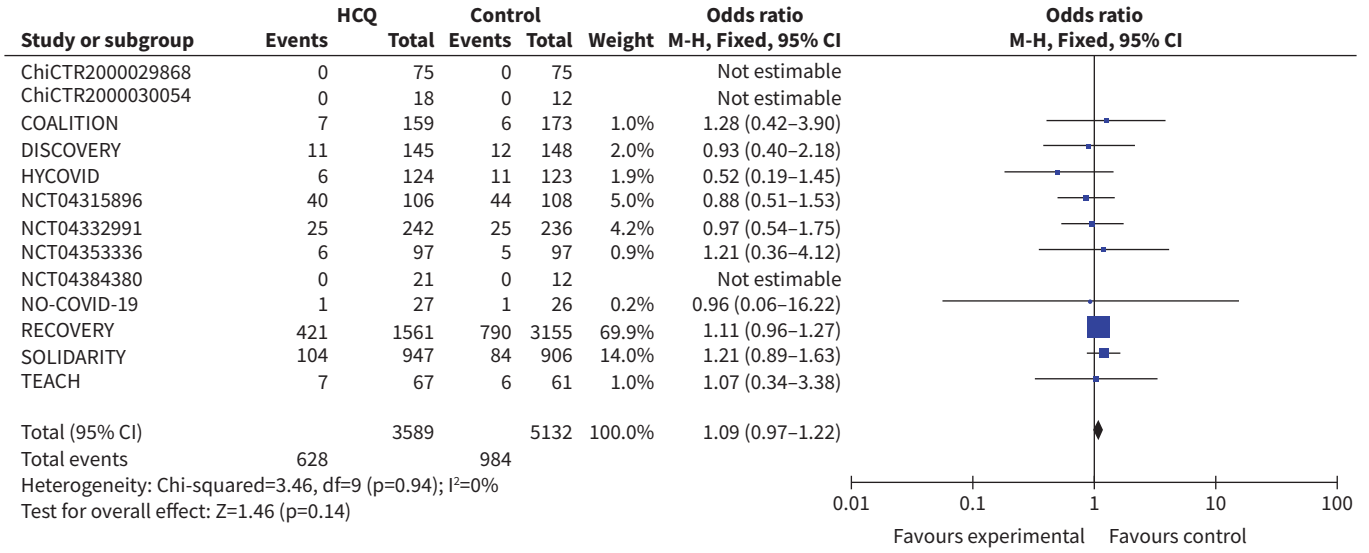
We identified five studies [33, 47–50] with 9067 subjects, including one additional study [50] and one preprint [47] following publication of the guidelines. The PRINCIPLE trial testing azithromycin in outpatients showed no evidence of benefit of azithromycin in nonhospitalised patients [51], but it is not included in the present meta-analysis focusing on hospitalised patients only. The ATOMIC2 trial by Hinks *et al.* [47] was included in the analysis, as patients were enrolled in hospital, although eligibility included the requirement to be eligible for ambulatory management. The COALITION study by Cavalcanti *et al.* [33] compared azithromycin and hydroxychloroquine compared to hydroxychloroquine or standard care. Since hydroxychloroquine was widely used as standard care in many other studies included in the guidelines, the guideline panel determined that this study could be used to infer the efficacy of azithromycin. Including all studies mortality in the treatment group was 657 (20.7%) out of 3169, and in the control group was 1250 (21.2%) out of 5898. The pooled effect estimate was OR 0.97 (95% CI 0.87–1.08, p=0.53) with no heterogeneity (I^2=0%). Excluding COALITION and ATOMIC2, did not impact the conclusion (OR 0.97 95% CI 0.87–1.08). The forest plot is shown in figure 2. The certainty of evidence was graded as moderate (supplementary table S4).

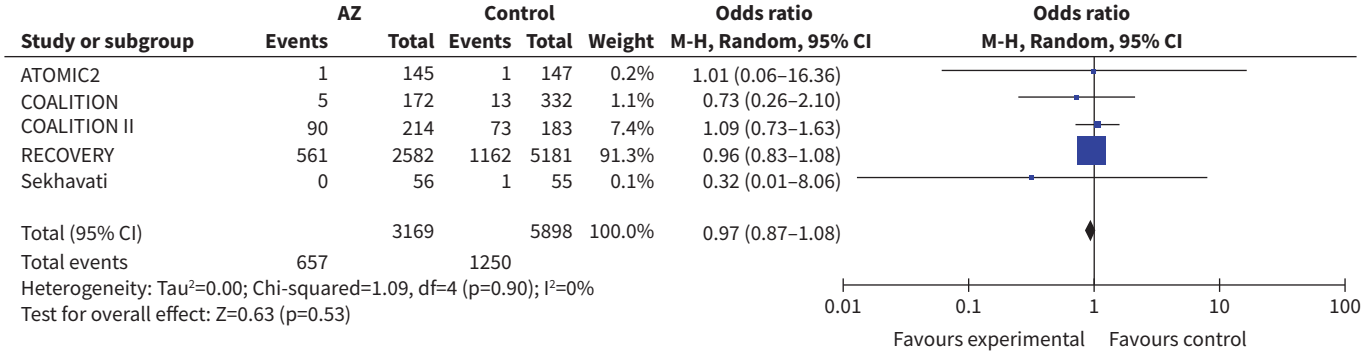
Hydroxychloroquine and azithromycin in combination

We identified two studies [33, 52] with 462 subjects, including one additional study [52] following publication of the guidelines and which was identified after the original search dates. Across these two studies, mortality in the treatment group was six (2.6%) out of 233, and in the control group was eight (3.5%) out of 229. The pooled effect estimate was OR 0.73 (95% CI 0.25–2.15, p=0.57) with no heterogeneity (I^2=0%). The forest plot is shown in figure 2. The search identified one active comparator trial (HAHPS) comparing the efficacy of hydroxychloroquine *versus* azithromycin [53]; however, this study was not included in the analysis as it did not address any of the guideline PICO questions, but is discussed here. In common with other studies, the HAHPS study was stopped early due to futility. The data were assessed using a proportional odds modelling from a Bayesian perspective and concluded a 60% posterior probability that hydroxychloroquine was inferior to azithromycin. For the remaining two studies included in the meta-analysis the certainty of evidence was graded as low (supplementary table S5).

Lopinavir/ritonavir

We identified four studies [30, 42, 54, 55] with 8303 subjects, including one additional study [42] following publication of the guidelines. The DISCOVERY trial by Ader *et al.* [42] (an add-on trial to





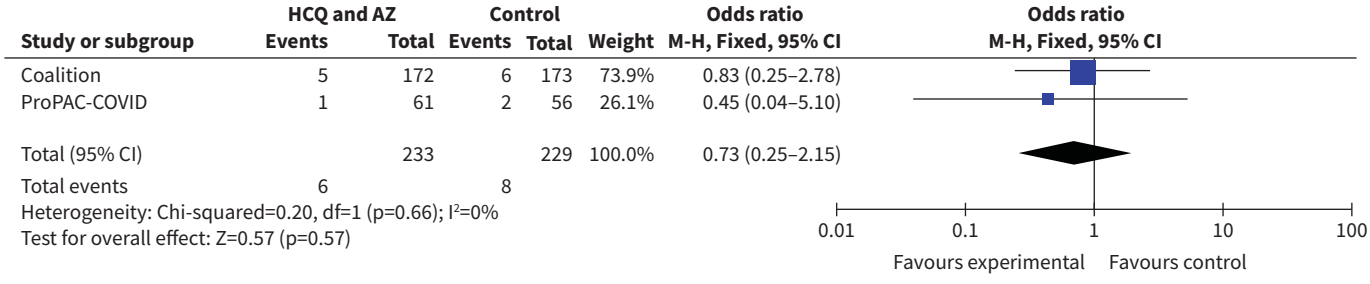


FIGURE 2 Forest plots showing the effects of hydroxychloroquine (HCQ), azithromycin (AZ) and hydroxychloroquine in combination with azithromycin on mortality of hospitalised adult patients with coronavirus disease 2019. Study name has been used unless no name was available, in which case the trial registration identifier has been used. The weight represents the percentage contribution of each study to the summary effect estimate.

SOLIDARITY [30]) in which patients are randomly assigned either lopinavir/ritonavir, lopinavir/ritonavir/interferon-β1a, hydroxychloroquine or remdesivir in comparison to standard of care in a 1:1:1:1 ratio, added another 293 hospitalised patients to the lopinavir/ritonavir analysis. The primary outcome was improved clinical status determined by a seven-point ordinal scale; however, due to treatment futility this arm and the hydroxychloroquine arm were stopped prematurely. No benefit to clinical status was observed from the data obtained (adjusted OR 0.83, 95% CI 0.55–1.26; p=0.39) and no impact was made on the overall mortality odds ratio published in the original guideline. Mortality in the treatment group was 555 (17.0%) out of 3259, and in the control group was 950 (18.8%) out of 5044. The pooled effect estimate was OR 1.02 (95% CI 0.91–1.15, p=0.72) with no heterogeneity (I^2=0%). The forest plot is shown in figure 3. The certainty of evidence was graded as high (supplementary table S6).

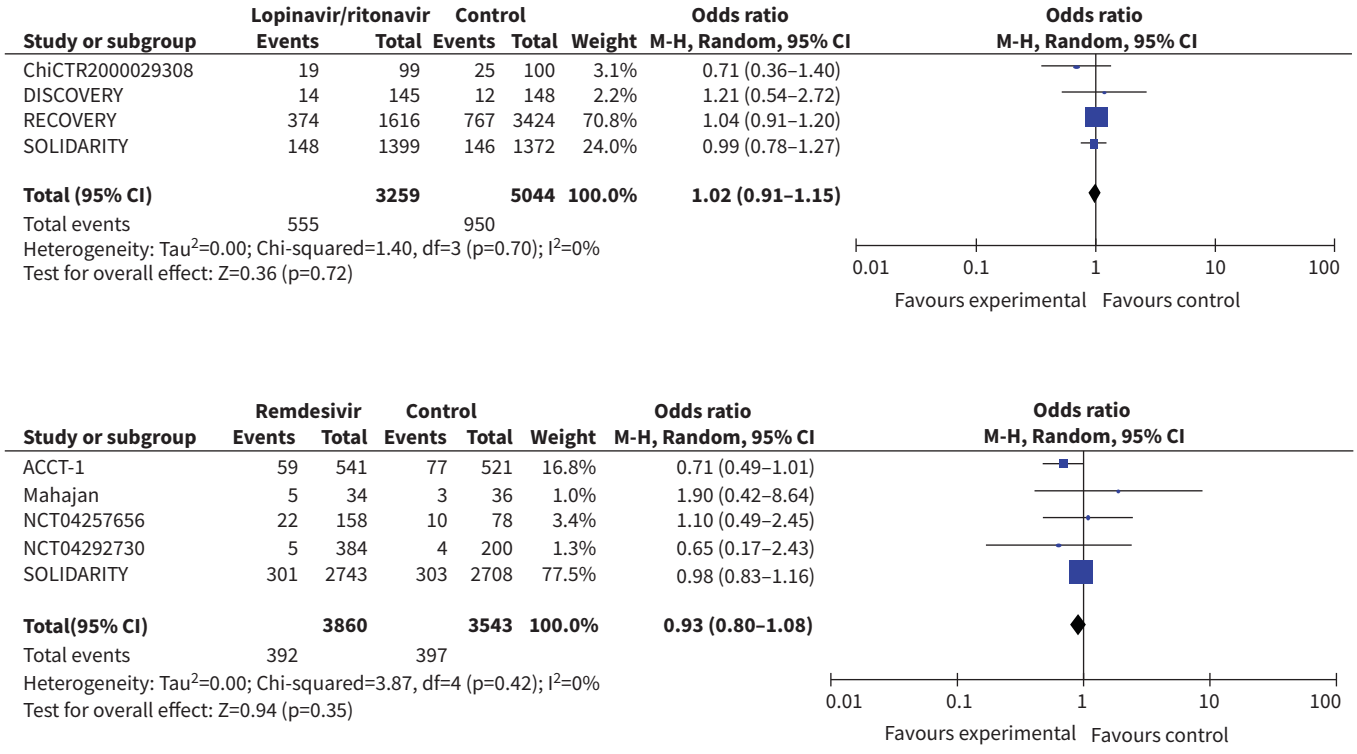


FIGURE 3 Forest plots showing the effects of lopinavir/ritonavir and remdesivir on mortality of hospitalised adult patients with coronavirus disease 2019. Study name has been used unless no name was available, in which case the trial registration identifier has been used. The weight represents the percentage contribution of each study to the summary effect estimate.

Remdesivir

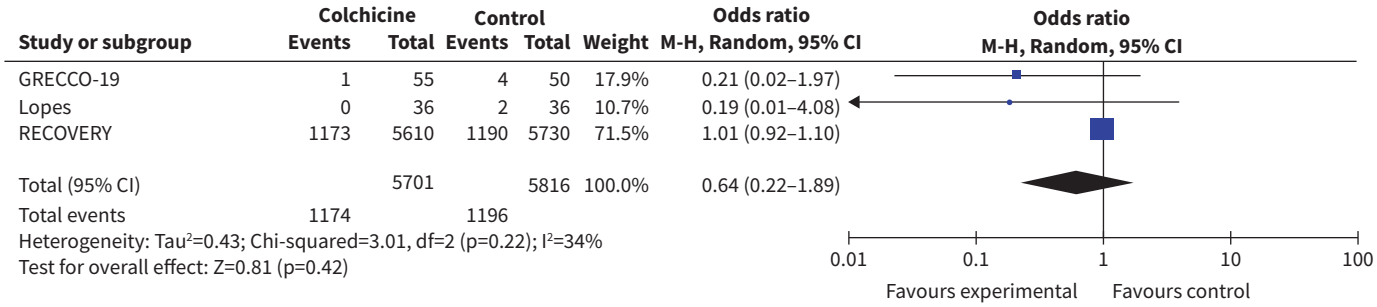
We identified five studies meeting the inclusion criteria [30, 56–59] with 7403 subjects, including one additional study [59] following publication of the guidelines. Mortality in the treatment group was 392 (10.2%) out of 3860, and in the control group was 397 (11.2%) out of 3543. The pooled effect estimate was OR 0.93 (95% CI 0.80–1.08, p=0.35) with no heterogeneity (I^2=0%). The forest plot is shown in figure 3. No recommendation was made regarding the use of remdesivir in the original guidelines [8]. A randomised, open-label trial excluded from our analysis due to having no appropriate comparator treatment assessed the differential benefits of receiving a 5-day course of remdesivir treatment (n=200) *versus* receiving a 10-day course of treatment (n=197) in hospitalised patients. The results showed no statistically significant difference between the two treatment durations [60]. The certainty of evidence was graded as moderate (supplementary table S7).

Colchicine

We identified three studies [61–63] with 11 517 subjects, including one preprint [63] following publication of the guidelines. The COLCORONA trial showed no statistically significant benefit of colchicine in outpatients with COVID-19, but was not included as this analysis focused on hospitalised patients only [64]. The interim analysis from Lopes *et al.* [61], which was included in the original guidelines, was updated to reflect the data from all trial participants (increasing participant number from 35 (18 placebo *versus* 17 colchicine) to 72 (36 placebo *versus* 36 colchicine)). Mortality in the treatment group was 1174 (20.6%) out of 5701 and 1196 (20.6%) out of 5816 in the control group. The pooled effect estimate was OR 0.64 (95% CI 0.22–1.89, p=0.42), but with moderate heterogeneity (I^2=34%). The two smaller studies, which were rated as high risk of bias in the original guideline document showed benefits in favour of colchicine [61, 62], while the much larger RECOVERY trial found no evidence of benefit OR 1.01 (95% CI 0.92–1.10) [63]. The forest plot is shown in figure 4. The certainty of evidence was graded as low (supplementary table S8).

Interferon-β

We identified four studies [30, 65–67] with 4307 subjects, including one additional study [67] following publication of the guidelines. Alavi Darazam *et al.* [67] performed a three-arm study randomly assigning a



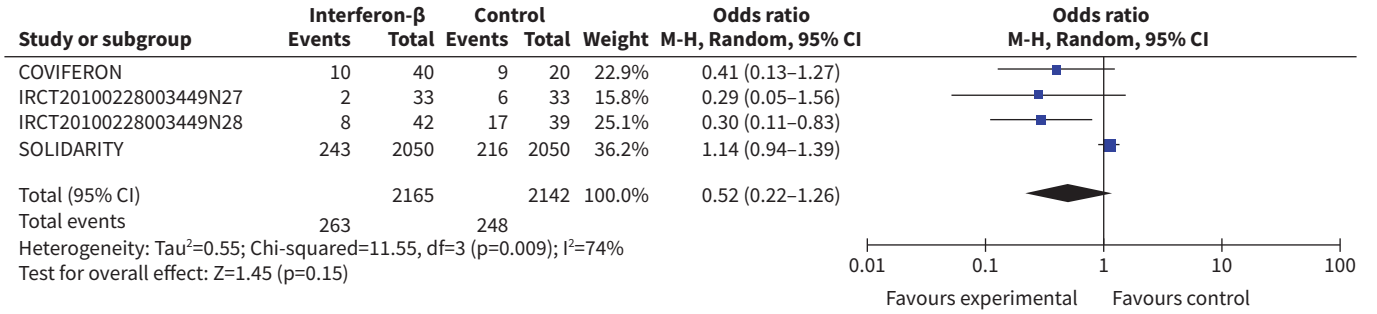


FIGURE 4 Forest plots showing the effects of colchicine and interferon-β on mortality of hospitalised adult patients with coronavirus disease 2019. Study name has been used unless no name was available, in which case the trial registration identifier has been used. The weight represents the percentage contribution of each study to the summary effect estimate.

1:1:1 ratio of systemic interferon-β1a, interferon-β1b and a control group. The primary end-point for this study was time to clinical improvement as defined by a seven-step ordinal scale or discharge. In this study, interferon-β1a showed a significant improvement in time to clinical improvement when compared to control (hazard ratio (HR) 2.36, 95% CI 1.10–5.17; p=0.031), whereas interferon-β1b did not (HR 1.42, 95% CI 0.63–3.16; p=0.395). The largest study (SOLIDARITY) included in the meta-analysis showed no significant benefit, with a trend towards harm [30]. For the purpose of this analysis looking at mortality outcome, data from arms containing interferon-β1a and interferon-β1b were combined. Mortality in the treatment group was 263 (12.1%) out of 2165 and 248 (11.6%) out of 2142 in the control group. The pooled effect estimate was OR 0.52 (95% CI 0.22–1.26, p=0.15). The forest plot is shown in figure 4. A study of nebulised interferon-β1a was identified [68]. This trial randomised 50 patients to nebulised interferon and 51 patients to placebo and demonstrated a statistically significant improvement in clinical status (OR 2.32, 95% CI 1.07–5.04; p=0.033). It was not considered appropriate to pool nebulised and systemic interferon data, and therefore this trial is not included in the meta-analysis. The certainty of evidence was graded as low (supplementary table S9).

Discussion

Mortality is the critical outcome for testing the efficacy of therapeutics in hospitalised patients with COVID-19, a condition with a high mortality rate globally [1]. This systematic review and meta-analysis confirms that corticosteroids and anti-IL-6 receptor monoclonal antibodies reduce mortality in hospitalised patients with COVID-19. The sub-analyses with different corticosteroids suggest no class effect, as there were no subgroup differences between dexamethasone, hydrocortisone and methylprednisolone. Further studies will be required to establish the most appropriate dose and duration of therapy. In terms of the anti-IL-6 receptor monoclonal antibodies, it is also noted that while the majority of published evidence concerns tocilizumab, there were no significant subgroup differences, suggesting that sarilumab can be considered equally efficacious. For corticosteroids, the greatest benefits were observed in patients requiring mechanical ventilation with significant benefits observed in patients requiring oxygen, but no benefits in those not requiring oxygen. For anti-IL-6 receptor monoclonal antibodies, the majority of studies were performed in patients requiring oxygen or noninvasive ventilation with reduced mortality observed in these groups.

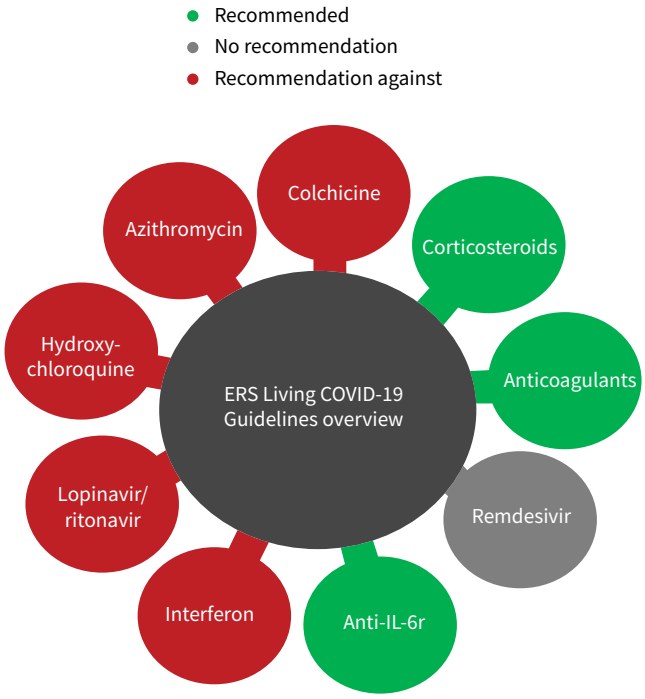


FIGURE 5 Summary of recommendations from the European Respiratory Society (ERS) guidelines for hospitalised patients with coronavirus disease 2019 (COVID-19).

We found no mortality benefit of hydroxychloroquine or azithromycin, or the combination of hydroxychloroquine and azithromycin, lopinavir/ritonavir, remdesivir, colcichine or interferon-β. These results are consistent with the earlier results included in the ERS guidelines and support the original recommendations regarding these agents included in the guidelines. A summary of the guideline recommendations is shown in figure 5.

As the medical science community continues to work relentlessly on identifying the best treatment methods in COVID-19, the resulting literature is published at an unprecedented rate, meaning that guidelines are "out of date" at the time of their publication. To minimise the disconnect between new evidence and recommendations, "living guidelines" allow for frequent, rapid literature searches to identify where new evidence means new practice-changing evidence. These important updates can then be published immediately and communicated to the appropriate communities much faster than a standard guideline, which is typically updated every 3–4 years.

Our update to the systematic review and meta-analysis has seen the addition of 20 randomised controlled trials published since January 2021. The trials include an additional 25 171 hospitalised adult patients with COVID-19. As described in the original guidelines, the main aim in managing hospitalised patients is to reduce mortality and prevent worsening of health status from the point of hospitalisation. Mortality is a priority outcome, due to the high mortality rate of COVID-19 in combination with the high reproductive rate (R_0) of SARS-CoV-2, estimated as 2.5 [69].

Our results extend the results of the original ERS guidelines in which IL-6 receptor antagonist monoclonal antibodies had not accumulated sufficient evidence to show a significant effect on mortality, but with the additional literature a significant benefit is demonstrated in the present analysis.

It was well documented at the start of the pandemic that hydroxychloroquine was the treatment most widely studied, and therefore unsurprisingly, the largest number of trials we identified were for this agent. A meta-analysis performed by Axfors *et al.* [70] found that the use of hydroxychloroquine was statistically detrimental (OR 1.11, 95% CI 1.02–1.2; p=0.02). Unlike Axfors *et al.*, we did not include prophylaxis trials or unpublished data; our findings from hospitalised patients showed a very similar trend, but with wider confidence intervals (OR 1.10, 95% CI 0.97–1.23; p=0.53). With the addition of five new hydroxychloroquine trials which include almost 1000 patients further confirming the detrimental effects of

hydroxychloroquine use in COVID-19 patients, the ERS guideline panel has recommended that there is no need to continue studying this treatment as a potential therapy in this population. Future iterations of the ERS guidelines will not address hydroxychloroquine. >8000 patients were added to the azithromycin analysis, with the vast majority taking part in the RECOVERY platform trial; however, this did not show any beneficial evidence for azithromycin use in COVID-19 management and this treatment will not be updated in future guidelines. No improvements were observed from therapeutic use of lopinavir/ritonavir, and this too will not be updated in future guidelines. It is acknowledged that there is a need to add new drugs for which there are recently published trials including antibodies, convalescent plasma, baricitinib and anti-granulocyte–macrophage colony-stimulating factor, and these will feature in future guidelines as further data accumulates. In addition, new randomised controlled trial data have been published in recent weeks showing that therapeutic anticoagulation may be beneficial in hospitalised patients outside the intensive care unit [71] and that continuous positive airway pressure is superior to conventional oxygen therapy in patients requiring ventilatory support [72]. These results will be incorporated into the next version of the treatment guidelines.

We acknowledge there are limitations to this study. As the pandemic continues, reports show higher proportions of children and adolescents becoming infected with COVID-19 and our search covers only the adult population. Our search has remained in the hospitalised population with the focus on mortality outcome; however, many countries have implemented successful vaccination programmes and as a result fewer people are being admitted to hospital with severe SARS-CoV-2 infection. As the impact of COVID-19 changes, the research needs to be flexible and reflect this with more studies needed in the community, inclusive of the younger population and with consideration of new outcomes such as prevention and reduction of long-COVID symptoms.

Conclusion

Corticosteroids and anti-IL-6 receptor monoclonal antibodies reduce mortality in COVID-19 patients.

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